

NCT04425629

EudraCT: 2020-003690-21
IND: 148069

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 AMBULATORY PATIENTS WITH COVID-19

Compound: REGN10933+REGN10987
Clinical Phase: 1/2/3
Protocol Number: R10933-10987-COV-2067
Protocol Version: Amendment 10 US
Amendment 10 US Date of Issue: *See appended electronic signature page*
Amendment 9 US Date of Issue: 14 Jul 2021
Amendment 8 Date of Issue: 12 Mar 2021
Amendment 7 Date of Issue: 18 Dec 2020
Amendment 6 Date of Issue: 14 Nov 2020
Amendment 5 Date of Issue: 08 Aug 2020
Amendment 4 Date of Issue: 11 Jul 2020
Amendment 3 Date of Issue: 04 Jul 2020
Amendment 2 Date of Issue: 19 June 2020
Amendment 1 Date of Issue: 03 June 2020
Original Date of Issue: 29 May 2020

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AMENDMENT HISTORY

Amendment 10 US

The primary purpose of this amendment is to end enrollment of the REGN10933+REGN10988 2400 mg IV dose level. Since 1200 mg IV is the only remaining dose in this study, treatment assignment for patients enrolled in this amendment and later will no longer be blinded. Additional modifications and clarifications have been made, including with respect to the long COVID portion of the study.

Description of Change	Brief Rationale	Section(s)
Added a note that states enrollment in cohort 1 was closed on 14 May 2021.	To ensure up-to-date study information	Section 6.1.3 Phase 3 Section 7.2.1 Inclusion Criteria
For cohort 2 and cohort 3, the REGN10933+REGN10987 2400 mg IV treatment arm will be dropped, such that all newly-enrolled patients in cohort 2 and cohort 3 will receive REGN10933+REGN10987 at the 1200 mg IV dose (or body-weight adjusted equivalent for patients who are <18 years of age). Since 1200 mg IV is the only remaining dose in the study, patients enrolled in this amendment and later will no longer be randomized to 1200 mg IV with a probability of 1, and their treatment assignment will no longer be blinded.	To maximize enrollment, and hence data obtained, in the 1200 mg arm This change is not due to any safety concern related to the 2400 mg IV dose.	Section 3.2.2.2 Phase 3 Dose Selection Section 6.1.3 Phase 3 Figure 7 Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Amendment 10 US and Later [new] Figure 8 Study Flow Diagram, Phase 3 (Cohort 3 Patients ≥18 Years) Amendment 10 US and Later [new] Section 8.6 Method of Treatment Assignment Section 8.7 Blinding Section 8.8 Emergency Unblinding Section 8.9.1 Packaging, Labeling, and Storage
Additional samples for assessment of drug concentration have been included as below: <ul style="list-style-type: none"> Day 60 for cohort 3 patients ≥18 years Day 90 for cohort 2 patients and cohort 3 patients <18 Years (schedules A and B) Day 120 for cohort 2 patients and cohort 3 patients <18 Years (schedules C and D) 	To obtain additional REGN10933+REGN10987 pharmacokinetics data	Table 7 Schedule of Events: Phase 3 (Cohort 3 ≥18 Years) Table 8 Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)
In phase 3 cohort 1 patients, 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 protocol amendment 9 US but have already completed their end of study visit may be re-consented for retrospective collection of this information.	To contextualize any symptoms or diagnoses that may confound or be associated with long COVID	Table 6 Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients) Section 9.1.1 Footnotes for the Schedule of Events Tables, #24 [new] Section 9.2.12 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 phase 3 cohort 1 patients, 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 9.2.11 Monitoring for SARS-CoV-2 Reinfection Section 10.1.3 Events that Require Expedited Reporting to Sponsor

Description of Change	Brief Rationale	Section(s)
		Section 10.1.4 Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor [new]
For all day 120 and day 169 questionnaires in phase 3 cohort 1 patients, a visit window of +7 days will be applied. For all other day 120 and day 169 assessments and sample collections in these patients, a visit window of ±7 days will be applied.	To ensure operational clarity	Table 6 Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients) Section 9.1.1 Footnotes for the Schedule of Events Tables, #19
Clarified that patients who are withdrawn from the study before day 29 will be asked to allow an early termination visit consisting of day 29 assessments and sample collections. Patients who are withdrawn from the study after day 29 will be asked to allow an early termination visit consisting of end-of-study assessments and sample collections.	To ensure operational clarity.	Section 9.1.2 Early Termination from the Study
Risk-benefit information was updated.	To provide current study drug information	Section 3.3 Risk-Benefit
Minor updates (typographical, editorial, administrative) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 9 US

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

Description of Change	Brief Rationale	Section(s)
<i>Evaluation of Long COVID</i>		
<p>Long COVID will be assessed through day 169 in phase 3 cohort 1. Patient-reported symptoms and related outcomes will be evaluated. 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.</p>	<p>To better understand the patient experience of long COVID, and to evaluate whether treatment of initial SARS-CoV-2 infection with study drug may provide subsequent clinical benefit in the prevention of long COVID</p>	<p>Clinical Protocol Synopsis: Study Design Section 1.4 Long-Term Outcomes in Patients with COVID-19 Section 2.3 Exploratory Objectives Section 3.2.1.6 Assessment of Long COVID Section 4.3 Exploratory Endpoints Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.3.2 Evaluation of Long COVID in Phase 3 [new] Figure 4 Study Flow Diagram, Phase 3 (Cohort 1) Table 5 Schedule of Events: Phase 3 (Cohort 1 Patients) Table 6 Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables, #14, 16; #18, 19, 20, 21, 23 [new] Section 9.2.15 Assessment of Long COVID [new] Section 11.4.3.3 Exploratory Analysis [new] Table 10 Symptoms Evaluated in the Symptom Evolution of Long COVID-19 (SE-LC19) Instrument</p>
<p>For patients in cohort 1, any positive SARS-CoV-2 local test result, obtained from the day of consent to protocol amendment 9 US until day 169, will be recorded and reported as an AESI.</p>	<p>To provide additional contextual information regarding SARS-CoV-2 infection to inform long COVID analyses</p>	<p>Table 5 Schedule of Events: Phase 3 (Cohort 1 Patients) Table 6 Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients) Section 9.1.1 Footnotes for the Schedule of Events Tables, #22 [new] Section 9.2.11 Monitoring for SARS-CoV-2 Reinfection [new] Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor</p>
<p>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</p>	<p>To ensure appropriate collection of safety-related data.</p>	<p>Section 9.2.4.2 Adverse Event Monitoring Section 9.2.15 Assessment of Long COVID Section 10.1.1 General Guidelines</p>

Description of Change	Brief Rationale	Section(s)
related to study drug, the AE will follow standard AE reporting and recording.		
To ensure clarity in the Schedule of Events, a separate schedule has been developed for cohort 3, containing all procedures as the prior schedule for this cohort.	To ensure operational clarity in light of changes made to the cohort 1 schedule of events.	Section 6.1.3 Phase 3 Table 7 Schedule of Events: Phase 3 (Cohort 3 \geq 18 Years)
Miscellaneous		
Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ) will be collected pre-dose for patients who are enrolled in cohort 2 and cohort 3 after this amendment is implemented.	To capture baseline assessment for comparative analyses.	Table 7 Schedule of Events: Phase 3 (Cohort 3 \geq 18 Years) Table 8 Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)
Clarified that, for the optional pharmacogenomics sub-study, newly-enrolled patients who consent to the sub-study will have blood samples collected for both DNA and RNA; patients who were previously enrolled and later consent to the sub-study will only have a blood collection for DNA.	To ensure appropriate collection of sub-study samples.	Section 9.2.13 Pharmacogenomics Sub-Study (Optional)
Clarified that for post-day 29 follow-up, phone or telemedicine are the preferred methods of contact, but other modes of communication (eg, email) are acceptable if a patient cannot be contacted through other methods.	To provide operational flexibility.	Section 9.2.5 Post-Day 29 Follow-Up
For patients <12 years of age, clarified that immunogenicity will be analyzed only in pre-dose and day 29 pharmacokinetic (PK)-anti-drug antibodies (ADA) samples.	To ensure accuracy of sample collection.	Section 9.1.1 Footnotes for the Schedule of Events Tables, #15
Clarified that unscheduled visits may also include collection of NP swabs, blood, serum, or plasma, as necessary.	To provide schedule flexibility.	Section 9.1.3 Unscheduled Visits
Added language clarifying that enrollment in the phase 3 PK sub-study is closed.	Sub-study has met planned enrollment.	Section 9.2.8 Drug Concentration Measurements and Samples
Risk-benefit information was updated to reflect phase 3 clinical trials in the treatment and prevention of COVID-19.	To provide current study drug information.	Section 3.3 Risk-Benefit Section 3.3.1 Summary of Efficacy and Safety Profile in Clinical Trials [New] Section 3.3.2 Summary of Risks
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 8

The primary purpose of this amendment is to 1) end randomization to placebo in all phase 3 cohorts, and 2) revise the statistical analysis for cohort 1, including the primary endpoint, key secondary endpoints, hierarchical testing, and plan for interim/final analyses.

Description of Change	Brief Rationale	Section(s)
Phase 3 Randomization		
As of 25 February 2021, patients will no longer be randomized to placebo	Per IDMC recommendation	Table 1 Summary of Main Phase 3 Adaptations Section 6.1.3 Phase 3 Section 8.6 Method of Treatment Assignment
Phase 3 Statistical Analysis		
<p>The following summarizes the planned statistical analysis for phase 3 cohort 1:</p> <ul style="list-style-type: none"> • The primary endpoint will be proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 • The key secondary endpoints will be proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 to through day 29, and time to COVID-19 symptoms resolution. Symptoms will include a subset of those captured in the SE-C19, as described in the main text • The full analysis set (FAS) includes all randomized patients with COVID-19 symptoms (starting from the 800th symptomatic patient randomized in the study overall), regardless of whether they have risk factors for severe COVID-19 • The modified full analysis set (mFAS) includes all patients in the FAS with detectable SARS-CoV-2 RNA by RT-qPCR in nasopharyngeal swabs at randomization and ≥ 1 risk factor for severe COVID-19. The mFAS will be used to analyze the primary and key secondary endpoints • Concurrent with the final analysis of the primary endpoint for the 2400 mg treatment group, an interim analysis will be conducted on the primary endpoint for the 1200 mg treatment group • A hierarchy is provided for the primary and key secondary endpoints to control for multiplicity, including a Gamma family spending function to control for alpha in the interim and final analyses • Other endpoints, including those assessing emergency room (ER) visits and other medically-attended visits (MAVs), will be evaluated descriptively • Additional minor details were updated for consistency with the planned analysis <p>Details of the revised statistical analysis are provided in the main text.</p>	<p>Primary endpoint changed based on health authority feedback.</p> <p>Other changes implemented to ensure that efficacy assessment of REGN10933 + REGN10987 is conducted with the most clinically-relevant endpoints</p>	<p>Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Figure 3 Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6) Figure 4 Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years) Figure 5 Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients < 18 Years) Section 6.3 Planned Interim Analysis Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Table 9 Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with ≥ 1 Risk Factor for Severe COVID-19 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 Section 11.4.4 Control of Multiplicity Table 11 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis</p>

Description of Change	Brief Rationale	Section(s)
		Table 12 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis Section 11.5 Interim Analysis
The full analysis set (FAS) and modified full analysis set (mFAS) will not require that patients be randomized and treated ; patients who are randomized and not treated will also be considered part of the FAS or mFAS.	Per health authority feedback	Section 11.3.1 Efficacy Analysis Sets
Additional details have been provided to describe the SE-C19 instrument.	To provide additional information related to a key secondary endpoint	Section 9.2.13 Exploratory Patient-Reported Symptoms Table 7 Symptoms Evaluated in the SE-C19 [new]
Clarified that, in total, up to approximately 8500 patients will be enrolled in phase 3 cohort 1.	To ensure an accurate description of planned enrollment	Table 1 Summary of Main Phase 3 Adaptations Section 7.1 Number of Patients Planned
Added an exploratory objective to assess the clinical efficacy of different dose levels of REGN10933 + REGN10987, as measured by COVID-19-related hospitalizations or all-cause death.	To better understand potential differences in clinical efficacy between REGN10933 + REGN10987 dose levels	Section 2.3 Exploratory Objectives
Time to COVID-19 symptoms resolution will be evaluated as an exploratory endpoint in phase 3 cohort 2.	To assess the potential impact of REGN10933 + REGN10987 on COVID-19 symptoms	Section 4.3 Exploratory Endpoints
Safety Assessment		
For patients who are <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information. A phone call on day 2 is not required. These patients (or their caregivers) should continue to be instructed to contact the site within the first 24 hours post-infusion if they experience any side effects. This change is consistent with a memorandum that was previously provided to study sites.	Per health authority feedback; to ensure appropriate post-infusion monitoring for younger patients <12 years old	Section 6.1.3 Phase 3 Section 9.1.1 Footnotes for the Schedule of Events Tables, #17
Clarified that any SAE resulting in death that occurs prior to study day 169 should be reported, regardless of patient withdrawal or early termination.	To ensure appropriate capturing of vital status	Section 10.1.1 General Guidelines
Other Changes and Clarifications		
For all study phases, the viral sequencing exploratory endpoint has been removed. The exploratory objective has been revised to the following: <ul style="list-style-type: none"> To evaluate viral variants at baseline and post-treatment In addition, clarified that the results of viral sequencing will be reported separately from the CSR.	To provide flexibility with respect to planned viral sequencing analyses	Section 2.3 Exploratory Objectives Section 9.2.10.3 Virology
Added exploratory objective for phase 3 cohort 3: <ul style="list-style-type: none"> To describe clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits or all-cause death 	To assess clinical outcomes among patients who are pregnant at randomization	Section 2.3 Exploratory Objectives

Description of Change	Brief Rationale	Section(s)
Clarified that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.	To clarify flexibility of enrollment in phase 3 cohorts	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
In cohort 2, there will be a minimum enrollment of 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg.	Per health authority feedback	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
The following phase 3 operational clarifications or changes have been made: <ul style="list-style-type: none"> • Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day. • Study visits are not required on days when only electronic survey data are collected • TEAEs that led to a medically-attended visit will be collected starting on day 1 post-infusion, when applicable (day 1 post dose collection was previously missing from the schedule of events) • In phase 3 cohort 2, vital status was incorrectly marked as a screening assessment. This error has been corrected • On days 60 and 90, the window for EQ-5D-5L (and EQ-5D-Y) assessment is ±3 days. On days 120 and 169, the window is ±7 days 	To ensure operational clarity, including avoiding unnecessary study visits and ensuring appropriate capturing of relevant adverse events and concomitant procedures	Section 8.10 Concomitant Medications and Procedures Table 5 Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years) Table 6 Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 8, 14
The following changes to concomitant medication recording have been made: <ul style="list-style-type: none"> • In addition to targeted concomitant medication, concomitant procedures will also be recorded when applicable • In addition to the listed targeted concomitant medications, “any other vaccines” and “oxygen” will also be recorded as applicable 	To capture additional clinical information	Section 9.2.4.3 Record Targeted Concomitant Medications and Concomitant Procedures
The following clarification has been made with respect to medically-attended visits related to COVID-19: <ul style="list-style-type: none"> • During each indicated collection visit (as provided in the schedule of events), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection 	To ensure appropriate capturing of clinically-relevant information	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Clarified that cohort 2 and cohort 3 will only be enrolled where permitted by local requirements.	To provide enrollment flexibility per regional requirements	Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #1
Clarified that in addition to WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L, the return to usual health and return to usual activities surveys will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Neutralizing antibody (NAb) analyses will be conducted in phase 2 and phase 3 (all cohorts).	To provide additional assessment of potential for neutralizing antibodies against	Section 4.2 Secondary Endpoints

Description of Change	Brief Rationale	Section(s)
	REGN10933 + REGN10987	
Clarified that assessment of immunogenicity will be a secondary objective for cohort 2 and cohort 3 of phase 3, and that assessment of drug concentration will be a secondary objective for cohort 3 of phase 3; the objectives were previously listed incorrectly as primary objectives.	To ensure accurate descriptions of planned analyses	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints
The risk-benefit section has been updated to reflect the current Investigator's Brochure (edition 5). This includes the addition of hypersensitivity reactions (including infusion-related reactions and injection site reactions) as an important identified risk. Additional contextual information related to COVID-19 vaccination as a theoretical consideration has also been provided.	To provide current information regarding the potential risks and benefits of REGN10933 + REGN10987	Section 3.3 Risk-Benefit
In light of the increasing number of therapeutic and preventative COVID-19 agents approved or conditionally authorized reference to individual agents has been removed. References to FDA and EMA have been provided as a general resource for currently-available agents.	To ensure current, accurate, and consistent information	Section 1.6 Current Landscape of Therapeutic and Preventative Agents for COVID-19 [deleted] Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19
Updates to background information, minor clarifications for consistency, and other minor updates (typographical, editorial) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 7

The primary purpose of this amendment is to modify the phase 3 portion of the study in response to health authority feedback. Related modifications (eg, with respect to patients who are pregnant) and other clarifications have also been implemented.

Description of Change	Brief Rationale	Section(s)
<p>All-cause death was added to the cohort 1 (≥ 18 years) primary endpoint (ie, COVID-19-related medically-attended visits or all-cause death) and to several secondary endpoints in cohort 1 and cohort 2 (< 18 years). The phase 3 sample size was not updated as a result of this change.</p>	<p>Per health authority feedback; to capture an additional event of clinical importance</p>	<p>Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis</p>
<p>In cohort 1, additional secondary endpoints were designated as key endpoints, and the statistical hierarchy was updated to control for multiplicity.</p>	<p>To ensure rigorous statistical analysis</p>	<p>Section 4.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control for Multiplicity</p>
<p>Patients who are pregnant at randomization, regardless of age, will be enrolled in a separate double-blinded cohort (cohort 3):</p> <ul style="list-style-type: none"> • Cohort will be randomized 1:1 to REGN10933+REGN1087 1200 mg or 2400 mg, tiered as applicable based on weight • Patients in the cohort will not be randomized to placebo • Randomization will not be stratified • Depending on their age, patients in cohort 3 will follow the cohort 1 (≥ 18 years) or cohort 2 (< 18 years) schedule of events • For patients in cohort 3 who are ≥ 18 years, additional samples will be collected for drug concentration and immunogenicity assessment • Analysis will be descriptive and will focus on safety and PK 	<p>To increase collection of safety and PK information related to REGN10933 + REGN10987 among patients who are pregnant</p>	<p>Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9 Section 9.1.1 Footnotes for the Schedule of Events Tables, #12, 15</p>
<p>The following changes will be made to cohort 2 (and patients < 18 years in cohort 3):</p> <ul style="list-style-type: none"> • Enrollment will be limited to patients who are symptomatic at randomization and have ≥ 1 risk factor for severe COVID-19 (ie, enrollment is discontinued for asymptomatic patients) • Removed the presence/absence of COVID-19 symptoms as a stratification factor for randomization • Increased the frequency of vital signs assessments performed during and after infusion for patients < 12 years old • For patients who are < 12 years old, an additional phone call will be made on day 2 (within 24 hours of infusion) for collection of targeted safety information, and these patients (or their caregivers) should be 	<p>Per health authority request; to focus enrollment on patients with highest potential benefit and ensure appropriate safety monitoring during and within 24 hours after study drug administration</p>	<p>Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4, 9</p>

Description of Change	Brief Rationale	Section(s)
<p>instructed to contact the site within the first 24 hours post-infusion if they experience any side effects.</p> <ul style="list-style-type: none"> Clarified that a minimum of 6 patients <10 kg and 6 patients between ≥ 10 kg and <40 kg will be enrolled 		<p>Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 6.1.3 Phase 3 Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #6, #17 Table 6 Schedule of Events: Phase 3 (Cohort 2)</p>
<p>In addition to what is currently being collected, the following safety information will be collected in all phase 3 cohorts:</p> <ul style="list-style-type: none"> All treatment-emergent adverse events that led to a medically-attended visit (hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit), regardless of relatedness to COVID-19, through day 29 All treatment-emergent serious adverse events and deaths, from day 30 to day 169 In addition to standard collection of pregnancy outcome information, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study, the incidence and outcome of any SARS-CoV-2 infection will be collected during day 120 and day 169 follow-up phone calls and reported in the pregnancy report form 	<p>Per health authority request and for more comprehensive analysis of medically attended visits and the safety profile of REGN10933 + REGN10987</p>	<p>Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 5.3 Safety Variables Section 6.1.3 Phase 3 Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 16 Section 9.2.4.2 Adverse Event Monitoring Section 9.2.5 Post-Day 29 Follow-up by Phone Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor</p>
<p>Clarified that viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.</p>	<p>Per health authority request</p>	<p>Section 9.2.10.3 Virology</p>
<p>Eligibility criteria have been modified to allow planned use of any authorized or approved vaccine for SARS-CoV-2, if (at the time of screening) it is planned after 90 days following study drug administration. This screening allowance may be modified as applicable if CDC recommendations change.</p> <ul style="list-style-type: none"> Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for SARS-CoV-2 is excluded Prior, current, or future plans to participate in a clinical research study of an investigational vaccine for SARS-CoV-2 is also excluded 	<p>Per current CDC recommendations (CDC, 2020a)</p>	<p>Section 7.2.2 Exclusion Criteria, #13, 14</p>
<p>The followings clarifications were made with respect to assessment of women of childbearing potential (WOCBP) and women who are pregnant:</p> <ul style="list-style-type: none"> Pregnancy testing at screening must be performed in all WOCBP, regardless of pregnancy status 	<p>To ensure accurate information is collected regarding pregnancy</p>	<p>Section 9.2.1.4 Medical History Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events that Required Expedited Reporting to the Sponsor</p>

Description of Change	Brief Rationale	Section(s)
<ul style="list-style-type: none"> • Pregnancy or breastfeeding status at screening must be collected as medical history, if applicable • A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent 		
<p>Definitions of risk factors for severe COVID-19 were changed as follows:</p> <ul style="list-style-type: none"> • Cohort 1: clarified that body mass index (BMI) greater than or equal to 30 (not greater than 30) constitutes a risk factor for severe COVID-19 • Cohort 1: clarified that age greater than or equal to 50 years constitutes a risk factor for severe COVID-19 • Cohort 2: for patients at least 2 years old, BMI \geq95th percentile for age and sex, based on CDC growth charts, will constitute a risk factor • Cohort 2: added a new risk factor for severe COVID-19 as an inclusion criterion: Any underlying genetic, neurologic, or metabolic condition, or congenital heart disease deemed by the investigator to constitute a risk factor for severe COVID-19 (note that immunocompromised/on immunosuppressive treatment is already considered a risk factor and is accounted for separately) 	To clarify risk factors for severe COVID-19 and ensure alignment with CDC guidance, where applicable	Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9
Updated concomitant medications list such that any medication used to treat an adverse event will be recorded	To ensure collection of clinically relevant concomitant medications	Section 9.2.4.3 Record Targeted Concomitant Medications
Clarified that for the screening SARS-CoV-2 diagnostic test, the sample must be collected \leq 72 hours of randomization. Samples are not valid for screening if collected $>$ 72 hours from randomization, even if the test is performed, or results reported, within the 72-hour window.	To ensure appropriate screening for SARS-CoV-2 infection	Section 7.2.1 Inclusion Criteria
Removed language stating that if diagnostic SARS-CoV-2 testing was performed outside of the allowed window, a new test is required for study inclusion. Language was retained in error. Per study exclusion criteria, patients will be excluded if they have a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected $>$ 72 hours prior to randomization	To ensure accurate information	Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Provided example of monoclonal antibody (bamlanivimab) that is considered exclusionary for study enrollment	For clarity	Section 7.2.2 Exclusion Criteria, #2, 3
Members of the clinical site study team and their immediate family members are now excluded from enrolling in the study	To ensure integrity of study data and analysis	Section 7.2.2 Exclusion Criteria, #14
<p>In cohort 1, the following blood samples will no longer be collected:</p> <ul style="list-style-type: none"> • Serum for cytokines and CK-MB • Plasma for hsTroponin <p>Note that the descriptions of exploratory biomarker, analyses, as well as exploratory patient-reported symptom analyses conducted during prior study phases or time periods have been retained in protocol for historical purposes.</p>	To reduce burden of blood sample collections	Table 5 Schedule of Events: Phase 3 (Cohort 1) Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses Section 9.2.13 Exploratory Patient-Reported Symptoms

Description of Change	Brief Rationale	Section(s)
Blood chemistry samples that are collected will not be analyzed for ferritin.	To reduce sample analyses with less relevant clinical significance	Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.2.7 Laboratory Testing
Columns have been added to explicitly indicate collection of EQ-5D-5L and EQ-5D-Y-5L at day 60 and day 90. This was previously indicated by a footnote in the schedule of events.	To improve schedule clarity	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Added that an interim analysis of phase 3 cohort 2 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.	To provide more details for the phase 3 statistical analysis plan	Section 11.5 Interim Analysis
Removed incorrectly marked medical history assessment on day 7.	To ensure accuracy	Table 6 Schedule of Events: Phase 3 (Cohort 2)
Removed and/or simplified schedule of events footnotes that contained information relevant to phase 1 and phase 2, which are now closed.	To simplify interpretation of phase 3 schedule of events	Section 9.1.1 Footnotes for the Schedule of Events Tables, #2, 3, 4, 6, 7, 9, 11, 12, 14, 15
Clarified that approximately 600 patients will be enrolled in the PK sub-study	To ensure accuracy	Section 9.2.8 Drug Concentration Measurements and Samples
Updated phase 1 endpoint to align with phase 1/2 statistical analysis plan.	To ensure accurate description of statistical analysis that was performed	Section 4.1 Primary Endpoints
Updates to background information and other minor updates were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 6

The purpose of this amendment is to adapt the phase 3 portion of the study based on data from phase 1 and phase 2. Major adaptations include changes to the patient population, treatment arms, objectives/endpoints, and sample size.

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

Description of Change	Brief Rationale	Section(s)
<i>Patient Eligibility (Major Phase 3 Adaptation)</i>		
<ul style="list-style-type: none"> Females who are pregnant or breastfeeding can enroll in the study Patients from 0 to <18 years will be enrolled as a separate cohort (cohort 2), where permitted by local requirements. Patients ≥18 years of age will be enrolled in cohort 1 Patients in cohort 1 must have ≥1 risk factor for severe COVID-19. Patients in cohort 2 must have ≥1 risk factor for severe COVID-19 or live with a housemate who has ≥1 risk factor for severe COVID-19 	To adapt the phase 3 portion of the study based on phase 2 data and to evaluate REGN10933 + REGN10987 in younger patients and pregnant/breastfeeding women with COVID-19	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 5.1 Demographic and Baseline Characteristics Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, #1, 2, 9 Section 7.2.2 Exclusion Criteria, #10, 11, 12

Description of Change	Brief Rationale	Section(s)
<ul style="list-style-type: none"> Patients with a known positive SARS-CoV-2 serology test will be excluded Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected >72 hours prior to randomization will be excluded Patients with active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test, will be excluded <p><i>Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.</i></p>		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events That Require Expedited Reporting to Sponsor Section 11.4.1 Patient Disposition Section 13.2 Informed Consent
Treatment Arms (Major Phase 3 Adaptation)		
<ul style="list-style-type: none"> For cohort 1, the REGN10933+REGN10987 8000 mg IV treatment arm will be dropped. The REGN10933 + REGN10987 2400 mg IV treatment arm and placebo arm will be retained. A new treatment arm will be added to assess REGN10933+REGN10987 1200 mg IV For cohort 2, the highest dose tested will be REGN10933 + REGN10987 2400 mg IV. Weight-tiered dosing will be used in this cohort 	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.2 Adaptive Master Protocol Design Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 3.2.2 Rationale for Dose Selection Section 6.1.3 Phase 3 [new] Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignments
Objectives/Endpoints (Major Phase 3 Adaptation)		
<ul style="list-style-type: none"> For cohort 1, the primary endpoint will be COVID-19-related medically-attended visits (MAVs). Key pre-specified secondary endpoints include various types of COVID-19-related MAVs and related outcomes For cohort 2, the primary endpoints will be safety/tolerability and drug concentrations in serum over time For cohort 2, secondary analyses will be descriptive Virologic analyses for both cohorts will be secondary and descriptive Cohort 1 will enroll up to 300 patients in an optional sub-study to assess, as an exploratory objective, the potential impact of REGN10933+REGN10987 on the endogenous immune response 	To adapt the phase 3 portion of the study based on phase 2 data	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.1.3 Phase 3 [new] Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnote #4 Section 9.2.11 Immunoprofiling Sub-Study (Optional) [new]

Description of Change	Brief Rationale	Section(s)
Sample Size (Major Phase 3 Adaptation)		
<ul style="list-style-type: none"> Enrollment in phase 3 cohort 1 is anticipated to be approximately 5400 patients Phase 3 cohort 1 will continue until at least 80 hospitalizations or ER visits are observed in patients enrolled under protocol amendment 6 (or subsequent amendment) into the primary analysis population (patients in modified full analysis set [mFAS] with at least 1 risk factor) and the total number of hospitalizations or ER visits during the study in the primary analysis population is more than 120 Phase 3 cohort 2 will enroll up to approximately 180 patients 	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Other Phase 3 Adaptations		
<p>Phase 3 cohort 1 schedule of events will be adapted to include the following major changes from phase 2:</p> <ul style="list-style-type: none"> Patients will be followed up by phone on days 120 and 169 (end of study) for assessments including vital status Virologic assessments will be more limited in scope. Nasopharyngeal (NP) swabs will only be collected on days 1, 7, 15, and 29 For targeted safety information, treatment-emergent serious adverse events (SAEs), if determined by the investigator to be related to study drug, will be recorded from day 30 to day 169 A subset of patients will be enrolled in a PK sub-study at selected participating sites. <p><i>Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.</i></p>	Per health authority feedback, and to adapt the phase 3 study design based on phase 2 data	Section 6.1 Study Description and Duration Section 6.1.3 Phase 3 [new] Figure 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 9.2.5 Post-Day 29 Follow-up by Phone Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 12, 13, 14, 15 Section 9.2.8 Drug Concentration Measurements and Samples Section 10.1.1 General Guidelines Section 10.1.2 Reporting Procedure
<p>Phase 3 cohort 2 will follow similar schedule of events as cohort 1, with key exceptions as follows:</p> <ul style="list-style-type: none"> Blood sample collection schedules for laboratory and biomarker analyses will vary according to body weight Additional NP swab sample will be collected on day 3 Blood sample collection schedules for pharmacokinetics and immunogenicity will utilize sparse sampling and vary based on randomly assigned sampling schedules Limited biomarker samples will be collected Patient-reported electronic surveys/questionnaires will only be collected in patients ≥ 12 years Treatment-emergent grade ≥ 3 AEs will be collected through day 29 	To ensure appropriate assessment of safety and efficacy of REGN10933 + REGN10987 and to adjust blood volumes appropriately for younger pediatric patients	Section 6.1.3 Phase 3 [new] 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 7.2.1 Inclusion Criteria, #1a Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignment Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 13, 14, 15

Description of Change	Brief Rationale	Section(s)
		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.9 Immunogenicity Measurements and Samples
Details of COVID-19-related medically-attended visits were revised.	To ensure appropriate assessment of the clinical efficacy of REGN10933 + REGN10987	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Risk factors for hospitalization due to COVID-19 were removed as a stratification factor for randomization. Patients in both cohorts will be stratified by country, and (in cohort 2 only) by the presence or absence of COVID-19 symptoms.	Both cohorts in phase 3 will have ≥ 1 risk factor for severe COVID-19	Section 8.6 Method of Treatment Assignments
Immunogenicity will be assessed by anti-drug antibodies (ADA) and neutralizing antibody (NAb) analyses, as a secondary endpoint in cohort 1 and a primary endpoint in cohort 2.	To ensure comprehensive assessment of potential immunogenic response following REGN10933 + REGN10987 administration	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 5.5 Immunogenicity Variables Section 9.2.9 Immunogenicity Measurements and Samples Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.8 Analysis of Immunogenicity Data
Patient eligibility criteria were updated to: <ul style="list-style-type: none"> • Clarify the acceptable timing for a historical record of positive SARS-CoV-2 test result • Clarify informed consent requirements for cohort 2 patients • Add that patients must be able to understand and complete study-related questionnaires (cohort 1 and cohort 2 patients aged ≥ 12 years only) • Clarify that patients must not have been admitted to a hospital for COVID-19 prior to randomization, or hospitalized (inpatient) for any reason at randomization • Clarify exclusions related to prior, current, or planned COVID-19 treatments 	To ensure appropriate enrollment and data analysis for phase 3 and to provide operational clarity and flexibility	Section 7.2.1 Inclusion Criteria, #2, 6, 8 Section 7.2.2 Exclusion Criteria, #1, 3; #8, 9 [removed]; #10, 11, 12, 13 [added]
For phase 3 cohort 1 efficacy analysis, the Sponsor may request the IDMC to perform 1 or more interim analyses for efficacy	To ensure appropriate assessment of potential efficacy signals	Section 11.5 Interim Analysis
Other Changes and Clarifications		
For patients in this study who are also index cases of household contacts in the R10933-10987-COV-2069 prophylaxis study, data from this study may be used as part of analyses on the COV-2069 study.	To assess the potential impact of REGN10933+REGN10987 treatment of an index case participating in this study on infection rates in household contacts participating in COV-2069.	Section 6.1.3 Phase 3

Description of Change	Brief Rationale	Section(s)
Prior to unblinding for interim analysis of phase 1/2 and analysis of phase 2, changes were made to the statistical analysis plan, including endpoints and analysis descriptions. These changes have been updated in the protocol	To ensure consistency and accuracy of the study statistical plans.	Section 3.2.1.3 Rationale for Phase 1 and Phase 2 Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.3 Planned Interim Analysis Section 11.5 Interim Analysis
Emergency unblinding procedures were clarified, including manual unblinding in case of IWRS unavailability.	Per health authority request	Section 8.8 Emergency Unblinding
Baseline blood samples may be collected at either day -1 or day 1 (ie, screening or pre-dose) prior to randomization. For patients in phase 3 cohort 2.	To provide operational flexibility.	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), #12
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
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
<p>Descriptions of the statistical plan were updated as follows:</p> <ul style="list-style-type: none"> • Statistical hypotheses and analysis set definitions were updated • Details regarding control of multiplicity were added • Phase 3 efficacy analysis methods were added • For phase 3, plans for interim analyses were added 	To update descriptions of the statistical plan	Section 3.1 Hypotheses Section 6.3 Planned Interim Analysis Section 11 Statistical Plan Section 11.1 Statistical Hypotheses Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Descriptions of viral sequencing parameters were updated to expand beyond analyses of potential viral resistance.	For accuracy	Section 9.2.10.3 Virology
Detailed descriptions of exploratory patient-reported symptoms were added.	To provide context for patient-reported symptom assessments	Section 9.2.13 Exploratory Patient-Reported Symptoms
REGN10989 monotherapy will no longer be considered as part of this adaptive master protocol. References to REGN10989 have correspondingly been removed throughout 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	Throughout the document

Description of Change	Brief Rationale	Section(s)
	longer include monotherapy arms.	
References to phase 1 and phase 2 were removed from the study synopsis.	For operational clarity, since phase 1 and phase 2 are now closed	Clinical Study Protocol Synopsis
References to “low dose” and “high dose” were removed.	To ensure clarity with the addition of different dose levels in phase 3	Throughout the document
Updates to background information, administrative updates, and other minor updates to align with phase 3 adaptations were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 5

Description of Change	Brief Rationale	Section(s)
Added new cohort of patients in phase 2 to evaluate asymptomatic patients with SARS-CoV-2 infection. Total planned enrollment for phase 2 has been increased to 1300 patients to accommodate this cohort.	To broaden patient eligibility and enable broader assessment of potential treatment impact on viral burden and other measures	Section 3.2.1.3 Rationale for Primary Objectives Section 3.2.1.5 Stratification According to Risk of Hospitalization Due to COVID-19 Section 6.1 Study Description and Duration Section 6.1.2 Phase 2 Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4 Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
In phase 2, added new secondary clinical endpoint to assess development of symptoms consistent with COVID-19.	To assess the impact of treatment on the development of COVID-19 symptoms in patients who are initially asymptomatic with SARS-CoV-2 infection	Section 4.1 Secondary Endpoints
In phase 2, added new secondary clinical endpoint to assess duration of symptoms consistent with COVID-19.	To assess the impact of treatment on the duration of symptoms	Section 4.1 Secondary Endpoints
Removed screening requirement that patients have ≥ 1 of the following symptoms at randomization: fever, cough, shortness of breath.	To broaden patient eligibility and to facilitate assessment of potential treatment impact on other clinical manifestations of COVID-19	Section 7.2.1 Inclusion Criteria, #3 [deleted]
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 4 Schedule of Events: Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Revised exclusion criteria medications to exclude patients with prior, current, or planned future use of EUA-approved medications (eg, remdesivir), convalescent serum, IVIG, other anti-SARS-CoV2 antibodies, or systemic steroids, thereby allowing antecedent use of other COVID-19 investigational medications such as hydroxychloroquine and azithromycin. Clarified that excluded agents are permitted only if medically indicated.	To broaden patient eligibility	Figure 3 Study Flow Diagram, Phase 2 Section 7.2.2 Exclusion Criteria, #3 Section 7.2.2 Exclusion Criteria, #4 [consolidated with #3], #5, [deleted] Section 8.10.1 Prohibited and Permitted Medications

In phase 2, added blood samples for hematology, blood chemistry, and coagulation tests on days 7 and 15. In phase 2, added blood samples for cardiac biomarkers at baseline and on days 7, 15, and 29.	To enable more comprehensive analysis of safety and efficacy by including additional biomarkers of inflammation and cardiac and/or other organ injury	Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.2 Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #10 Section 9.2.7 Laboratory Tests Section 9.2.10.8 Serum and Plasma for Cardiac Biomarkers [section added]
Removed post-dose collection of SE-C19 and PGIS and extended daily collection of SE-C19 and PGIS until day 29	To ensure that assessments are only captured once in each 24 hour period , and to provide additional information on patient-reported symptoms at later time points	Table 4 Schedule of Events: Phase 2
Minor clarifications were made to descriptions of other biomarker analyses.	To better describe planned analyses	Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.7 Cytokines
Clarified collection of medical history: COVID-19, if applicable, with start date as date of onset of first symptoms.	To ensure appropriate collection of symptom onset	Section 9.2.1.4 Medical History
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
Updated phase 2 interim analysis plans.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
Minor editorial updates made to reflect addition of asymptomatic cohort.	To ensure accuracy and consistency	Section 1.3 Outpatient Care as a Potential COVID-19 Treatment Setting Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19 or Asymptomatic SARS-CoV-2 Infection Section 3.1 Hypotheses Section 3.2.1 Rationale for Study Design
Removed a duplicate secondary endpoint for phase 3; other minor editorial and administrative updates were made.	To ensure accuracy and consistency	Section 1.1 Emergence of SARS-CoV-2 and COVID-19 Section 4.1 Secondary Endpoints Section 8.6 Method of Treatment Assignment Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #4

Amendment 4

Description of Change	Brief Rationale	Section(s)
Nasal swabs and saliva samples will no longer be collected in phase 2 and are no longer planned for phase 3. Only nasopharyngeal (NP) swabs will be collected in phase 2 and phase 3.	To allow adequate assessment of virologic efficacy, as NP swab is the current gold standard to detect SARS-CoV-2	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints, Procedures and Assessments Section 2.2 Secondary Objectives Section 4.1 Secondary Endpoints Section 6.1.2 Phase 2 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection Section 11.4.3.2 Secondary Efficacy Analysis
Phase 2 sample size has been increased to enable additional enrollment.	To allow adequate assessment of virologic efficacy	Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Interim analysis plan was updated to allow more flexibility in timing.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection 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 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
An additional secondary virologic endpoint has been added.	To allow adequate assessment of virologic efficacy	Section 4.1 Secondary Endpoints
The following clarifications have been made to the phase 2 Schedule of Events: <ul style="list-style-type: none"> • Clarified that at concomitant medications are continuously monitored • Visit windows have been added • Removed incorrect vital sign assessments marked in dosing column • Clarified footnote describing phone visit requirements • Day 2 column shading was removed, as day 2 does not include a phone visit 	To improve clarity of study schedule	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3 Table 4 Schedule of Events: Phase 2

Amendment 3

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. Provisional phase 3 secondary endpoints have also been updated for potential inclusion of NP swab samples.	To ensure adequate assessment of virologic efficacy.	Section 2.2 Secondary Objectives Section 4.1 Primary Endpoint Section 4.1 Secondary Endpoints Table 4 Schedule of Events: Phase 2 Section 6.1.2 Phase 2 Section 6.1.3 Phase 3 Figure 3 Study Flow Diagram, Phase 2 Section 9.2.3.1 Saliva, Nasal Swab, and Nasopharyngeal Swab Collection 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 ensure 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 3.2.1.3 Rationale for Primary Objectives Section 5.3 Safety Variables Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #7 Section 9.1.3 Unscheduled Visits Section 9.2.4.2 Adverse Event Monitoring Section 10 Safety Evaluation and Reporting (and sub-sections therein) Section 11.4.5.1 Adverse events
Clarified objective, endpoint, and procedure for assessing viral resistance	Per health authority request	Section 2.3 Exploratory Objectives Section 4.3 Exploratory Endpoints Section 9.2.10.3 Virology
Clarified EC and IC terminology related to dose rationale	To clarify in vitro data descriptions	Section 3.2.2 Rationale for Dose Selection
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 4.1 Secondary Endpoints Section 11.4.3.1 Primary Efficacy Analysis
Nasopharyngeal swab sampling added to day 11, 15, 18, and 25 (phase 1 only)	To provide matching sample types across time points	Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2
Study will be conducted in the US and other countries	To broaden reach of study	Section 6.1 Study Description and Duration

Description of Change	Brief Rationale	Section(s)
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 11.4 Statistical Methods
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, #2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #5 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
Endpoints in phase 1 related to intensive care unit (ICU) and mechanical ventilation moved to exploratory; other statistical clarifications made to primary and secondary efficacy analysis, multiplicity control, and interim analysis	To ensure consistency with planned statistical analysis	Section 4.1 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
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 <u>and</u> 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 9.2.8 Drug Concentration Measurements and Samples Section 9.2.9 Immunogenicity Measurements and Samples Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses Section 9.2.12 Pharmacogenomic Analysis (Optional)
The following operational changes and clarifications have been made: <ul style="list-style-type: none"> • Phone visits have a window of ± 1 day • Day 29 visit may occur at any in-person location • Clarified that home-based visits may be done by home health staff 	To provide additional flexibility for sample collection and assessments	Section 6.1.1 Phase 1 Section 6.1.2 Phase 2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Early termination visit will consist of day 29 assessments, with follow-up phone contact on day 29	To clarify early termination assessments	Section 1 Early Termination from the Study
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with eCRF	Section 9.2.4.3 Record Targeted Concomitant Medications

Description of Change	Brief Rationale	Section(s)
Respiratory rate will only be measured in phase 1; temperature will not be measured rectally	To clarify required assessments	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #6 Section 9.2.4.1 Vital Signs
Updated description of SE-C19 survey	To clarify the scoring system used	Section 9.2.10.8 Exploratory Patient-Reported Symptoms
Removed delineation of visit locations in Schedule of Events; visits may occur at any in-person location except where additional phone visits are indicated	To improve clarity of study schedule and design	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Clarifications of study procedures	To improve clarity of procedures and planned analyses	Section 9.2.1.4 Medical History Section 9.2.7 Laboratory Testing Section 9.2.10.2 Serum and Plasma Biomarkers Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.4 Complement Section 9.2.10.7 Cytokines
Minor typographical, grammatical, editorial, and formatting updates	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 1

Description of Change	Brief Rationale	Section(s)
Mandatory sequestering is only applicable to patients in the phase 1 sentinel safety group	Clarification of study design	Section 6.1 Study Description and Duration Figure 2 Study Flow Diagram, Phase 1 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #2, #3 Section 9.2.3.2 COVID-19-related Medically-Attended Visit Details
Day 1 vital sign requirements (including pulse oximetry) added for patients in the phase 1 sentinel safety group	Per health authority request	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #8
Additional vital sign procedural details provided	To ensure study consistency with health authority request	Section 9.2.4.1 Vital Signs
Independent Data Monitoring Committee (IDMC) description updated	Operational details to be provided in the IDMC charter	Section 6.2.1 Independent Data Monitoring Committee
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
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC ₅₀	Effective concentration of 50% viral neutralization
EC ₉₉	Effective concentration of 99% viral neutralization
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FcγR	Fc gamma receptor
GCP	Good clinical practice
GLP	Good laboratory practice
IRB	Institutional Review Board
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
INR	International normalized ratio
IRT	Interactive response technology

IRWS	Interactive web response system
IV	Intravenous
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAV	Medically-attended visit
MERS-CoV	Middle East respiratory syndrome coronavirus
mFAS	Modified full analysis set
NAb	Neutralizing antibodies
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
NT-proBNP	N-terminal pro B-type natriuretic peptide
PK	Pharmacokinetic
PT	Prothrombin time
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN10933+REGN10987	Co-administered REGN10933+REGN10987 combination therapy
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SE-C19	Symptom Evolution of COVID-19
SE-LC19	Symptom Evolution of Long COVID-19
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TWA	Time-weighted average
WHO	World Health Organization
WOCBP	Women of childbearing potential

TABLE OF CONTENTS

AMENDMENT HISTORY	2
Amendment 10 US.....	2
Amendment 9 US.....	4
Amendment 8.....	6
Amendment 7.....	10
Amendment 6.....	13
Amendment 5.....	19
Amendment 4.....	21
Amendment 3.....	22
Amendment 2.....	22
Amendment 1	24
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	25
CLINICAL STUDY PROTOCOL SYNOPSIS.....	35
1. INTRODUCTION	42
1.1. Emergence of SARS-CoV-2 and COVID-19	42
1.2. Clinical Outcomes in Hospitalized Patients with COVID-19	42
1.3. Ambulatory Care as a Potential COVID-19 Treatment Setting	42
1.4. Long-Term Outcomes in Patients with COVID-19.....	43
1.5. The Role of Spike (S) Protein in SARS-CoV-2 Pathogenesis	43
1.6. REGN10933+REGN10987: Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein	43
1.7. A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19	44
2. STUDY OBJECTIVES	44
2.1. Primary Objectives	44
2.2. Secondary Objectives	45
2.3. Exploratory Objectives	46
3. HYPOTHESIS AND RATIONALE	47
3.1. Hypotheses.....	47
3.2. Rationale.....	48
3.2.1. Rationale for Study Design.....	48
3.2.1.1. Phase 1 Sentinel Safety Group	48

3.2.1.2.	Adaptive Master Protocol Design.....	49
3.2.1.3.	Rationale for Phase 1 and Phase 2 Objectives.....	49
3.2.1.4.	Stratification According to Risk of Hospitalization (Phase 2)	51
3.2.1.5.	Rationale for Phase 3 Adaptations.....	51
3.2.1.6.	Assessment of Long COVID.....	56
3.2.2.	Rationale for Dose Selection	57
3.2.2.1.	Phase 1 and Phase 2 Dose Selection.....	57
3.2.2.2.	Phase 3 Dose Selection.....	58
3.3.	Risk-Benefit.....	59
3.3.1.	Summary of Efficacy and Safety Profile in Clinical Trials.....	59
3.3.2.	Summary of Risks.....	60
4.	ENDPOINTS	63
4.1.	Primary Endpoints	63
4.2.	Secondary Endpoints	64
4.3.	Exploratory Endpoints.....	68
5.	STUDY VARIABLES.....	70
5.1.	Demographic and Baseline Characteristics	70
5.2.	Efficacy Variables	70
5.3.	Safety Variables.....	70
5.4.	Pharmacokinetic Variables	70
5.5.	Immunogenicity Variables.....	70
5.6.	Pharmacodynamic and Other Biomarker Variables	70
6.	STUDY DESIGN	71
6.1.	Study Description and Duration	71
6.1.1.	Phase 1.....	71
6.1.2.	Phase 2.....	72
6.1.3.	Phase 3.....	72
6.1.3.1.	Enrollment of Phase 3 Participants Prior to Phase 3 Adaptations.....	74
6.1.3.2.	Evaluation of Long COVID in Phase 3	74
6.1.3.3.	Sharing of Data Across Studies	74
6.1.4.	Study Design Figures.....	75
6.1.5.	Study Stopping Rules	79

6.1.5.1.	Individual Patient Stopping Rules	79
6.1.5.2.	Study Stopping Criteria	79
6.1.6.	End of Study Definition.....	79
6.2.	Study Committees.....	79
6.2.1.	Independent Data Monitoring Committee.....	79
6.2.2.	Sponsor Review Committee	80
6.3.	Planned Interim Analysis.....	80
6.4.	Periodic Data Reviews.....	80
7.	SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS.....	81
7.1.	Number of Patients Planned	81
7.2.	Study Population.....	81
7.2.1.	Inclusion Criteria	81
7.2.2.	Exclusion Criteria	82
7.3.	Premature Withdrawal from the Study	83
7.4.	Replacement of Patients	83
8.	STUDY TREATMENTS.....	84
8.1.	Investigational and Reference Treatments.....	84
8.2.	Background Treatment	84
8.3.	Rescue Treatment(s)	84
8.4.	Dose Modification and Study Treatment Discontinuation Rules	84
8.4.1.	Dose Modification	84
8.4.2.	Study Drug Discontinuation	84
8.5.	Management of Acute Reactions.....	84
8.5.1.	Infusion-Related Reactions and Hypersensitivity Reactions.....	84
8.5.1.1.	Interruption of the Intravenous Infusion.....	84
8.5.1.2.	Termination of the Intravenous Infusion	85
8.6.	Method of Treatment Assignment.....	85
8.7.	Blinding	88
8.8.	Emergency Unblinding.....	89
8.9.	Treatment Logistics and Accountability.....	89
8.9.1.	Packaging, Labeling, and Storage	89
8.9.2.	Supply and Disposition of Treatments	90

8.9.3.	Treatment Accountability	90
8.9.4.	Treatment Compliance.....	90
8.10.	Concomitant Medications.....	90
8.10.1.	Prohibited and Permitted Medications.....	90
9.	STUDY SCHEDULE OF EVENTS AND PROCEDURES.....	91
9.1.	Schedule of Events	91
9.1.1.	Footnotes for the Schedule of Events Tables	104
9.1.2.	Early Termination from the Study.....	107
9.1.3.	Unscheduled Visits	107
9.2.	Study Procedures	107
9.2.1.	Procedures Performed Only at the Screening/Baseline Visit	107
9.2.1.1.	Informed Consent	107
9.2.1.2.	Diagnostic Test for SARS-CoV-2	107
9.2.1.3.	Demographics	107
9.2.1.4.	Medical History	107
9.2.1.5.	Weight and Height.....	108
9.2.2.	Treatment.....	108
9.2.3.	Efficacy Procedures	108
9.2.3.1.	Nasopharyngeal Swab Collection.....	108
9.2.3.2.	COVID-19-Related Medically-Attended Visit Details	108
9.2.4.	Safety Procedures	109
9.2.4.1.	Vital Signs	109
9.2.4.2.	Adverse Event Monitoring	109
9.2.4.3.	Record Targeted Concomitant Medications and Concomitant Procedures.....	109
9.2.5.	Post-Day 29 Follow-Up.....	110
9.2.6.	Pregnancy Test for Women of Childbearing Potential.....	110
9.2.7.	Laboratory Testing.....	111
9.2.8.	Drug Concentration Measurements and Samples.....	111
9.2.9.	Immunogenicity Measurements and Samples	112
9.2.10.	Exploratory Pharmacodynamic/Biomarker Analyses.....	112
9.2.10.1.	Neutrophil–Lymphocyte Ratio	112
9.2.10.2.	Serum and Plasma Biomarkers.....	112

9.2.10.3.	Virology.....	113
9.2.10.4.	Serological Immunoassays for Anti-SARS-CoV-2 Antibodies	113
9.2.10.5.	Serum and Plasma for Exploratory Research	113
9.2.10.6.	Complement.....	114
9.2.10.7.	Cytokines	114
9.2.10.8.	Serum and Plasma for Cardiac Biomarkers.....	114
9.2.11.	Monitoring for SARS-CoV-2 Reinfection.....	114
9.2.12.	Recording New Medical Diagnoses or Conditions	114
9.2.13.	Immunoprofiling Sub-Study (Optional)	115
9.2.14.	Pharmacogenomics Sub-Study (Optional)	115
9.2.15.	Exploratory Patient-Reported Symptoms	116
9.2.16.	Assessment of Long COVID	117
9.2.16.1.	Patient-Reported Evaluation of Long COVID	118
9.2.16.2.	Nasopharyngeal Swab Sample and Blood Sample Collections (Long COVID Assessment).....	120
10.	SAFETY EVALUATION AND REPORTING	122
10.1.	Recording and Reporting Adverse Events.....	122
10.1.1.	General Guidelines	122
10.1.2.	Reporting Procedure	123
10.1.3.	Events that Require Expedited Reporting to Sponsor	123
10.1.4.	Other Adverse Events of Special Interest That Do Not Require Expedited Reporting to Sponsor	124
10.2.	Definitions	124
10.2.1.	Adverse Event.....	124
10.2.2.	Serious Adverse Event.....	124
10.2.3.	Adverse Events of Special Interest	125
10.2.4.	Infusion-Related Reactions and Hypersensitivity Reactions.....	125
10.2.5.	Severity	125
10.2.6.	Causality	126
10.3.	Safety Monitoring.....	127
10.4.	Notifying Health Authorities, Institutional Review Board, Ethics Committee, and Investigators	127
11.	STATISTICAL PLAN.....	128

11.1.	Statistical Hypothesis.....	128
11.2.	Justification of Sample Size.....	129
11.3.	Analysis Sets.....	131
11.3.1.	Efficacy Analysis Sets	131
11.3.2.	Safety Analysis Set	132
11.3.3.	Pharmacokinetic Analysis Set	133
11.3.4.	Immunogenicity Analysis Sets	133
11.4.	Statistical Methods.....	133
11.4.1.	Patient Disposition.....	133
11.4.2.	Demography and Baseline Characteristics	134
11.4.3.	Efficacy Analyses	134
11.4.3.1.	Primary Efficacy Analysis.....	134
11.4.3.2.	Secondary Efficacy Analysis.....	135
11.4.3.3.	Exploratory Analysis	137
11.4.4.	Control of Multiplicity.....	138
11.4.5.	Safety Analysis	141
11.4.5.1.	Adverse Events	141
11.4.5.2.	Other Safety.....	142
11.4.5.3.	Treatment Exposure.....	143
11.4.5.4.	Treatment Compliance.....	143
11.4.6.	Pharmacokinetics.....	143
11.4.6.1.	Analysis of Drug Concentration Data.....	143
11.4.7.	Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses.....	143
11.4.8.	Analysis of Immunogenicity Data	143
11.5.	Interim Analysis.....	144
11.6.	Statistical Considerations Surrounding the Premature Termination of a Study	144
12.	QUALITY CONTROL AND QUALITY ASSURANCE	145
12.1.	Data Management and Electronic Systems	145
12.1.1.	Data Management.....	145
12.1.2.	Electronic Systems.....	145
12.2.	Study Monitoring.....	145
12.2.1.	Monitoring of Study Sites.....	145

12.2.2.	Source Document Requirements	146
12.2.3.	Case Report Form Requirements	146
12.3.	Audits and Inspections	146
12.4.	Study Documentation	147
12.4.1.	Certification of Accuracy of Data	147
12.4.2.	Retention of Records	147
13.	ETHICAL AND REGULATORY CONSIDERATIONS	148
13.1.	Good Clinical Practice Statement	148
13.2.	Informed Consent	148
13.3.	Patient Confidentiality and Data Protection	149
13.4.	Institutional Review Board/Ethics Committee	149
13.5.	Clinical Study Data Transparency	150
14.	PROTOCOL AMENDMENTS	150
15.	PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE	150
15.1.	Premature Termination of the Study	150
15.2.	Closeout of a Site	150
16.	CONFIDENTIALITY	151
17.	FINANCING AND INSURANCE	151
18.	PUBLICATION POLICY	151
19.	REFERENCES	152
20.	INVESTIGATOR’S AGREEMENT	159
	SIGNATURE OF SPONSOR’S RESPONSIBLE OFFICERS	160

LIST OF TABLES

Table 1:	Summary of Main Phase 3 Adaptations	51
Table 2:	REGN10933+REGN10987 IV Doses for Each Weight Group, Phase 3 Cohort 2 (Ages 0 to <18 Years)	87
Table 3:	Schedule of Events: Phase 1	92
Table 4:	Schedule of Events: Phase 2 (and Phase 3 Prior to Protocol Amendment 6)	94
Table 5:	Schedule of Events: Phase 3 (Cohort 1 Patients)	96
Table 6:	Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients)	98

Table 7:	Schedule of Events: Phase 3 (Cohort 3 \geq 18 Years).....	99
Table 8:	Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years).....	101
Table 9:	Symptoms Evaluated in the Symptom Evolution of COVID-19 (SE-C19) Instrument.....	116
Table 10:	Symptoms Evaluated in the Symptom Evolution of Long COVID-19 (SE-LC19) Instrument.....	119
Table 11:	NCI-CTCAE Severity Grading System for Adverse Events (v5.0)	126
Table 12:	Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with \geq 1 Risk Factor for Severe COVID-19.....	130
Table 13:	Statistical Testing Hierarchy, Primary Phase 2 Analysis	138
Table 14:	Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis	139
Table 15:	Example Alpha Spending Function for Analysis of Primary Endpoint	141

LIST OF FIGURES

Figure 1:	Phase 1 Sentinel Safety Group	48
Figure 2:	Study Flow Diagram, Phase 1	75
Figure 3:	Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6).....	75
Figure 4:	Study Flow Diagram, Phase 3 (Cohort 1).....	76
Figure 5:	Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Prior to Amendment 10 US	76
Figure 6:	Study Flow Diagram, Phase 3 (Cohort 3 Patients \geq 18 Years) Prior to Amendment 10 US	77
Figure 7:	Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Amendment 10 US and Later	77

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 Ambulatory Patients with COVID-19
Site Locations	The study will be conducted in approximately 120 sites in the United States and other countries.
Principal Investigator	Anita Kohli, MD

Note: The phase 1 and phase 2 portions of the study have been completed. Therefore, this synopsis provides information pertaining to phase 3 only. Refer to the main text for information regarding phase 1 and phase 2.

Objectives

Primary Cohort 1 (≥18 Years Old, Not Pregnant at Randomization)

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (<18 Years Old, Not Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 over time

Cohort 3 (Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987

Secondary Cohort 1

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3

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

Study Design	This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with COVID-19.
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In phase 3, eligible patients in cohort 1 and cohort 2 were initially randomized 1:1:1 to a single dose of placebo or one of two dose levels of REGN10933+REGN10987. In cohort 1,

REGN10933+REGN10987 dose levels consisted of 1200 mg and 2400 mg. In cohort 2, body-weight equivalents of these two dose levels were used. Patients in cohort 3 were initially randomized 1:1 to one of two dose levels of REGN10933+REGN10987 (ie, no randomization to placebo), at 1200 mg and 2400 mg or body-weight equivalents as applicable.

Note that as of 25 February 2021 (per IDMC recommendation and subsequently formalized in protocol amendment 8), patients are no longer randomized to placebo (Section 8.5.1). On 14 May 2021, enrollment in cohort 1 was closed. As of protocol amendment 10 US, the 2400 mg dose level was dropped in cohort 2 and cohort 3, such that cohort 2 and cohort 3 patients are only assigned to the 1200 mg dose level (or body-weight equivalent for those under 18 years of age).

On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and exploratory analyses. After infusion, patients will be monitored for at least 1 hour and released from the study site, if medically appropriate. Patients <12 years of age will be monitored for at least 2 hours after infusion, with more frequent vital sign assessments.

Targeted safety information and COVID-19-related medically-attended visit details will be collected on an ongoing basis; minimally, patients (or their caregivers) will be queried during weekly phone visits through the first 29 days of the study. For patients <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information; these patients (or their caregivers) should be instructed to contact the site within 24 hours post-infusion if they experience any side effects. Patients (or their caregivers) will also be asked to notify study personnel as soon as possible about any unplanned medically-attended visits that occur during the study.

Patients enrolled in cohort 1 will have NP swabs and blood samples collected approximately every week through day 29 and will provide self-reported information about COVID-19 symptoms through electronic surveys (both daily and weekly). A subset of patients in cohort 1 will be enrolled in a PK sub-study. Patients in cohort 1 may also be enrolled in an optional immunoprofiling sub-study assessing the potential impact of REGN10933+REGN10987 on the endogenous immune response to SARS-CoV-2.

Patients enrolled in cohort 2 will also have NP swabs and blood samples collected approximately every week through day 29, with an NP swab additionally collected on day 3. To reduce overall patient burden of blood sampling in this younger cohort, the frequency of blood sample collection and the total amount of blood collected per visit will vary according to body weight. In addition, patients in this cohort will be randomly assigned to one of four staggered PK-ADA sampling schedules. This will be done according to a central randomization scheme using an interactive web response system (IWRS).

As part of protocol amendment 9 US, an additional series of assessments and sample collections will be performed in cohort 1 to better understand the biology of long COVID and the potential impact of prior REGN10933+REGN10987 treatment (during the acute phase of SARS-CoV-2 infection) on the development of long COVID symptoms. These analyses will be exploratory in nature.

Patients in phase 3 cohort 1 will follow the prior phase 3 Schedule of Events until day 90. They will then follow the long COVID Schedule of Events until day 169. Patients who consent to protocol amendment after day 90 will enter the long COVID Schedule of Events on the corresponding day on which they provide consent.

Patients in cohort 1 will complete a series of health-related questionnaires, including the SE-LC19 developed by the Sponsor. These self-report questionnaires will be conducted on a daily basis in the week leading up to the day 120 visit, and in the week leading up to the day 169 visit. On day 120 and day 169, patients will complete several additional questionnaires, will have an NP swab sample collected for analysis of SARS-CoV-2 virology, and will have blood samples collected for research purposes related to long COVID. Also on day 120 and day 169, any new medical condition diagnosed after randomization will be captured as an adverse event of special interest (AESI), but will not require expedited reporting to the Sponsor.

In addition to these procedures, previously described assessments (separate from the long COVID portion of the study) will be performed at day 120 and day 169 safety assessments, and (for those who were enrolled in the PK sub-study) an additional blood draw will be collected at day 120 for analysis of drug concentration and immunogenicity. These assessments are separate from the long COVID portion of the study.

Study Duration In phase 3, the duration of the study is 170 days for each patient.

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

Sample Size Up to approximately 8500 patients will be required for phase 3 cohort 1. For cohort 2, up to approximately 180 patients will be required. No enrollment targets are planned for cohort 3.

Target Population This study will enroll non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. In phase 3, patients must meet the following criteria to be eligible for inclusion in the study. Other inclusion criteria also apply and are described in the main text:

- Meets 1 of the following 3 criteria:
 - a. **Cohort 1:** ≥ 18 years of age and not pregnant at randomization
 - b. **Cohort 2:** < 18 years of age and not pregnant at randomization
 - c. **Cohort 3:** Pregnant at randomization

Note: Cohort 2 and cohort 3 will only be enrolled where permitted by local requirements. Enrollment in cohort 1 was closed on 14 May 2021.
 - Has SARS-CoV-2-positive diagnostic test from a sample collected ≤ 72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva
- Note: Historical record of positive result is acceptable, as long as the sample was collected ≤ 72 hours prior to randomization.*
- Has symptoms consistent with COVID-19, as determined by the investigator, with onset ≤ 7 days before randomization
 - **Cohort 1 and Cohort 2 only:** has ≥ 1 risk factor for severe COVID-19
- Risk factors are defined as follows:
- a. Age ≥ 50 years (**cohort 1 only**)
 - b. Obesity, defined as:
 - BMI ≥ 30 kg/m² (**cohort 1 only**)
 - BMI (kg/m²) ≥ 95 th percentile for age and sex based on CDC growth charts (**cohort 2 ≥ 2 years only**)
 - c. Cardiovascular disease, including hypertension
 - d. Chronic lung disease, including asthma
 - e. Type 1 or type 2 diabetes mellitus
 - f. Chronic kidney disease, including those on dialysis
 - g. Chronic liver disease
 - h. *[Risk factor removed]*
 - i. Immunosuppressed, based on investigator's assessment
- Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications*
- j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 (**cohort 2 only**)

A patient who meets any of the following criteria will be excluded from the study. Other exclusion criteria also apply and are described in the main text:

- Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
- Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
- Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)
Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening
- Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for COVID-19
- Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
- Has a known positive SARS-CoV-2 serologic test
- Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization

Treatments: Cohort 1 Patients**Study Drug**

Closed to enrollment as of 14 May 2021

Cohort 3 Patients ≥18 Years

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose

Cohort 2 and Cohort 3 Patients <18 Years

REGN10933+REGN10987 1200 mg will be adjusted according to body weight, as defined as below. All doses, consisting of 1:1 REGN10933 and REGN10987, will be given as IV single dose:

- ≥40 kg: 1200 mg
- ≥20 kg to <40 kg: 450 mg
- ≥10 kg to <20 kg: 224 mg
- ≥5 kg to <10 kg: 120 mg
- ≥2.5 kg to <5 kg: 60 mg
- <2.5 kg: 30 mg

Endpoints**Primary****Cohort 1**

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29

Cohort 2

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3

- Proportion of patients with treatment-emergent serious adverse events through day 29

- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥ 2) through day 29

Secondary Cohort 1

Key secondary endpoints (other secondary endpoints are provided in the main text)

- Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution

Cohort 2 and Cohort 3

There are no key secondary endpoints in cohort 2 and cohort 3. All secondary endpoints are descriptive; refer to the main text.

Procedures and Assessments Procedures and assessments will include the following:

Efficacy

- COVID-19-related medically-attended visit details
- NP swabs for SARS-CoV-2 RT-qPCR

Safety

- Treatment-emergent SAEs, treatment-emergent AESIs (grade ≥ 2 IRRs, grade ≥ 2 hypersensitivity reactions, and any TEAE that led to a medically-attended visit), and treatment-emergent grade ≥ 3 AEs (in cohort 2 only)
- Blood collection for safety labs
- Vital signs and concomitant medications
- Vital status
- Pregnancy status, pregnancy outcome (women of childbearing potential only)

Statistical Plan This section summarizes the statistical plan for primary and key secondary analyses of phase 3 cohort 1. For analysis of cohort 2 and cohort 3, refer to the main text. Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.

Statistical Hypothesis The statistical hypotheses for the primary endpoint of phase 3 cohort 1 are as follows:

- H_0 : The risk of a patient having ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo
- H_1 : The risk of a patient having ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo

Justification of Sample Size The sample size of phase 3 cohort 1 is based on having sufficient power to analyze the primary endpoint in the modified full analysis set (mFAS).

Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled, as well as blinded phase 3 data, the Sponsor assumes that 83% of randomized patients will have a positive SARS-CoV-2 RT-qPCR test at baseline (and can therefore be included in the mFAS). The Sponsor also assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS.

The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in the mFAS). With this sample size, the study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with REGN10933+REGN10987 treatment). If there is a greater treatment difference, such as a 60%

reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death.

The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in the mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (ie, when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (ie, a 50% reduction). If there is a greater treatment difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death.

From 25 February 2021 onward, the Sponsor plans to randomize up to 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group, in addition to the patients already enrolled under protocol amendment 6 and protocol amendment 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the observed difference. Blinded sample size re-estimation may be performed based on the pooled observed event rates.

Statistical Analysis

Efficacy Analysis Sets (Cohort 1)

Only patients with COVID-19 symptoms will be included in phase 3. All symptomatic patients from the 800th randomized symptomatic patient will be included in phase 3. For phase 3 cohort 1, the full analysis set (FAS) includes all randomized symptomatic patients and is based on the treatment allocated (as randomized). The FAS includes patients with and without risk factors for severe COVID-19.

In phase 3, the mFAS includes all randomized patients with a positive SARS-CoV-2 central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and with at least one risk factor for severe COVID-19 at baseline. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

For the analyses of the 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after protocol amendment 6 is implemented) will be included in the above analysis sets.

Primary Efficacy Analysis (Cohort 1)

The primary efficacy endpoint for phase 3 cohort 1 is the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29, which will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The primary analysis will be performed based on mFAS. As key secondary analyses, the same analyses will be performed for patients with high baseline viral load ($>10^6$ copies/mL) and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity and supportive analyses will be described in the SAP.

Key Secondary Efficacy Analysis (Cohort 1)

Time to COVID-19 symptoms resolution will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed in the mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be

reported. The hazard ratio and 95% CI for time to COVID-19 symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group and randomization strata. The p-value from the stratified log-rank test will be reported. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤ 3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

COVID-19 symptoms included in the analysis are as follows: Body aches such as muscle pain or joint pain, Chest pain, Chills, Cough, Diarrhea, Dizziness, Fatigue, Feverish, Headache, Loss of appetite, Loss of taste/smell, Nausea, pressure/tight chest, Red or watery eyes, Runny nose, Shortness of breath/difficulty breathing, Sore throat, Sputum/Phlegm, and Stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except Cough, Fatigue, and Headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

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, two 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 symptoms to respiratory failure and death (Wu, 2020). Among hospitalized patients, intensive care and/or supplemental oxygen intervention (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, and >50% lung involvement on imaging; 5% with respiratory failure, shock, or multiorgan failure) (Wu, 2020). 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 (Guan, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support (Richardson, 2020).

1.3. Ambulatory Care as a Potential COVID-19 Treatment Setting

Although severe COVID-19 can occur across all age groups, accumulating data have identified several factors that can place patients at risk of more serious illness and potentially lead to hospitalization, emergency room visits, or other medically-attended visits. These include age, pregnancy, as well as variety of comorbidities such as obesity and cardiovascular disease (Chen, 2020b). An anti-viral therapeutic that could be administered to ambulatory patients (ie, outpatients) has the potential to significantly reduce COVID-19-related medically-attended visits, particularly among those with 1 or more baseline risk factors. Currently, there is a great need for therapies capable of reducing viral load and slowing or preventing COVID-19 disease progression.

1.4. 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.

1.5. The Role of Spike (S) Protein in SARS-CoV-2 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 (Huang, 2020). The 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 (Hoffmann, 2020) (Ou, 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 (Datta, 2020), a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.6. REGN10933+REGN10987: Human Monoclonal Antibodies that Target 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) (see Section 3.3 for additional information).

Casirivimab and imdevimab (1200 mg; 600 mg of each mAb) is currently authorized under Emergency Use Authorization (EUA) for the treatment of outpatients 12 years and older who are at high risk for developing severe COVID-19 ([FDA, 2020](#)).

1.7. A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory 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. Multiple COVID-19 therapies will be required, both to address the medical requirements of distinct patient populations and to bolster treatment supplies as caseloads continue to rise worldwide. The availability of multiple treatment options, and the continued collection of data on conditionally authorized treatments, are both critically important in the setting of a global pandemic.

This is an adaptive, phase 1/2/3 master protocol to further evaluate the efficacy and safety of co-administered REGN10933+REGN10987 in ambulatory patients (ie, outpatients) with COVID-19.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Phase 1

The primary objectives of phase 1 are:

- To evaluate the safety and tolerability 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

Phase 2

The primary objective of phase 2 is to evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2.

Phase 3

Cohort 1 (≥18 Years Old, Not Pregnant at Randomization)*

The primary objective is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (<18 Years Old, Not Pregnant at Randomization)*

The primary objectives are:

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

Cohort 3 (Pregnant at Randomization)*

The primary objective is to evaluate the safety and tolerability of REGN10933+REGN10987.

*Refer to Section 7.2.1 for study cohort definitions.

2.2. Secondary Objectives

Phase 1

The secondary objectives of phase 1 are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To estimate the clinical efficacy of REGN10933+REGN10987 compared to placebo
- To compare quantitative reverse transcription polymerase chain reaction (RT-qPCR) results acquired with different sample types (nasopharyngeal [NP], nasal, and saliva)
- To characterize the PK profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2

The secondary objectives of phase 2 are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the 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 3

The secondary objectives of phase 3 are:

Cohort 1*

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2*

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3*

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

*Refer to Section [7.2.1](#) for study cohort definitions.

2.3. Exploratory Objectives

The exploratory objectives (phase 1, phase 2, and phase 3) are:

- To evaluate viral variants at baseline and post-treatment
- 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 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To explore 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
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 compared to placebo

Additional exploratory objective for phase 1 only:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo

Additional exploratory objective for phase 3 only:

- To assess the clinical efficacy of different dose levels of REGN10933+REGN10987, as measured by COVID-19-related hospitalizations or all-cause death
- To describe the relationship between virologic effects of REGN10933+REGN10987 and risk of COVID-19-related medically-attended visit or all-cause death
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on the generation of endogenous humoral and/or cellular immune responses to SARS-CoV-2 (optional sub-study) (cohort 1)
- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo (cohort 2 age ≥ 12 years)
- To describe the clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death (cohort 3)
- To evaluate the impact of REGN10933+REGN10987 treatment, given during acute SARS-CoV-2 infection, on long COVID symptoms (cohort 1 only)

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 1

Treatment of ambulatory patients with COVID-19 with REGN10933+REGN10987 will be tolerated and will reduce viral load.

Phase 2

Treatment of ambulatory patients with SARS-CoV-2 infection with REGN10933+REGN10987 will reduce viral load.

Phase 3

Treatment of ambulatory patients (≥ 18 years) with COVID-19 with REGN10933+REGN10987 will improve clinical outcomes.

Treatment of ambulatory patients (< 18 years) with COVID-19 with REGN10933+REGN10987 will be well tolerated.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

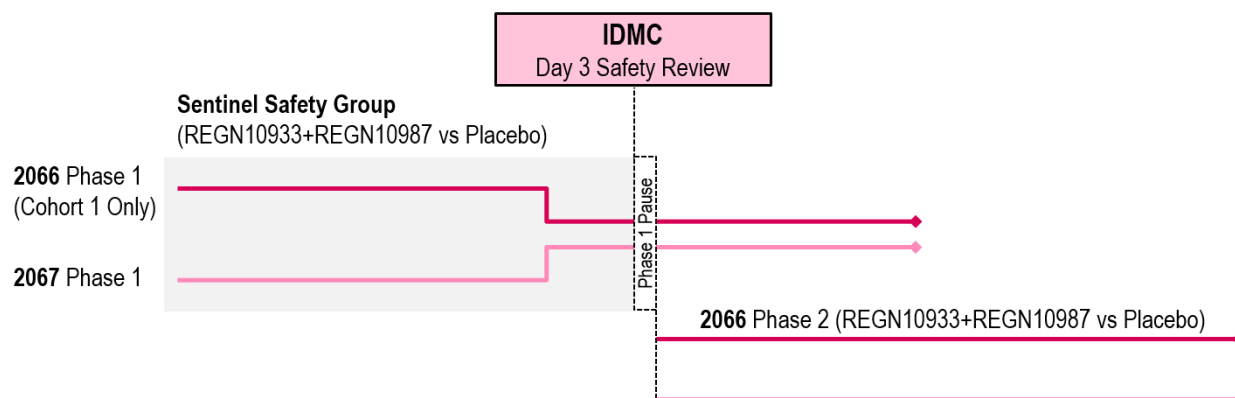
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in ambulatory patients with COVID-19 (including, in phase 2, those with asymptomatic SARS-CoV-2 infection). The multicenter conduct of this 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.

Phase 1 will include a sentinel safety group (Figure 1), 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 ambulatory adult patients 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 6.1.5.2.

After the IDMC reviews and provides a positive recommendation for the phase 1 sentinel safety group, enrollment of studies assessing REGN10933+REGN10987 (including REGN10933+REGN10987 treatment arms in phase 2 of this study and R10933-10987-COV-2066) 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.

Review of Sentinel Safety Group (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 adult (≥ 18 years) 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 and 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 at different dose levels of REGN10933+REGN10987, the addition of 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 adaptations, including determination of phase 3 primary endpoints and phase 3 sample size estimation.

3.2.1.3. Rationale for Phase 1 and Phase 2 Objectives

Safety and Tolerability

The primary objective of phase 1 is 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 in phase 1 to inform safety assessments in later phases.

Many patients who are ambulatory and experiencing relatively early stages of COVID-19 may nevertheless present with complicated disease presentation at baseline or could quickly and unexpectedly deteriorate and progress to have a complicated disease presentation. As such, their TEAE profile could be complex and dynamic. 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 treatment-emergent SAEs and treatment-emergent AESIs (grade ≥ 2 hypersensitivity reactions and grade ≥ 2 infusion-related reactions), as well as targeted treatment-emergent grade 3 or 4 TEAEs in phase 1, will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987. This subset of treatment-emergent 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 healthcare delivery system.

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 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). In phase 2, virologic efficacy will also be evaluated in asymptomatic patients with laboratory-confirmed SARS-CoV-2 infection. The 21-day assessment period is similarly appropriate for this cohort, based on evidence that peak viral load occurs just before or soon after the onset of COVID-19 symptoms (Cao, 2020) (Wang, 2020c).

Prior to unblinding for analysis of interim phase 1/2 data and analysis of phase 2 data, the cutoff date of the primary virologic endpoint was pre-specified in the statistical analysis plan (SAP) as day 7 rather than day 22. This was done as the result of the phase 1/2 analysis, which showed that the majority of viral clearance had occurred prior to day 7. For more information, refer to Section 3.2.1.5 and (Weinreich, 2020).

Clinical Efficacy

Clinical efficacy will also be evaluated. Patients enrolled in this study will be in the early phase of their infection (Section 7.2.1), and are therefore expected to be presymptomatic or have milder, less advanced disease compared with individuals diagnosed at later stages of COVID-19. By directly targeting host entry by SARS-CoV-2, REGN10933+REGN10987 may impact the early stages of the disease course, preventing symptom onset, mitigating early disease progression, and reducing the likelihood that patients will experience the more advanced symptoms associated with hospitalization and/or other urgent medical visits. Phase 2 will therefore assess the proportion of

patients requiring COVID-19-related medically-attended visits (defined in Section 9.2.3.2) subsequent to their initial disease diagnosis and released home.

3.2.1.4. Stratification According to Risk of Hospitalization (Phase 2)

In phase 2, randomization will be stratified based on risk factors for hospitalization due to COVID-19 (refer to Section 8.5.1 for complete definition of phase 2 risks factors; also note that other stratification factors will be used as described in Section 8.5.1).

Although more advanced COVID-19 illness can occur in individuals of all ages, it primarily occurs in older adults or those with underlying medical conditions, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, obesity (body mass index [BMI] ≥ 30 kg/m²), cancer, and chronic kidney disease (CDC, 2020b) (Lighter, 2020) (Wu, 2020) (Zhou, 2020).

Hospitalization rates for COVID-19 increase with age, with one study reporting a 1% hospitalization rate for those 20 to 29 years, 4% rate for those 50 to 59 years, and 18% for those >80 years of age (Liu, 2020). Moreover, the majority of those hospitalized or in ICUs are older adults. Among 4,226 COVID-19 cases reported in the United States during February and March 2020, for example, 45% of hospitalizations and 53% of ICU admissions for COVID-19 were among adults ≥ 65 years of age (CDC, 2020c).

In addition to older patients, younger patients with underlying medical conditions may be at higher risk for hospitalization due to COVID-19. Among 7,162 patients reported in the United States with COVID-19 who had data available on their underlying health conditions, for example, patients with underlying conditions were hospitalized at higher rates compared to those without underlying conditions (27.3% to 29.8% compared to 7.2% to 7.8%). The most common underlying conditions in the study were diabetes mellitus, cardiovascular disease and chronic lung disease (CDC, 2020b).

Obesity is prevalent condition that may also be a risk factor for hospitalization with COVID-19, with one study reporting that young obese patients (BMI ≥ 30 kg/m²) were more likely to be hospitalized or admitted to an ICU compared to young patients who were not obese (Lighter, 2020). In the United States, nearly 40% of adults are obese and may be at higher risk of hospitalization due to COVID-19 (CDC, 2017).

3.2.1.5. Rationale for Phase 3 Adaptations

A summary of the most substantial phase 3 adaptations is provided in Table 1. These adaptations are being implemented based on available data from phase 1 and phase 2, which are summarized in the sub-sections below (and, for dose selection, in Section 3.2.2.2) and in the Investigator's Brochure. Modifications to these phase 3 adaptations were subsequently made in response to health authority feedback and are captured in the table below.

Table 1: Summary of Main Phase 3 Adaptations

Study Component	Adaptation ¹
Patient Eligibility	<ul style="list-style-type: none"> Patients from 0 to <18 years will be enrolled as a separate cohort (cohort 2), where permitted by local requirements. Patients ≥ 18 years old will be enrolled in cohort 1

	<ul style="list-style-type: none"> • Patients who are pregnant or breastfeeding can enroll in the study. Patients who are pregnant at randomization will be enrolled in cohort 3, where permitted by local requirements • Patients in cohort 1 and cohort 2 must have ≥ 1 risk factor for severe COVID-19 • Patients with a known positive SARS-CoV-2 serology test will be excluded • Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected >72 hours prior to randomization will be excluded • Patients with active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test, will be excluded
Treatment Arms	<ul style="list-style-type: none"> • For cohort 1, the treatment arms will be REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 1200 mg IV, and placebo. Note that as of 25 February 2021 (per IDMC recommendation), patients in this cohort will no longer be randomized to placebo. • For cohort 2, the treatment arms will be weight-tiered dosing that matches REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 1200 mg IV, and placebo IV. Note that as of 25 Feb 2021, patients in this cohort will no longer be randomized to placebo. • For cohort 3, the treatment arms will be REGN10933+REGN10987 2400 mg IV and REGN10933+REGN10987 1200 mg IV. No placebo arm will be used. Weight-tiered dosing will be used for patients <18 years of age.
Objectives /Endpoints	<ul style="list-style-type: none"> • For cohort 1, primary endpoint will be the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death. The key pre-specified secondary endpoints include time to COVID-19 symptoms resolution. A hierarchical testing strategy will be used to control for multiplicity. • For cohort 2 and cohort 3, the primary endpoints will be safety/tolerability • For cohort 2, secondary endpoint analyses will be descriptive • Virologic analyses for all cohorts will be secondary and descriptive • Cohort 1 will enroll up to 300 patients in an optional sub-study to assess, as an exploratory objective, the potential impact of REGN10933+REGN10987 on the endogenous immune response
Sample Size	<ul style="list-style-type: none"> • Enrollment in phase 3 cohort 1 is anticipated to be up to approximately 8500 patients • Cohort 2 will enroll up to approximately 180 patients; there will be a minimum enrollment of 20 patients <10 kg (10 per treatment group) and 20 patients between ≥ 10 kg and <40 kg (10 per treatment group) • No minimum or maximum enrollment is planned for cohort 3 • Cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed

¹ Phase 3 adaptations were initially implemented in protocol amendment 6. Modifications to the phase 3 adaptations were subsequently implemented in response to health authority feedback (protocol amendment 7) and prior to phase 3 statistical analyses (protocol amendment 8). Refer to the amendment history table for more detailed information.

Virologic Efficacy

An interim analysis of pooled phase 1/2 data (n=275) was conducted to assess preliminary virologic and clinical efficacy of REGN10933+REGN10987. Among patients who were SARS-CoV-2 seronegative at baseline, those who received REGN10933+REGN10987 had a greater reduction in viral load through day 7 compared with those who received placebo, as measured by time-weighted average (TWA) change from baseline. For example, seronegative patients receiving either REGN10933+REGN10987 2400 mg or 8000 mg (combined analysis) had a TWA viral load change of $-1.94 \log_{10}$ copies/ml, versus $-1.37 \log_{10}$ copies/ml in the placebo arm (difference between combined dose group and placebo, $-0.56 \log_{10}$ copies/mL; nominal $p=0.0165$). Post-hoc analysis of virologic outcomes by baseline viral load found that patients with the highest viral load at baseline had the largest treatment benefit.

A subsequent analysis of the remaining patients in phase 2 (n=524) formally corroborated the virologic efficacy findings observed in the phase 1/2 analysis in a prespecified and statistically rigorous manner. There was a statistically significant reduction in the TWA change from baseline in viral load (\log_{10} copies/mL) from day 1 through day 7 in patients treated with either dose of REGN10933+REGN10987 or the combined dose group ($-1.66 \log_{10}$ copies/ml) compared to placebo ($-1.30 \log_{10}$ copies/ml) (difference between combined dose group and placebo, $-0.36 \log_{10}$ copies/mL; $p=0.0003$). Statistically significant reductions were observed in the overall population that were SARS-CoV-2 RT-qPCR positive at baseline, and were more pronounced in those with high baseline viral load ($>10^7$ copies/mL or $>10^6$ copies/mL) or those who were seronegative at baseline. Descriptively, the greater reduction in viral load with REGN10933+REGN10987 treatment compared to placebo could be observed as early as 2 days post-treatment (the first time point assessed) and was maintained at each subsequent time point through day 11, when the mean viral load in each of the REGN10933+REGN10987 treatment groups fell below the lower limit of quantification ($<2.87 \log_{10}$ copies/mL).

By contrast, patients who were seropositive at baseline had mean baseline viral loads approximately 3-log lower than patients who were seronegative at baseline, and the change from baseline in viral load through day 7 for seropositive patients treated with either dose of REGN10933+REGN10987 was similar to the reduction in patients treated with placebo. These results suggest that the true benefit of a potent antiviral might be concentrated in the higher risk groups (eg, seronegative at baseline and higher baseline viral load).

Clinical Efficacy

The above virologic data collectively provide definitive evidence that REGN10933+REGN10987 markedly enhances SARS-CoV-2 viral clearance. Moreover, data from a pooled phase 1/2 analysis indicate that the viral load reduction translated into clinical benefit by significantly reducing COVID-19-related MAVs, defined as hospitalizations, ER visits, urgent care visits, or physician office or telemedicine visits for COVID-19. Specifically, a prespecified and multiplicity-controlled analysis of pooled phase 1/2 data in symptomatic patients who were SARS-CoV-2 RT-

qPCR positive at baseline (n=799; mFAS=665) showed a statistically significant reduction in MAVs in the REGN10933+REGN10987 treated groups compared to placebo (2.8% combined dose groups vs 6.5% placebo; p=0.0240). Most of the MAVs occurred in patients who were higher risk, defined as seronegative at baseline, had higher baseline viral load, or had at least 1 pre-existing risk factor for severe COVID-19 (eg, age >50 years old, obesity, co-morbid conditions). In exploratory analyses, treatment with REGN10933+REGN10987 showed the greatest benefit in these high-risk groups, with reductions in the proportion of patients with MAVs compared to placebo of 62% (3.2% combined treatment versus 8.5% placebo) for those with baseline viral loads >10⁴ copies/mL, 65% (3.4% combined treatment versus 9.7% placebo) for those who were seronegative at baseline, and 72% (2.6% combined treatment versus 9.2% placebo) for those who had at least 1 risk factor for severe COVID-19. Treatment with REGN10933+REGN10987 did not reduce MAVs for those who were seropositive at baseline (2.9% combined treatment versus 1.9% placebo) or for those who were without pre-existing risk factors for severe disease (2% combined treatment versus 1.9% placebo), suggesting that MAVs in these groups are less modifiable with treatment.

Considering the clinical benefits observed in phase 2, phase 3 will focus on confirming the clinical benefit of REGN10933+REGN10987 in reducing the risk of having a COVID-19-related hospitalization or all-cause death for high-risk patients, thereby demonstrating the clinical benefit of reducing viral burden. Virologic secondary analyses will be conducted during phase 3, but these will be descriptive in nature.

Note: A primary efficacy analysis of the phase 3 portion found that treatment with REGN10933+REGN10987 was well-tolerated and significantly reduced COVID-19-related hospitalization or all-cause death, rapidly resolved symptoms, and reduced viral load (Weinreich, 2021b). Refer to Section 3.3.1 for more details.

Requirement of ≥1 Risk Factor for Severe COVID-19

The placebo-treated patients in the phase 1/2 portion of the study provided key insights into the natural history of COVID-19. Patients who were seronegative at baseline or who had at least 1 risk factor for severe COVID-19 had higher baseline viral loads compared to those who were seropositive or those who did not have pre-existing risk factors for severe disease. These patients took longer to reduce viral load and accounted for the majority of patients with MAVs. As described above, it was also these high-risk patients that had the greatest benefit with REGN10933+REGN10987 treatment in reducing MAVs. Treatment with REGN10933+REGN10987 did not appear to reduce MAVs in patients who were seropositive at baseline or in patients without risk factors for severe disease, suggesting the true benefit of treatment is in patients who have not yet mounted a sufficient immune response or have baseline risk factors for severe disease. Based on these very important learnings from the available data and considering that risk factors can readily be assessed by the treating provider without additional testing, adult patients enrolled in phase 3 subsequent to amendment 6 will be required to have at least one risk factor for severe COVID-19.

Risk factors for COVID-19 that will be applied to the study populations in phase 3 are defined in Section 7.2.1. These risk factors encompass the CDC definition of “at increased risk” and “might be at an increased risk” patients for severe COVID-19. Modifications to this list of risk factors have been made for phase 3. Pregnant women are included because pregnancy is considered a risk

factor based on accumulating evidence that women who are pregnant are at increased risk for severe COVID-19 (Ellington, 2020) (Knight, 2020). Additional examples of immunosuppressed patients have also been added to more fully capture those noted to be at risk according to the CDC's definition.

In addition to the above risk factors, other modifications to eligibility criteria have been made in phase 3 to ensure further that at-risk patients are included. Although serological testing for negative serostatus will not be required for study entry, patients who have a known history SARS-CoV-2 infection prior to this study (demonstrated by a positive SARS-CoV-2 serology, antigen, molecular diagnostic test or other diagnostic assay other than the one used for eligibility into this study) will be excluded. Similarly, patients who report or have a known history of COVID-19 any time prior to the current episode of COVID-19 will be excluded.

Inclusion of Patients Under 18 Years of Age

Patients age 0 to <18 years with symptomatic COVID-19 and at least 1 risk factor for severe COVID-19 (defined in Section 7.2.1) will be included in the phase 3 portion of the study as a separate cohort to assess the safety, PK, immunogenicity, and efficacy of REGN10933+REGN10987.

Most children with COVID-19 seem to experience mild disease that can be managed symptomatically in the outpatient setting. However, children with risk factors including underlying medical conditions such as obesity, diabetes, chronic lung disease, or immunosuppression might be at increased risk for severe COVID-19 (Kim, 2020) (Shekerdeman, 2020). Surveillance data reported to CDC through May 2020 indicated that the COVID-19-related hospitalization rate among children 0 to 9 years and 10 to 19 years old with underlying health conditions was approximately 6 times greater compared to children in the same age group with no reported underlying conditions (0 to 9 years, 22.3% versus 3.7%; 10 to 19 years, 14.9% versus 2.3%, respectively), and was similar to the hospitalization rate reported in adults, especially younger adults (eg, 20 to 29 years old), with and without underlying health conditions (17.5% versus 2.7%) (Stokes, 2020). Additionally, according to COVID-NET, a population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations in 99 counties in 14 states in the US, pediatric patients <12 years accounted for 58.2% of all hospitalized children and adolescents age 12 to 17 years accounted for 42% of all hospitalized children reported to COVID-NET between 1 Mar 2020 to 25 Jul 2020 (Kim, 2020).

Based on the phase 2 data described above, high-risk pediatric patients with COVID-19 could benefit from the anti-viral activity of REGN10933+REGN10987 and the potential clinical benefit of reducing COVID-19-related MAVs.

Since the rates of MAVs in pediatric patients with COVID-19 are unknown, these patients will be enrolled as a separate cohort and will not contribute to the primary efficacy endpoint. Instead, the primary objective for cohort 2 will be safety, with MAVs as a descriptive secondary objective.

REGN10933+REGN10987 mAbs are directed against an exogenous antigen, administration of REGN10933+REGN10987 and thus is not anticipated to affect endogenous pathways. Therefore, the safety profile in children is expected to be similar to that observed in adults. Safety data is reviewed in a continuous manner by the sponsor (blinded data) and by the IDMC (unblinded data).

Inclusion of Pregnant Women

Pregnant women are reported to be at an increased risk for severe COVID-19. Surveillance data reported to the CDC from January to June 2020 reported that pregnant women with COVID-19 were more likely to be hospitalized compared to nonpregnant women (31.5% versus 5.8%, respectively) (Ellington, 2020). Data reported to CDC through September 2020 showed that compared with nonpregnant women, pregnant women were more frequently admitted to an ICU (10.5 versus 3.9 per 1,000 cases; adjusted risk ratio = 3.0; 95% CI = 2.6–3.4), received invasive ventilation (2.9 versus 1.1 per 1,000 cases; adjusted risk ratio = 2.9; 95% CI = 2.2–3.8) and received ECMO (0.7 versus 0.3 per 1,000 cases; adjusted risk ratio = 2.4; 95% CI = 1.5–4.0) (Zambrano, 2020). Partly based on these data, the CDC considers pregnancy among the risk factors that places patients “at increased risk” for severe COVID-19. These outcome data suggest pregnant women could benefit from the anti-viral activity of REGN10933+REGN10987 and potential clinical benefit of reducing COVID-19-related MAVs. As such, pregnant women will be included in the phase 3 portion of the trial. These patients will be included as a separate double-blinded cohort, randomized only to different dose levels of REGN10933+REGN10987 (see Section 8.5.1 for details). The absence of a placebo arm will help to ensure that adequate descriptive safety information is collected for study drug in a population whose enrollment is anticipated to be relatively small and thus preclude hypothesis-driven analysis.

As an added safety measure in phase 3, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study, the incidence and outcome of any SARS-CoV-2 infection in these infants will be collected during follow-up phone calls. This collection is in addition to standard collection of pregnancy outcome information (Section 10.1.3).

Addition of Optional Immunoprofiling Sub-Study

An optional sub-study will be conducted at specified sites in phase 3 cohort 1 (and cohort 3 patients ≥ 18 years old) to explore the cellular and humoral immune response to SARS-CoV-2 infection. The intent of the sub-study is to explore the potential impact of treatment on the endogenous immune response to infection, as this is considered a theoretical risk for REGN10933+REGN10987 (Section 3.2.2.2). Refer to Section 9.2.13 for more information about this sub-study.

Phase 3 Sample Size Adjustment

In light of the modifications to the phase 3 primary endpoint, adjustments to the phase 3 sample size were necessary to ensure adequate power to evaluate the primary endpoint. Refer to Section 11.2 for more information on sample size justification.

3.2.1.6. Assessment of Long COVID

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 in patients in cohort 1. 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 9.2.16.1). 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 and [Table 10](#)

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 9.2.16.2.

3.2.2. Rationale for Dose Selection

3.2.2.1. Phase 1 and Phase 2 Dose Selection

Phase 1 and phase 2 will assess a single IV dose of REGN10933+REGN10987 as combination therapy administered 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). These study phases will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2400 mg (1200 mg per mAb), which is expected to be an efficacious dose (see below). The study

phases will also evaluate REGN10933+REGN10987 at a higher dose, 8000 mg (4000 mg 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 (Xu, 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 (EC₉₉)* observed against live virus SARS-CoV-2 and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC₉₉ against SARS-CoV-2 is 0.14 µg/mL (REGN10933), 0.78 µg/mL (REGN10987), and 0.01 µg/mL (REGN10989).

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, REGN10987, and REGN10989. 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, and ~0.1 µg/mL for REGN10989.

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 1200 mg 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).

3.2.2.2. Phase 3 Dose Selection

Adult Patients

Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6 and received study drug doses selected for phase 1 and 2.

Phase 3 will assess 2 dose levels of REGN10933+REGN10987, 1200 mg and 2400 mg, administered in a 1:1 ratio (600 mg and 1200 mg per mAb, respectively). The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are noncompeting 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). In the most recent analysis of phase 1 and 2 results in study R10933-10987-COV-2067, the 2400 mg and 8000 mg doses of REGN10933+REGN10987 demonstrated similar virologic and clinical efficacy as assessed by medically attended visits (MAVs), and both doses had similar and acceptable safety profiles. Given the similarities between the 2400 mg and 8000 mg doses, the 2400 mg dose will be studied in this phase 3 study as the highest dose, along with a lower dose of

1200 mg. Based on the observed linear PK for both mAbs, the 1200 mg dose is expected to provide 50% of the REGN10933 and REGN10987 exposures of the 2400 mg dose.

Subsequently, the 2400 mg dose arm was removed in protocol amendment 10 US based on a consistent efficacy and safety profile between the 2400 mg and 1200 mg doses, indicating the absence of a dose response. As cohort 1 enrollment had been closed on 14 May 2021, this change only impacts cohort 2 and cohort 3.

Pediatric Patients

Initial dose selection in the pediatric population (<18 years of age) utilized a body weight-tiered flat dose approach for both the higher and lower doses. For each weight-tiered dose targeting the higher dose in adults (2400 mg), the goal is to select doses that are predicted by population PK modeling to ensure that the lower fifth percentile of concentration in serum 28 days after dosing (C_{28}) is similar to, or greater than, the observed lower fifth percentile of C_{28} in adults for the 2400 mg dose. An additional consideration is to ensure that predicted C_{max} and AUC_{0-28} for each weight-tiered dose do not exceed values previously achieved in adults. Both REGN10933 and REGN10987 have demonstrated linear PK, and as such, the same 50% reduction employed in selecting the lower adult dose in phase 3 (2400 mg to 1200 mg) was applied to each of the pediatric body weight-tiered flat doses targeting the 1200 mg adult dose (Table 2).

To facilitate the predicted exposures in pediatric patients a 2-compartment population PK model with linear clearance developed for adults was used to simulate concentrations in serum over time for various doses in each pediatric weight group using allometrically scaled estimates of clearance and volume of distribution [gestational-age corrected allometrically scaled estimates were used for subjects <10 kg] (Robbie, 2012). For the pediatric doses in each weight group for the equivalent adult 2400 mg dose shown in Table 2, the predicted fifth percentile of C_{28} for all pediatric weight groups was greater than the observed fifth percentile of C_{28} for the adult 2400 mg dose; the predicted 50th percentile of C_{28} for all pediatric weight groups ranged from 1.0 to 1.3x and 1.3 to 1.6x the observed 50th percentile of C_{28} for REGN10933 and REGN10987 for the adult 2400 mg dose, respectively. The predicted 95th percentiles of C_{max} and AUC_{0-28} for each pediatric dose equivalent of the 2400 mg adult dose were below the observed 50th percentiles of C_{max} and observed mean AUC_{0-28} values for both REGN10933 and REGN10987 for adults at 8000 mg, a dose shown to have an acceptable safety and tolerability profile.

3.3. Risk-Benefit

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

For additional information concerning clinical and pre-clinical 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 intravenous 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 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 one day and resolved within two 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 subcutaneous 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 subcutaneous 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 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 (intravenous [IV] administration) or injection site reactions (subcutaneous [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 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

4.1. Primary Endpoints

The definition of a COVID-19-related medically-attended visit is provided in Section 9.2.3.2. Note that a patient with multiple COVID-19 related MAVs will be counted as having one event.

Phase 1

The primary endpoints for phase 1 are:

- Proportion of patients with treatment-emergent serious adverse events (SAEs) through day 29
- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥ 2) through day 29
- Time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Note: Time-weighted average of change from baseline 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.

Phase 2

The primary endpoint for phase 2 is time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Phase 3

Cohort 1

The primary endpoint for phase 3 is proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29.

Cohort 2

The primary endpoints for phase 3 are:

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥ 2) through day 29
- Concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3

The primary endpoints for phase 3 are:

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4

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

4.2. Secondary Endpoints

The definition of a COVID-19-related medically-attended visit is provided in Section 9.2.3.2. Note that a patient with multiple COVID-19 related MAVs will be counted as having one event.

Phase 1

Virologic

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

Clinical

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

PK/ADA

- Concentrations of REGN10933 and REGN10987 in serum and corresponding pharmacokinetics parameters

- Immunogenicity, as measured by anti-drug antibodies to REGN10933 and REGN10987

Phase 2

The secondary endpoints for phase 2 are:

Virologic

- Time to negative RT-qPCR in nasopharyngeal swabs with no subsequent positive RT-qPCR
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal samples
- Time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to post-baseline study days
- Proportion of patients with high viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) at each visit
- Proportion of patients with viral loads below the limit of detection at each visit
- Proportion of patients with viral loads below the lower limit of quantitation at each visit

Clinical

- Proportion of patients with ≥ 1 COVID-19-related medically-attended visit through day 29
- Proportion of patients with ≥ 2 COVID-19-related medically-attended visits through day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients with ≥ 1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only)
- Duration of symptoms consistent with COVID-19

Safety

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4

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

PK/ADA

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

Phase 3

Cohort 1

The key secondary endpoints for phase 3 are:

- Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution.

Note: COVID-19 symptoms resolution is defined in Section 11.4.3.2.

The other secondary endpoints for phase 3 are:

Clinical

- Proportion of patients with ≥ 1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Proportion of patients with ≥ 1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥ 1 COVID-19-related medically-attended visit by type of visit (hospitalization, emergency room, urgent care, and/or physician's office/telemedicine) through day 29
- Proportion of patients with ≥ 2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of patients with ≥ 1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥ 1 COVID-19-related medically-attended visit or all-cause death through day 29
- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169

Virologic

- Time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples (patients enrolled prior to protocol amendment 6 only)
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal swab samples

Safety

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥ 2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥ 2) through day 29

PK/ADA

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

Cohort 2

The secondary endpoints for phase 3 are:

Clinical

- Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29
- Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Proportion of patients with ≥ 1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Proportion of patients with ≥ 1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥ 1 COVID-19-related medically-attended visit by type of visit(s) (hospitalization, emergency room, urgent care, and/or physician's office/telemedicine) through day 29
- Proportion of patients with ≥ 2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29

- Cumulative incidence of patients with ≥ 1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥ 1 COVID-19-related medically-attended visit or all-cause death through day 29
- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169

Virologic

- Time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal swab samples

ADA

- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Cohort 3

The secondary endpoints for phase 3 are:

PK/ADA

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

4.3. Exploratory Endpoints

The exploratory endpoints for phase 1 and phase 2:

- 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
- Change in SE-C19 item scores over time
- Change in PGIS score over time
- PGIC score at day 29

Additional exploratory endpoints for phase 1 only:

- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

Phase 3

The exploratory endpoints for phase 3 are:

- Viral load over time in patients with and without COVID-19-related medically-attended visits
- Change in WPAI+CIQ over time
- Change in EQ-5D-5L over time
- Time to COVID-19 symptoms resolution (cohort 2 ages ≥ 12 years)

Note: COVID-19 symptoms resolution is defined in Section 11.4.3.2.

The exploratory long COVID endpoints for phase 3 (cohort 1 only) are listed below.

- Proportion of patients with ≥ 1 symptom from SE-LC19 Category A by day 169
- Proportion of patients with ≥ 1 symptom from SE-LC19 Category B by day 169
- Proportion of patients with ≥ 1 symptom from SE-LC19 Category C by day 169
- Proportion of patients with ≥ 2 symptoms from SE-LC19 Category A by day 169
- Proportion of patients with ≥ 2 symptoms from SE-LC19 Category B by day 169
- Proportion of patients with ≥ 2 symptoms from SE-LC19 Category C by day 169

Note: SE-LC19 symptom categories are provided in [Table 10](#).

- 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 outlines variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.2. For a full listing of variables, refer to the corresponding statistical analysis plans.

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, risk factors for severe COVID-19, and medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include viral load (\log_{10} copies/mL), number of patients with a COVID-19-related medically-attended visit, number of patients admitted to a hospital, ICU, or outpatient telemedicine visit, and number of patients requiring mechanical ventilation.

5.3. Safety Variables

Safety variables include incidence of targeted TEAEs as described in Section 10.1.1.

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933 and REGN10987 in serum and time and select PK parameters. For phase 2 and phase 3, the variables are the concentration of REGN10933 and REGN10987 in serum and time. Samples will be collected at the visits specified in the relevant schedule of events.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb positivity (yes/no), and time point/visit. Samples will be collected at the visits specified in the relevant schedule of events.

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory endpoint variables may include, but not be limited to, parameters reported in complete blood counts with differential, levels of D-dimer, ferritin, CRP, LDH, cardiac biomarkers, per-symptom SE-C19 score, PGIS score, PGIC score, and other 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 is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with COVID-19, including (in phase 2) asymptomatic patients with SARS-CoV-2 infection. The study will be conducted in approximately 120 sites, in the US and other countries. To be eligible, patients must have laboratory-confirmed SARS-CoV-2 but must not have been previously hospitalized for COVID-19 or currently hospitalized for any reason. In phase 1, only patients with COVID-19 symptoms will be enrolled. In phase 2, symptomatic patients and asymptomatic patients will be enrolled into separate cohorts. In phase 3, symptomatic patients who are ≥ 18 years old and < 18 years old, and not pregnant at randomization, will be enrolled in two separate cohorts. Patients who are pregnant at randomization, regardless of age, will be enrolled in a third cohort (refer to Section 7.2 for study inclusion and exclusion criteria).

The schedules of events can be found in Section 9.1. Study design figures are provided in Section 6.1.4. Additional information on study procedures can be found in Section 9.2.

6.1.1. Phase 1

Note: As of protocol amendment 6, phase 1 has been completed and is closed.

On day 1, eligible patients will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (2400 mg), REGN10933+REGN10987 (8000 mg), or placebo. Patients will also have NP swab, nasal swab, and saliva samples taken and have blood drawn for safety, PK, ADA, and exploratory analyses.

Patients in the phase 1 sentinel safety group (Section 3.2.1.1) will be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for TEAEs (grade 3 or 4), treatment-emergent SAEs, and treatment-emergent AESIs (Section 10). This sequester period is mandatory. These patients will then have the option to leave their sequester on day 3 (if medically appropriate) after completing day 3 assessments. Alternatively, patients may choose to remain sequestered for any additional period of time up to day 7. After completing assessments on day 7, all patients who are still sequestered will be sent home, if medically appropriate.

Patients who are not in the sentinel safety group will not have a mandatory sequestering period. However, they will have the option to be sequestered for any period of time up to day 7. After completing assessments on day 7, all patients who are still sequestered will be sent home, if medically appropriate.

Since patients will be sequestered and/or home for the duration of the study, assessments and sample collections may occur through a variety of in-person and remote methods. This may include (but is not limited to) visits at the study site or place of infusion, visits at the place of sequester, home-based visits (defined as visits by home health staff, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study personnel only at study locations where appropriate personal protective equipment (PPE) can be used.

NP swabs, nasal swabs, and saliva samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Patients will also have blood drawn during a subset of these visits.

Information regarding SAEs, AESIs, and medically-attended related due to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

The study will end on day 29, when patients will have final assessments including NP swab, nasal swab, and saliva sample collections and blood draws for PK, ADA, and exploratory analyses.

6.1.2. Phase 2

Note: As of protocol amendment 6, phase 2 has been completed and is closed.

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).

On day 1, eligible patients will be randomized 1:1:1 to a single dose of REGN10933+REGN10987 (2400 mg), REGN10933+REGN10987 (8000 mg), or placebo. Patients will also have NP swabs taken and blood drawn for safety, PK, ADA, and exploratory analyses.

Patients will not be sequestered during phase 2. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home (if medically appropriate).

Since patients will be at home, subsequent assessments and sample collections will potentially occur through a variety of in-person and remote methods as described in phase 1. NP swabs will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Blood samples will also be collected periodically.

Information regarding treatment-emergent SAEs, treatment-emergent AESIs, and medically-attended visits related to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

On day 29, patients will have final assessments including NP swab collection and blood draws for PK, ADA, and exploratory analysis.

All patients in phase 2, regardless of cohort, will follow the same schedule of events.

6.1.3. Phase 3

In phase 3, eligible patients in cohort 1 and cohort 2 were initially randomized 1:1:1 to a single dose of placebo or one of two dose levels of REGN10933+REGN10987. In cohort 1, REGN10933+REGN10987 dose levels consisted of 1200 mg and 2400 mg. In cohort 2, body-

weight equivalents of these two dose levels were used. Patients in cohort 3 were initially randomized 1:1 to one of two dose levels of REGN10933+REGN10987 (ie, no randomization to placebo), at 1200 mg and 2400 mg or body-weight equivalents as applicable.

Note that as of 25 February 2021 (per IDMC recommendation and subsequently formalized in protocol amendment 8), patients are no longer randomized to placebo (Section 8.5.1). On 14 May 2021, enrollment in cohort 1 was closed. As of protocol amendment 10 US, the 2400 mg dose level was dropped in Cohort 2 and Cohort 3, such that Cohort 2 and Cohort 3 patients are only assigned to the 1200 mg dose level (or body-weight equivalent for those under 18 years of age).

On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and exploratory analyses. After infusion, patients will be monitored for at least 1 hour and released from the study site, if medically appropriate. Patients <12 years of age will be monitored for at least 2 hours after infusion, with more frequent vital sign assessments (refer to schedules of events for more information).

Targeted safety information (Section 10.1.1) and COVID-19-related medically-attended visit details (Section 9.2.3.2) will be collected on an ongoing basis; minimally, patients (or their caregivers) will be queried during weekly phone visits through the first 29 days of the study. For patients <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information; these patients (or their caregivers) should be instructed to contact the site within 24 hours post-infusion if they experience any side effects. Patients (or their caregivers) will also be asked to notify study personnel as soon as possible about any unplanned medically-attended visits that occur during the study.

Assessments and sample collections may potentially occur through a variety of in-person and remote methods. This may include (but is not limited to) visits at the study site or place of infusion, home-based visits (defined as visits by home health staff, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study personnel only at study locations where appropriate PPE can be used.

Patients enrolled in cohort 1 will follow the schedule events in Table 5. These patients will have NP swabs and blood samples collected approximately every week through day 29 and will provide self-reported information about COVID-19 symptoms through electronic surveys (both daily and weekly). A subset of patients in cohort 1 will be enrolled in a PK sub-study (Section 9.2.8). Patients in cohort 1 may also be enrolled in an optional immunoprofiling sub-study (Section 9.2.13) assessing the potential impact of REGN10933+REGN10987 on the endogenous immune response to SARS-CoV-2.

Patients enrolled in cohort 2 will follow the schedule events in Table 8. These patients will also have NP swabs and blood samples collected approximately every week through day 29, with an NP swab additionally collected on day 3. To reduce overall patient burden of blood sampling in this younger cohort, the frequency of blood sample collection and the total amount of blood collected per visit will vary according to body weight. In addition, patients in this cohort will be randomly assigned to one of four staggered PK-ADA sampling schedules. This will be done according to a central randomization scheme using an interactive web response system (IWRS).

Patients enrolled in cohort 3 who are ≥ 18 years of age will follow the schedule of events in Table 7; those <18 will follow the schedule of events in Table 8.

After the final in-person visit, all cohorts will have 2 follow-up phone calls to collect safety information, including (when applicable) additional information regarding pregnancy outcome (Section 9.2.5).

6.1.3.1. Enrollment of Phase 3 Participants Prior to Phase 3 Adaptations

Note that a subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. Patients enrolled prior to protocol amendment 6 followed the schedule of events in Table 4, which included a more intensive regimen of NP swab sample collection. These patients will be re-consented and will follow the phase 3 schedule of events in Table 5 beginning at the point at which they re-consent. Data from these patients may be subject to modified and/or additional analyses, contingent upon sample collection frequency, eligibility with inclusion/exclusion criteria adaptation, and other parameters. Additional information will be provided in the statistical analysis plan.

6.1.3.2. Evaluation of Long COVID in Phase 3

As part of protocol amendment 9 US, an additional series of assessments and sample collections will be performed in cohort 1 to better understand the biology of long COVID and the potential impact of prior REGN10933+REGN10987 treatment (during the acute phase of SARS-CoV-2 infection) on the development of long COVID symptoms. These analyses will be exploratory in nature (Section 11.4.3.3).

Patients in phase 3 cohort 1 will follow the prior phase 3 Schedule of Events (Table 5) until day 90. They will then follow the long COVID Schedule of Events (Table 6) until day 169. Patients who re-consent after day 90 will enter the long COVID Schedule of Events on the corresponding day on which they provide consent.

Patients in cohort 1 will complete a series of health-related questionnaires, including the SE-LC19 developed by the Sponsor. These self-report questionnaires will be conducted on a daily basis in the week leading up to the day 120 visit, and in the week leading up to the day 169 visit (Table 6 and Figure 4). On day 120 and day 169, patients will complete several additional questionnaires, will have an NP swab sample collected for analysis of SARS-CoV-2 virology, and will have blood samples collected for research purposes related to long COVID.

In addition to these procedures, previously described assessments (separate from the long COVID portion of the study) will be performed at day 120 and day 169 safety assessments, and (for those who were enrolled in the PK sub-study) an additional blood draw will be collected at day 120 for analysis of drug concentration and immunogenicity. These assessments are separate from the long COVID portion of the study.

Additional information concerning the procedures to be performed is provided in Section 9.2.16. Rationale for the study is provided in Section 3.2.1.6 .

6.1.3.3. Sharing of Data Across Studies

For patients in this study who are also index cases of household contacts in the R10933-10987-COV-2069 prophylaxis study, data may be used from R10933-10987-COV-2067 as part of R10933-10987-COV-2069 analyses. The data may include treatment arm allocation, virologic and serologic data and treatment outcomes. This will facilitate, in R10933-10987-COV-2069,

assessing the potential impact of REGN10933+REGN10987 treatment of index cases on infection rates in household contacts.

6.1.4. Study Design Figures

Figure 2: Study Flow Diagram, Phase 1

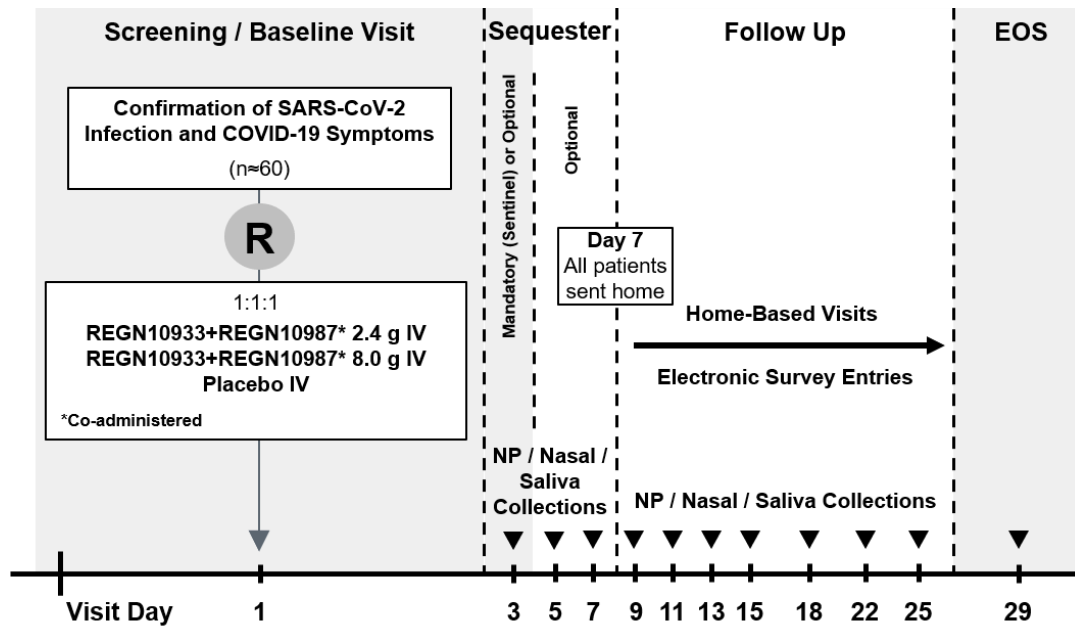


Figure 3: Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6)

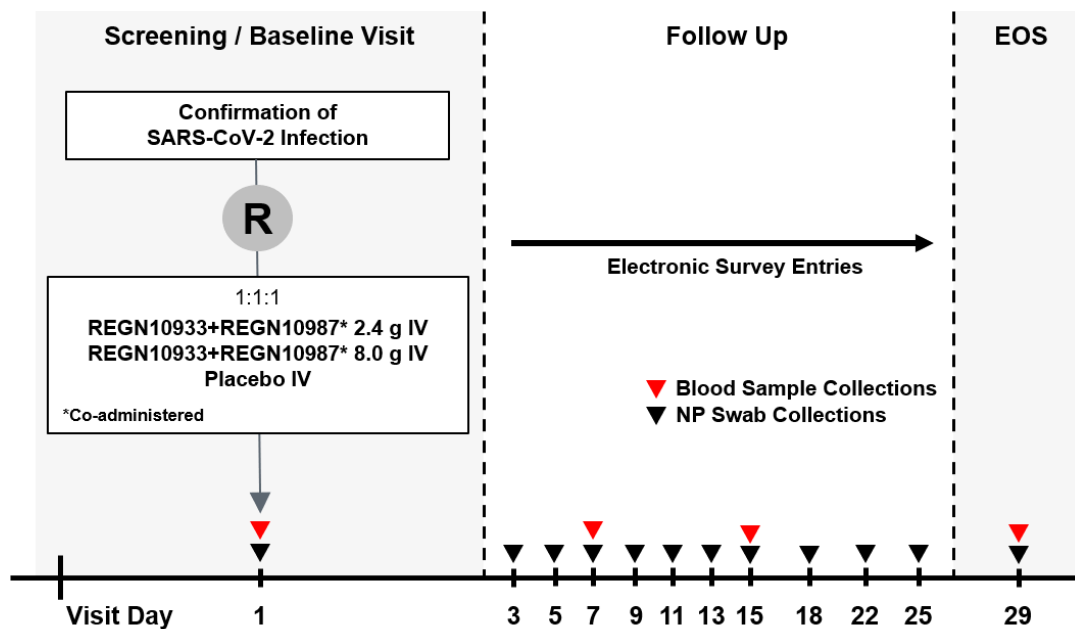


Figure 4: Study Flow Diagram, Phase 3 (Cohort 1)

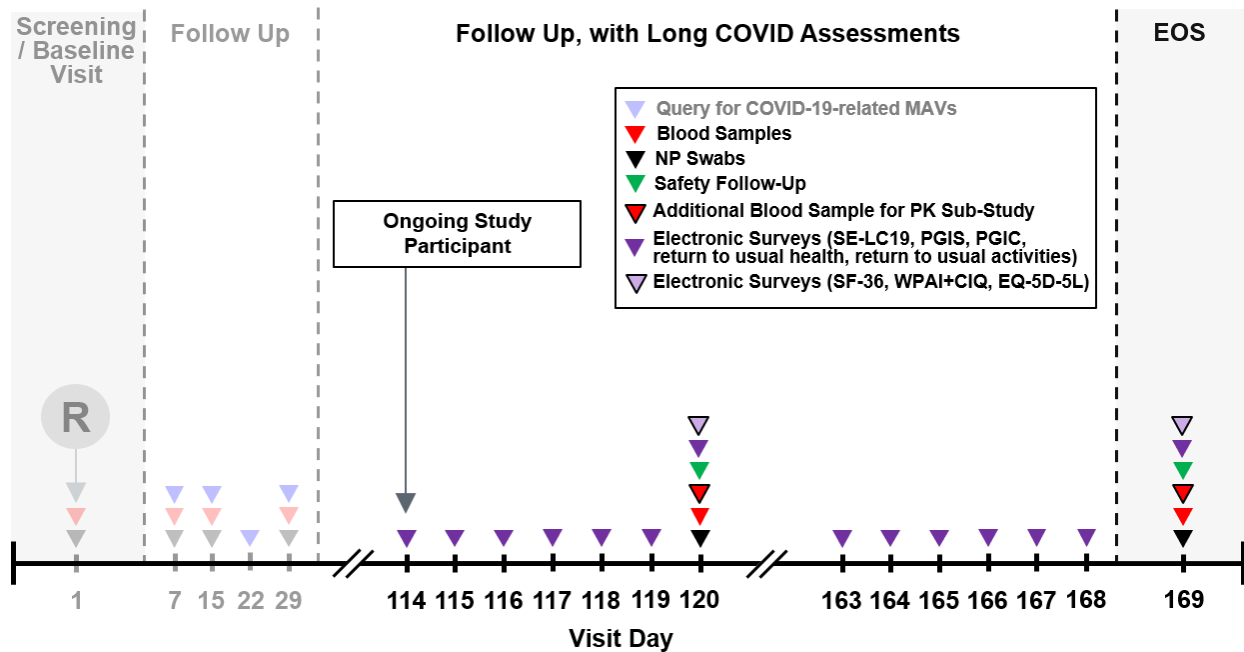


Figure 5: Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Prior to Amendment 10 US

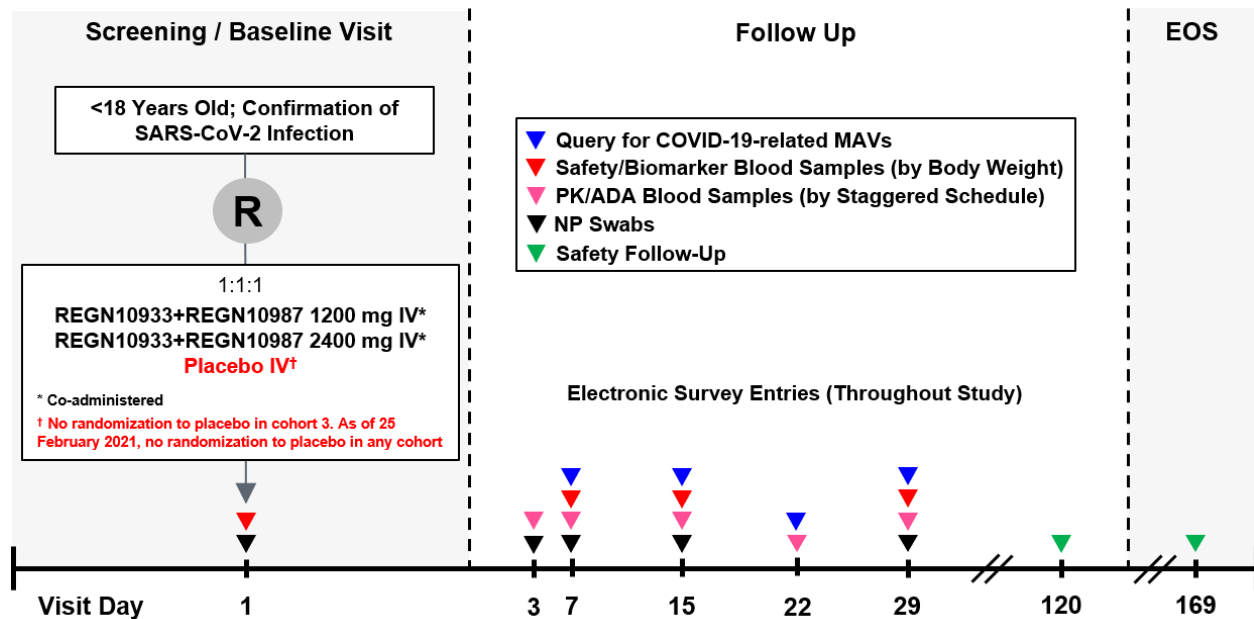


Figure 6: Study Flow Diagram, Phase 3 (Cohort 3 Patients ≥18 Years) Prior to Amendment 10 US

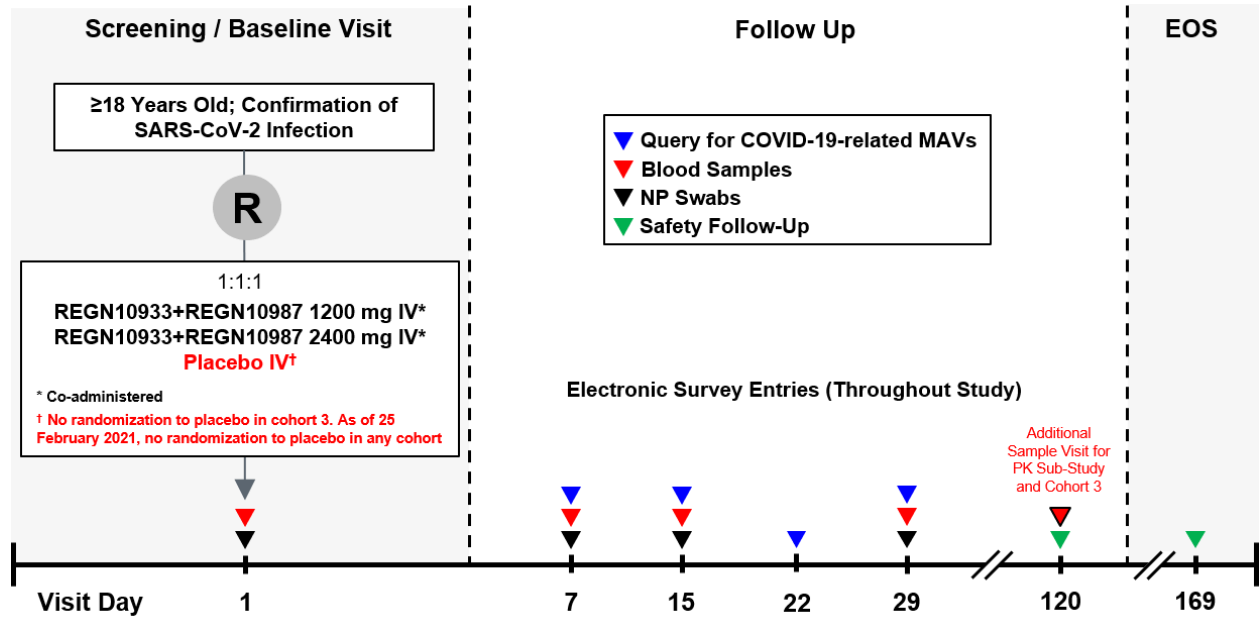


Figure 7: Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Amendment 10 US and Later

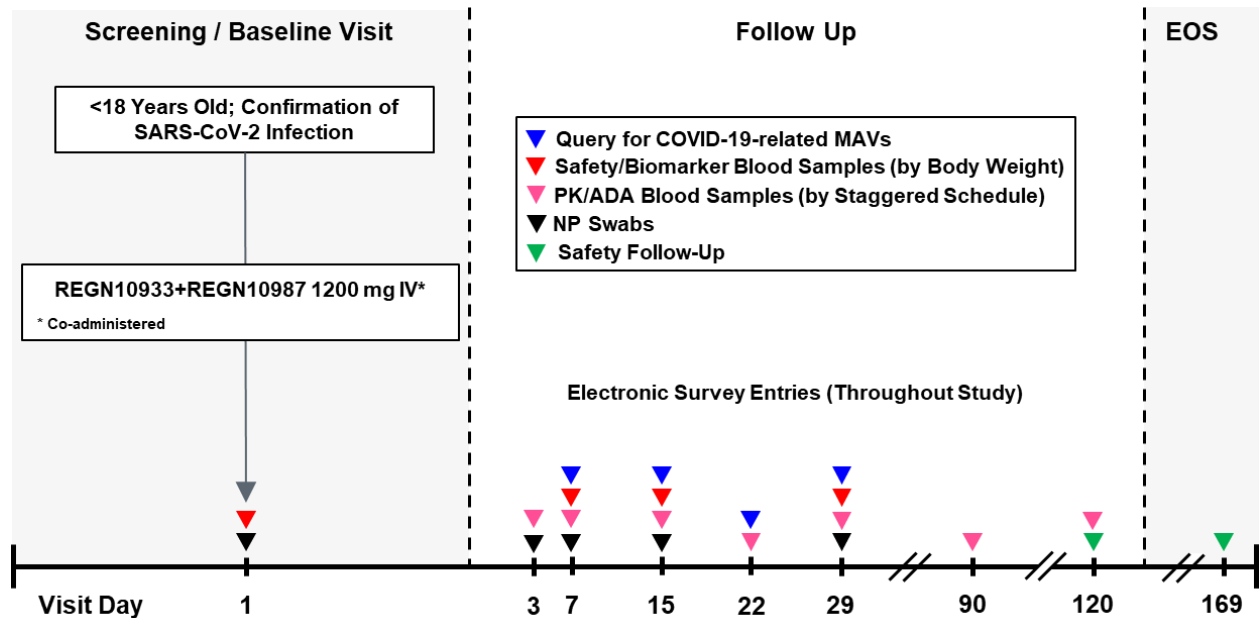
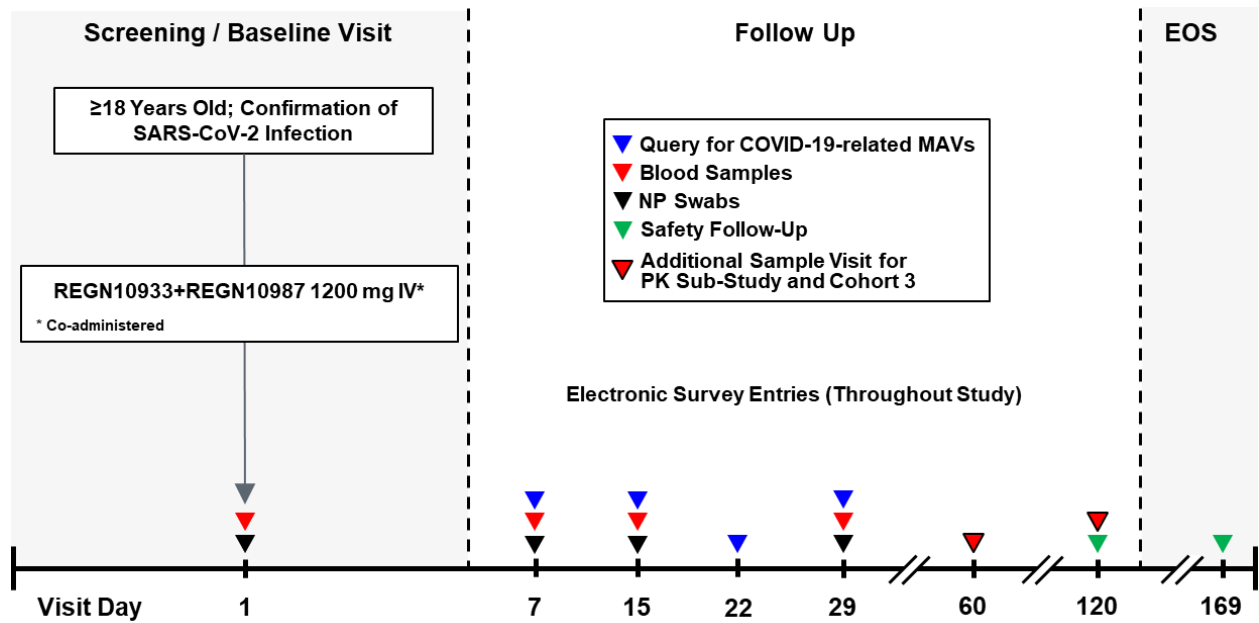


Figure 8: Study Flow Diagram, Phase 3 (Cohort 3 Patients ≥18 Years) Amendment 10 US and Later



6.1.5. Study Stopping Rules

6.1.5.1. 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.

6.1.5.2. Study Stopping Criteria

The Sponsor may decide to stop or make adaptations to the study based upon the recommendations by an IDMC recommendations 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

6.1.6. 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).

6.2. 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 through day 3 in the sentinel safety group as described in Section 3.2.1. 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 provided in Section 11.5, and blinding implications are discussed in Section 8.7.

Initial Phase 1/2

An interim descriptive analysis of first 275 symptomatic randomized patients was planned.

Phase 3

An interim analysis may be performed in phase 3. Refer to Section 11.4.4 and Section 11.5 for details regarding this analysis.

6.4. Periodic Data Reviews

Periodic reviews may be performed during phase 1 and phase 2 by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and in phase 2 may be used to determine study adaptations (eg, whether to drop a dose arm).

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Phase 1 will continue to enroll until approximately 100 patients are randomized. Phase 2 will continue to enroll until approximately 1300 patients are randomized.

It is estimated that up to approximately 8500 patients will be required for phase 3 cohort 1. For cohort 2, it is estimated that up to approximately 180 patients will be required. This will include minimum enrollment according to weight categories (refer to Section 8.6).

For information on the initial timing of enrollment for phase 1 and phase 2, refer to Section 3.2.1. For treatment allocation and randomization, refer to Section 8.6. Additional information on sample size can be found in Section 11.2.

7.2. Study Population

This study will enroll non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.

7.2.1. Inclusion Criteria

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

1. Meets 1 of the following 3 criteria:
 - a. **Cohort 1:** ≥ 18 years of age and not pregnant at randomization
 - b. **Cohort 2:** < 18 years of age and not pregnant at randomization
 - c. **Cohort 3:** Pregnant at randomization
Note: Cohort 2 and cohort 3 will only be enrolled where permitted by local requirements. Enrollment in cohort 1 was closed on 14 May 2021.
2. Has SARS-CoV-2-positive diagnostic test from a sample collected ≤ 72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva
Note: Historical record of positive result is acceptable, as long as the sample was collected ≤ 72 hours prior to randomization.
3. [Criterion removed]
4. Has symptoms consistent with COVID-19, as determined by the investigator, with onset ≤ 7 days before randomization
5. Maintains O₂ saturation $\geq 93\%$ on room air
6. Is willing and able to provide informed consent as below:
 - a. If at or above country's legal age of adulthood, signed by study patient or legally authorized representative
 - b. If below country's legal age of adulthood, signed by parent(s) or legal guardian(s).

Age-appropriate assent will be collected from the study patient according to local regulatory (competent authority/ethics) guidelines

7. Is willing and able to comply with study procedures
8. Is able to understand and complete study-related questionnaires (patients aged ≥ 12 years only)
9. **Cohort 1 and Cohort 2 only:** has ≥ 1 risk factor for severe COVID-19

Risk factors are defined as follows:

- a. Age ≥ 50 years (**cohort 1 only**)
- b. Obesity, defined as:
BMI ≥ 30 kg/m² (**cohort 1 only**)
BMI (kg/m²) ≥ 95 th percentile for age and sex based on CDC growth charts (**cohort 2 ≥ 2 years only**)
- c. Cardiovascular disease, including hypertension
- d. Chronic lung disease, including asthma
- e. Type 1 or type 2 diabetes mellitus
- f. Chronic kidney disease, including those on dialysis
- g. Chronic liver disease
- h. *[Risk factor removed]*
- i. Immunosuppressed, based on investigator's assessment
Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications
- j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 (**cohort 2 only**)

7.2.2. Exclusion Criteria

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

1. Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
2. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening

4. *[Criterion consolidated with criterion #3]*

5. *[Criterion removed]*
6. Has known allergy or hypersensitivity to components of study drug
7. Has been discharged, or is planned to be discharged, to a quarantine center
8. *[Criterion removed]*
9. *[Criterion removed]*
10. Has a known positive SARS-CoV-2 serologic test
11. Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
12. Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test
13. Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for COVID-19
14. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
15. Is a member of the clinical site study team or their immediate family member

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 follow up contact, as described in Section 1.

7.4. Replacement of Patients

In phase 1, patients who have missing or negative baseline virologic sample(s) or are missing ≥ 1 follow-up virologic sample(s) may be replaced. Patients prematurely discontinued from the 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 dose levels and method of treatment allocation for each phase of the study.

- Co-administered REGN10933+REGN10987 combination therapy
- Placebo IV single dose

8.2. Background Treatment

No background treatment will be allowed. Patients may self-administer non-prescribed medications (eg, antipyretics).

8.3. Rescue Treatment(s)

Patients can receive rescue therapy for 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

8.4.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.4.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

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 10.2.5) 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 AEs 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 AEs 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 one 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

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

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 1, randomization will not be stratified.

Phase 2 (and Phase 3 Prior to Protocol Amendment 6)

Patients will be randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 2, randomization will be stratified by:

- Presence/absence of COVID-19 symptoms (ie, symptomatic versus asymptomatic cohort)
- Country
- Risk factors for hospitalization due to COVID-19 (no risk factors for hospitalization due to COVID 19 versus ≥ 1 risk factor for hospitalization due to COVID-19)

The following are considered risk factors for the purposes of stratification (for rationale, refer to Section 3.2.1.5):

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

Phase 3**Cohort 1 (Prior to 25 February 2021)**

Patients in cohort 1 who are enrolled into phase 3 under protocol amendment 6 or 7 will be randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 3 cohort 1, Randomization will be stratified by country.

Cohort 1 (25 February 2021 and Later)*

Patients in cohort 1 who are enrolled into phase 3 under protocol amendment 8 or later will be randomized in a 1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose

In phase 3 cohort 1, randomization will be stratified by country.

Cohort 2 (Prior to 25 February 2021)

Patients in cohort 2 will be randomized in a 1:1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy, IV single dose at 1200 mg (or body weight equivalent), 2400 mg (or body weight equivalent), or placebo. The REGN10933+REGN10987 dose level will be adjusted according to body weight as defined in [Table 2](#).

In phase 3 cohort 2, randomization will be stratified by country.

Table 2: REGN10933+REGN10987 IV Doses for Each Weight Group, Phase 3 Cohort 2 (Ages 0 to <18 Years)

Body Weight Group	Dose Equivalent for REGN10933+REGN10987 1200 mg IV Dose (600 mg per mAb)	Dose Equivalent for REGN10933+REGN10987 2400 mg IV Dose (1200 mg per mAb)
≥40 kg	1200 mg (600 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to <40 kg	450 mg (225 mg per mAb)	900 mg (450 mg per mAb)
≥10 kg to <20 kg	224 mg (112 mg per mAb)	450 mg (225 mg per mAb)
≥5 kg to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg to <5 kg	60 mg (30 mg per mAb)	120 mg (60 mg per mAb)
<2.5 kg	30 mg (15 mg per mAb)	60 mg (30 mg per mAb)

Cohort 2 (25 February 2021 and Later)*

Patients in cohort 2 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy, IV single dose at 1200 mg (or body weight equivalent) or 2400 mg (or body weight equivalent). The REGN10933+REGN10987 treatment arms will be adjusted according to body weight as defined in [Table 2](#).

In phase 3 cohort 2, randomization will be stratified by country.

Cohort 3*

Patients in cohort 3 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy IV single dose (no placebo). Patients in cohort 3 who are ≥ 18 years of age will follow the REGN10933+REGN10987 dose levels described for cohort 1 (1200 mg and 2400 mg). Patients in cohort 3 who are < 18 years of age will follow the adjusted REGN10933+REGN10987 dose levels described in [Table 2](#).

In phase 3 cohort 3, randomization will not be stratified.

***Cohort 1, Cohort 2, and Cohort 3 (Protocol Amendment 10 US and Later)**

As of protocol amendment 10 US, all newly-enrolled patients will receive REGN10933+REGN10987 combination therapy at the 1200 mg IV dose. Patients who are < 18 years of age will follow the body-weight adjusted equivalent of REGN10933+REGN10987 1200 mg dose level described in [Table 2](#).

8.7. Blinding

Note: As of protocol amendment 10 US, the study consists of a single arm and blinding is no longer applicable. Treatment assignment to patients enrolled under protocol amendment 10 US and later will be open-label. The information in this section applies only to patients enrolled prior to protocol amendment 10 US.

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

Note: As of protocol amendment 10 US, the study consists of a single arm and blinding is no longer applicable. The information in this section applies only to patients enrolled prior to protocol amendment 10 US.

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event 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

Note: As of protocol amendment 10 US, the study consists of a single arm and blinding is no longer applicable. The information in this section related to blinding applies only to patients enrolled prior to protocol amendment 10 US.

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 2°C to 8°C. 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 2°C to 8°C 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 or procedure administered from the first dose of study drug to the final study visit will be considered a concomitant medication or procedure. This includes medications and procedures that were started before the study and are ongoing during the study.

For more information on recording of concomitant medications and procedures, refer to Section [9.2.4.3](#).

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](#)) unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures.

Based on CDC guidance and investigator discretion, deferring the use of any authorized or approved COVID-19 vaccine for at least 90 days after dosing may be considered to reduce

potential interference of the study drug with vaccine-induced immune responses. For more information, refer to the current CDC guidance ([CDC, 2020a](#)).

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Table 3: Schedule of Events: Phase 1

Day	Screening/Baseline Visit ¹				Mandatory / Optional Sequester ²		Optional Sequester ²		Follow Up								EOS			
	-1 to 1				2	3	4	5	6	7	8 ³	9	11	13	15 ³	18		22 ³	25	29
	Screen	Pre-Dose	Dose	Post-Dose																
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Window (Days)											±1	±1	±1	±1	±1	±1	±1	±1	±3	
Screening/Baseline Only																				
Informed consent	X																			
PGx sub-study consent (optional) ⁴	X																			
Inclusion/exclusion	X																			
Molecular diagnostic test for SARS-CoV-2 ⁵	X																			
Demographics	X																			
Medical history (including COVID-19 illness)	X																			
Weight and height	X																			
Randomization		X																		
Treatment																				
Study drug administration			X																	
Efficacy																				
Medically-attended COVID-19 visit details										X				X		X		X		
Saliva sample for SARS-CoV-2 RT-qPCR		X				X		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	X	X	
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X	X	
Safety																				
Vital signs		X ⁶	X ⁶	X ⁶																
Treatment-emergent grade ≥2 IRRs ⁷		← continuous monitoring →																		
Treatment-emergent grade 3 or 4 AEs ⁷		← continuous monitoring →																		
Treatment-emergent SAEs ⁷		← continuous monitoring →																		
Treatment-emergent grade ≥2 hypersensitivity ⁷		← continuous monitoring →																		
Targeted concomitant medications ⁸	X		X	X	X	X	X	X	X	X	X				X		X		X	
Pregnancy test (WOCBP) ⁹	X																		X	
Central Laboratory Testing																				

Day	Screening/Baseline Visit ¹				Mandatory / Optional Sequester ²		Optional Sequester ²		Follow Up									EOS		
	-1 to 1				2	3	4	5	6	7	8 ³	9	11	13	15 ³	18	22 ³		25	29
	Screen	Pre-Dose	Dose	Post-Dose																
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Window (Days)											±1	±1	±1	±1	±1	±1	±1	±1	±3	
Hematology (including differential)	X ¹⁰									X										X
Blood chemistry (including AST, ALT, CRP ferritin, LDH)	X ¹⁰									X										X
Coagulation tests (D-dimer, PT/INR, aPTT)	X ¹⁰									X										X
Central PK and Immunogenicity Testing																				
Serum for PK ¹¹		X ¹²		X ¹²		X		X	X						X				X	
Serum for ADA ¹³		X ¹³																	X	
Central Biomarker Testing																				
Serum for serology		X				X			X										X	
Serum for cytokines		X				X			X										X	
Plasma for complement		X				X			X										X	
Serum for research		X				X			X										X	
Plasma for research		X				X			X										X	
Exploratory Patient-Reported Symptoms																				
SE-C19 ¹⁴		X		X							Daily									X
PGIS ¹⁴		X		X							Daily									X
PGIC ¹⁴																			X	
Pharmacogenomics (Optional Sub-Study)																				
Blood for DNA ⁴		X ⁴																		
Blood for RNA ⁴		X ⁴																		

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGIC, Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; PGx, pharmacogenomics; PK, pharmacokinetics; PT; prothrombin time; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

Table 4: Schedule of Events: Phase 2 (and Phase 3 Prior to Protocol Amendment 6)

Note: For more information on patients in phase 3 who initially enrolled prior to phase 3 adaptations, refer to Section 6.1.3.

Day	Screening/Baseline Visit ¹				Follow Up													EOS	
	-1 to 1				2	3	4	5	7	8 ³	9	11	13	15 ³	18	22 ³	25		29
	Screen	Pre-Dose	Dose	Post-Dose															
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Window (Days)	X								±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	
Screening/Baseline Only																			
Informed consent	X																		
PGx sub-study consent (optional) ⁴	X																		
Inclusion/exclusion	X																		
Antigen or molecular diagnostic test for SARS-CoV-2 ⁵	X																		
Demographics	X																		
Medical history (including COVID-19 illness)	X																		
Weight and height	X																		
Randomization		X																	
Treatment																			
Study drug administration			X																
Efficacy																			
Medically-attended COVID-19 visit details									X				X		X			X	
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X	
Safety																			
Vital signs		X ⁶		X ⁶															
Treatment-emergent grade ≥2 IRRs ⁷			← continuous monitoring →																
Treatment-emergent SAEs ⁷			← continuous monitoring →																
Treatment-emergent grade ≥2 hypersensitivity ⁷			← continuous monitoring →																
Targeted concomitant medications ⁸	X		← continuous monitoring →																
Pregnancy test (WOCBP) ⁹	X																	X	
Central Laboratory Testing																			
Hematology (including differential)	X ¹⁰							X					X					X	

Day	Screening/Baseline Visit ¹				Follow Up													EOS	
	-1 to 1				2	3	4	5	7	8 ³	9	11	13	15 ³	18	22 ³	25		29
	Screen	Pre-Dose	Dose	Post-Dose															
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Window (Days)	X								±1	±1	±1	±1	±1	±1	±1	±1	±1	±3	
Blood chemistry (including AST, ALT, CRP ferritin, LDH)	X ¹⁰							X					X					X	
Coagulation tests (D-dimer, PT/INR, aPTT)	X ¹⁰							X					X					X	
Central PK and Immunogenicity Testing																			
Serum for PK ¹¹		X ¹²		X ¹²														X	
Serum for ADA ¹³		X ¹³																X	
Central Biomarker Testing																			
Serum for serology		X																X	
Serum for cytokines and CK-MB		X						X					X					X	
Serum for research and cardiac biomarkers		X						X					X					X	
Plasma for research and cardiac biomarkers		X						X					X					X	
Plasma for hsTroponin-T ¹⁴		X						X					X					X	
Exploratory Patient-reported Symptoms																			
SE-C19 ¹⁴		X																	Daily
PGIS ¹⁴		X																	Daily
PGIC ¹⁴																			X
Pharmacogenomics (Optional Sub-Study)																			
Blood for DNA ⁴		X ⁴																	
Blood for RNA ⁴		X ⁴																	

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CK-MB, creatine kinase-MB, CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGIC, Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; PT, prothrombin time; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

Table 5: Schedule of Events: Phase 3 (Cohort 1 Patients)

Day	Screening/Baseline Visit ¹				Follow Up ³								
	-1 to 1				2	3	4	7	15	22	29	60	90
	Screen	Pre-Dose	Dose	Post-Dose									
Visit Number	1				2	3	4	5	6	7	8	9	10
Window (Days)								±1	±3	±3	±3	±3	±3
Screening/Baseline Only													
Informed consent	X												
PGx sub-study consent (optional) ⁴	X												
Immunoprofiling sub-study consent (optional) ⁴	X												
Inclusion/exclusion	X												
Antigen or molecular diagnostic test for SARS-CoV-2 ⁵	X												
Demographics	X												
Medical history (including COVID-19 illness, risk factors)	X												
Weight and height	X												
Randomization (treatment assignment)		X											
Treatment													
Study drug administration			X										
Efficacy													
Query for COVID-19-related medically-attended visit details							X	X	X	X			
NP swab for SARS-CoV-2 RT-qPCR		X					X	X		X			
Safety													
Vital signs		X ⁶		X ⁶									
Treatment-emergent grade ≥2 IRRs ^{7,8}			X	X	← cont. mon. →								
TEAEs that led to <i>any</i> medically-attended visit ^{7,8}				X	← continuous monitoring →								
Treatment-emergent grade ≥2 hypersensitivity ^{7,8}			X	X	← continuous monitoring →								
Treatment-emergent SAEs ^{7,8,16}			X	X	← continuous monitoring →								
Targeted concomitant medications ^{7,8}	X		X	X	← continuous monitoring →								
Concomitant procedures ^{7,8}	X		X	X	← continuous monitoring →								
Vital status ¹⁶													
Pregnancy test (women of childbearing potential) ⁹	X												
Pregnancy status ¹⁶													
Safety information (newborns of study participants) ¹⁶													
Central Laboratory Safety Testing													
Hematology (including differential)	X ¹⁰						X	X		X			
Blood chemistry (including AST, ALT, CRP, LDH)	X ¹⁰						X	X		X			
Coagulation tests (D-dimer, PT/INR, aPTT)	X ¹⁰						X	X		X			

Day	Screening/Baseline Visit ¹				Follow Up ³									
	-1 to 1				2	3	4	7	15	22	29	60	90	
	Screen	Pre-Dose	Dose	Post-Dose										
Visit Number	1				2	3	4	5	6	7	8	9	10	
Window (Days)								±1	±3	±3	±3	±3	±3	
Central Laboratory Immunogenicity Testing (Not Enrolled in PK Sub-Study)														
Serum for ADA ¹³	X ¹³										X			
Central Laboratory Drug Concentration and Immunogenicity Testing (Enrolled in PK Sub-Study)														
Serum for drug concentration (PK) ¹²	X ^{10,12}										X ¹²			
Serum for ADA ¹³	X ¹³										X ¹³			
Central Laboratory Biomarker Testing														
Serum for serology	X ¹⁰										X			
Serum for research	X ¹⁰						X	X			X			
Plasma for research	X ¹⁰						X	X			X			
Exploratory Patient-reported Outcomes														
SE-C19 ¹⁴		X			Daily									
PGIS ¹⁴		X			Daily									
PGIC ¹⁴											X			
Item: return to usual health ¹⁴		X			Daily									
Item: return to usual activities ¹⁴		X			Daily									
EQ-5D-5L ¹⁴		X			Daily						X ¹⁴	X ¹⁴		
WPAI+CIQ ¹⁴							X	X	X	X				
SARS-CoV-2 Reinfection														
Details of positive SARS-CoV-2 local test result ²²													cont. mon. ²² →	
Immunoprofiling (Optional Sub-Study)														
Blood for PBMCs		X									X			
Pharmacogenomics (Optional Sub-Study)														
Blood for DNA ⁴		X ⁴												
Blood for RNA ⁴		X ⁴												

ADA, anti-drug antibodies; AE, adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

Table 6: Schedule of Events: Phase 3, Assessment of Long COVID (Cohort 1 Patients)

Day	Follow Up, with Long COVID Assessments ³													EOS
	114	115	116	117	118	119	120	163	164	165	166	167	168	169
Visit Number	-	-	-	-	-	-	11	-	-	-	-	-	-	12
Window (Days)	-	-	-	-	-	-	+7 or ±7 ¹⁹	-	-	-	-	-	-	+7 or ±7 ¹⁹
Questionnaires²⁰														
SE-LC19 ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIS ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC ¹⁴														X
Return to usual health ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Return to usual activities ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36 ¹⁴							X							X
WPAI+CIQ ¹⁴							X							X
EQ-5D-5L ¹⁴							X							X
Safety														
Treatment-emergent SAEs	← continuous monitoring ⁸ →													
Targeted concomitant medications	← continuous monitoring ⁸ →													
Concomitant procedures	← continuous monitoring ⁸ →													
Hematology (including differential)							X							X
Blood chemistry							X							X
Vital status ¹⁶							X							X
Pregnancy status ¹⁶							X							X
Safety information (newborns of study participants)							X							X
Sample Collections														
NP swab for SARS-CoV-2 RT-qPCR							X							X
Blood for PBMCs ²¹							X							X
Serum for exploratory long COVID research (SARS-CoV-2 serology, proteomics, and other research)							X							X
Plasma for exploratory long COVID research							X							X
Central Laboratory Drug Concentration and Immunogenicity Testing (Enrolled in PK Sub-Study; Not Related to Long COVID Analysis)														
Serum for drug concentration (PK)							X ¹²							
Serum for ADA							X ¹³							
Additional Adverse Events of Special Interest														
Details of positive SARS-CoV-2 local test result ²²	continuous monitoring from the day of consent to protocol amendment 9 US ²² →													
New medical diagnoses or conditions ²⁴							X							X
Pharmacogenomics (Optional Sub-Study)														
Blood for DNA ²³							X							

ADA, anti-drug antibodies; EOS, end of study; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; PK, pharmacokinetics; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

Table 7: Schedule of Events: Phase 3 (Cohort 3 ≥18 Years)

Day	Screening/Baseline Visit ¹				Follow Up ³								EOS		
	-1 to 1				2	3	4	7	15	22	29	60	90	120 ¹⁸	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7 ¹²	±7
Screening/Baseline Only															
Informed consent	X														
PGx sub-study consent (optional) ⁴	X														
Immunoprofiling sub-study consent (optional) ⁴	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2 ⁵	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details							X	X	X	X					
NP swab for SARS-CoV-2 RT-qPCR		X					X	X		X					
Safety															
Vital signs		X ⁶		X ⁶											
Treatment-emergent grade ≥2 IRRs ^{7,8}			X	X	← cont. mon. →										
TEAEs that led to <i>any</i> medically-attended visit ^{7,8}				X	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity ^{7,8}			X	X	← continuous monitoring →										
Treatment-emergent SAEs ^{7,8,16}			X	X	← continuous monitoring →										
Targeted concomitant medications ^{7, 8}	X		X	X	← continuous monitoring →										
Concomitant procedures ^{7,8}	X		X	X	← continuous monitoring →										
Vital status ¹⁶													X	X	
Pregnancy test (women of childbearing potential) ⁹	X														
Pregnancy status ¹⁶													X	X	
Safety information (newborns of study participants) ¹⁶													X	X	
Central Laboratory Safety Testing															
Hematology (including differential)		X ¹⁰					X	X		X					

Day	Screening/Baseline Visit ¹				Follow Up ³									EOS 169	
	-1 to 1				2	3	4	7	15	22	29	60	90		120 ¹⁸
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7 ¹²	±7
Blood chemistry (including AST, ALT, CRP, LDH)	X ¹⁰							X	X		X				
Coagulation tests (D-dimer, PT/INR, aPTT)	X ¹⁰							X	X		X				
Central Laboratory Drug Concentration and Immunogenicity Testing															
Serum for drug concentration (PK) ¹²	X ^{10,12}										X ¹²	X ¹²		X ¹²	
Serum for ADA ¹³	X ¹³										X ¹³			X ¹³	
Central Laboratory Biomarker Testing															
Serum for serology	X ¹⁰										X				
Serum for research	X ¹⁰							X	X		X				
Plasma for research	X ¹⁰							X	X		X				
Exploratory Patient-reported Outcomes															
SE-C19 ¹⁴		X			Daily										
PGIS ¹⁴		X			Daily										
PGIC ¹⁴											X				
Item: return to usual health ¹⁴		X			Daily										
Item: return to usual activities ¹⁴		X			Daily										
EQ-5D-5L ¹⁴		X			Daily						X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	
WPAI+CIQ ¹⁴		X					X	X	X	X					
Immunoprofiling (Optional Sub-Study)															
Blood for PBMCs		X									X				
Pharmacogenomics (Optional Sub-Study)															
Blood for DNA ⁴		X ⁴													
Blood for RNA ⁴		X ⁴													

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

Table 8: Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)

Day	Screening/Baseline Visit ¹				Follow Up ³									EOS	
	-1 to 1				2	3	4	7	15	22	29	60	90	120 ¹⁸	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7	±7
Screening/Baseline Only															
Parental informed consent and informed assent	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2 ⁵	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Randomization (PK-ADA schedule assignment) ¹⁵		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details		X					X	X	X	X					
NP swab for SARS-CoV-2 RT-qPCR		X				X	X	X							
Safety															
Vital signs (≥12 years)		X ⁶		X ⁶											
Vital signs (<12 years)		X ⁶	X ⁶	X ⁶											
Treatment-emergent grade ≥2 IRRs ^{7,8}			X	X ¹⁷	← cont. mon. →										
TEAEs that led to <i>any</i> medically-attended visit ^{7, 8}				X ¹⁷	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity ^{7, 8}			X	X ¹⁷	← continuous monitoring →										
Treatment-emergent grade 3 or 4 AEs ⁸			X	X ¹⁷	← continuous monitoring →										
Treatment-emergent SAEs ^{7, 8,16}			X	X ¹⁷	← continuous monitoring →										
Targeted concomitant medications ^{7,8}	X		X	X ¹⁷	← continuous monitoring →										
Concomitant procedures ^{7,8}	X		X	X ¹⁷	← continuous monitoring →										
Vital status ¹⁶													X	X	
Pregnancy test (women of childbearing potential) ⁹	X														
Pregnancy status ¹⁶													X	X	

Day	Screening/Baseline Visit ¹				Follow Up ³									EOS			
	-1 to 1				2	3	4	7	15	22	29	60	90	120 ¹⁸	169		
	Screen	Pre-Dose	Dose	Post-Dose													
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12		
Window (Days)								±1	±3	±3	±3	±3	±3	±7	±7		
Safety information (newborns of study participants) ¹⁶														X	X		
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥20 kg																	
Hematology (including differential)	X ¹⁰						X	X		X							
Blood chemistry (including AST, ALT, CRP, LDH)	X ¹⁰						X	X		X							
Serum for serology	X ¹⁰									X							
Serum for exploratory research	X ¹⁰						X	X		X							
Plasma for exploratory research	X ¹⁰						X	X		X							
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥10 kg to <20 kg																	
Hematology (including differential)	X ¹⁰						X	X		X							
Blood chemistry (including AST, ALT, CRP, LDH)	X ¹⁰						X	X		X							
Serum for serology	X ¹⁰									X							
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight <10 kg																	
Hematology (including differential)	X ¹⁰						X			X							
Blood chemistry (including AST, ALT, CRP, LDH)	X ¹⁰						X			X							
Serum for serology	X ¹⁰																
Central Laboratory Drug Concentration and Immunogenicity Testing (All Body Weight Tiers)																	
Serum for PK-ADA (Schedule A) ¹⁵	X ^{10,12}		X ¹²		X ¹²					X ¹²		X ¹²					
Serum for PK-ADA (Schedule B) ¹⁵	X ^{10,12}		X ¹²				X ¹²			X ¹²		X ¹²					
Serum for PK-ADA (Schedule C) ¹⁵	X ^{10,12}		X ¹²					X ¹²		X ¹²				X ¹²			
Serum for PK-ADA (Schedule D) ¹⁵	X ^{10,12}		X ¹²						X ¹²	X ¹²				X ¹²			
Exploratory Patient-reported Outcomes (Age ≥12 Years Only)¹⁴																	
SE-C19 ¹⁴		X			Daily												
PGIS ¹⁴		X			Daily												
PGIC ¹⁴											X						
Item: return to usual health ¹⁴		X			Daily												
Item: return to usual activities ¹⁴		X			Daily												
EQ-5D-Y ¹⁴		X			Daily									X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴
WPAI+CIQ ¹⁴		X					X	X	X	X							

Day	Screening/Baseline Visit ¹				Follow Up ³									EOS	
	-1 to 1				2	3	4	7	15	22	29	60	90		120 ¹⁸
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±3	±7

ADA, anti-drug antibodies; AE, adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

9.1.1. Footnotes for the Schedule of Events Tables

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. [Phase 1 footnote removed]
3. On visit days where in-person sample collections or assessments are not required, information may be collected by phone.
4. Patients (cohort 1; cohort 3 \geq 18 years old) must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for RNA may be collected at day -1 or day 1 (ie, screening or pre-dose) but must be collected prior to randomization. Blood sample for DNA should be collected at the day -1 or day 1 visit but may be collected at any visit. Refer to Section 9.2.14 for more information about the PGx sub-study.

Patients (cohort 1; cohort 3 \geq 18 years old) must provide separate consent to collect blood samples as part of the optional peripheral blood mononuclear cell (PBMC) sub-study. Blood samples for PBMCs must be collected at the visits indicated. Refer to Section 9.2.13 for more information about this sub-study.

5. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
6. Vital signs, including temperature, blood pressure, heart rate, and SpO₂ will be collected as described in Section 9.2.4.1.

For **patients in cohort 1 and patients \geq 12 years in cohort 2 and cohort 3**, vital signs will be taken once before the infusion and once after the infusion is completed. After infusion of study drug, these patients will be observed for at least 1 hour.

For **patients <12 years in cohort 2 and cohort 3**, vital signs will be taken before infusion, approximately every 30 minutes during the infusion, after the infusion is completed, approximately 1-hour post-infusion, and approximately 2 hours post-infusion. After infusion of study drug, these patients will be observed for at least 2 hours.

7. Treatment-emergent AESIs (grade \geq 2 IRRs, grade \geq 2 hypersensitivity, and TEAEs associated with **any** medically-attended visit) and treatment-emergent SAEs will be recorded until day 29. From day 30 to day 169, only treatment-emergent SAEs will be recorded. **For patients in cohort 2 and patients <18 years in cohort 3**, treatment-emergent grade 3 or 4 AEs will also be recorded until day 29. Refer to Section 10 for more information on reporting and recording requirements.

Targeted concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.4.3 for more information.

8. Continuously-monitored events will be recorded when they occur during the corresponding time period marked on the schedule of events. Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.
9. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only and regardless of pregnancy status. A negative test is **not required** prior to study drug

administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.6 for more information, including a definition of WOCBP.

Note that a paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.

10. The indicated blood samples may be collected at the either day -1 or day 1 (ie, screening or pre-dose), but must be collected prior to randomization. For patients in phase 3 cohort 2, efforts should be made to collect all screening/pre-dose blood samples on the same study visit, when feasible.
11. [Footnote removed]
12. Actual dosing time and drug concentration sample collection times, as applicable, will be recorded.

At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing 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.

In cohort 1 and cohort 3 (≥ 18 years old), patients will follow different blood sample collection schedules for drug concentration and immunogenicity depending on whether they enrolled in the PK sub-study (cohort 1), not enrolled in the PK sub-study (cohort 1), or are pregnant at randomization (cohort 3 patients ≥ 18 years old). For samples collected on day 120, the collection window is ± 28 days. Refer to Section 9.2.8 for more information on the PK sub-study.

13. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times, as applicable, will be recorded.
14. 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 provided below. On days when a questionnaire is not required it will be skipped, but the overall order will remain the same. Refer to Section 9.2 for additional information regarding these questionnaires.

Cohort 1: SE-LC19, PGIS, PGIC, return to usual health, return to usual activities, SF-36, WPAI+CIQ, EQ-5D-5L.

Cohort 2 (≥ 12 years): SE-C19, PGIS, PGIC, return to usual health, return to usual activities, EQ-5D-Y, WPAI+CIQ.

Cohort 3 (≥ 12 years): SE-C19, PGIS, PGIC, return to usual health, return to usual activities, EQ-5D-5L (or EQ-5D-Y), WPAI+CIQ.

On days 60 and 90, the window for questionnaire assessment is ± 3 days. On days 120 and 169, the window for questionnaire assessment is ± 7 days. Study visits are not required on days when only questionnaires are collected.

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.

15. In **cohort 2 (and patients <18 years in cohort 3)**, each patient will be assigned at randomization by IWRS to a blood sample collection schedule for drug concentration and immunogenicity analysis. Actual dosing time and PK-ADA sample collection times will be recorded. To conserve blood volume, a single blood draw for drug concentration and immunogenicity will be obtained. In patients <12 years, immunogenicity will be analyzed only in pre-dose and day 29 PK-ADA samples.
16. Patients will be followed at day 120 and day 169 for vital status, pregnancy status, targeted safety information, and additional safety information in newborns of study participants. Refer to Section 9.2.5 for more information on these follow-up assessments.
17. **For patients <12 years in cohort 2 and cohort 3**, follow-up by phone will be conducted within 6 to 8 hours of infusion to collect the information indicated.
18. Patients in phase 3 cohort 1 will follow the Schedule of Events in [Table 5](#) until day 90. They will then follow the long COVID Schedule of Events [Table 6](#) until day 169.
19. For all day 120 and day 169 questionnaires, a visit window of +7 days will be applied. For all other day 120 and day 169 assessments and sample collections, a visit window of ±7 days will be applied.
20. Refer to Section 9.2.16 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 9.2.16; additional information, including study visits and windows for these interviews, will be detailed in the separate study.
21. PBMC collections during the long COVID portion of the study are mandatory and are separate collections from those of the optional immunoprofiling sub-study.
22. Patients in phase 3 cohort 1 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 protocol amendment 9 US. Refer to Section 9.2.11 for additional information regarding collection and reporting.
23. Patients who consent to the optional pharmacogenomics (PGx) sub-study should have a blood sample for DNA collected 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 sample for the PGx sub-study should not have a second sample collected. Refer to Section 9.2.14 for more information about the PGx sub-study.
24. For phase 3 cohort 1 patients, any new medical condition(s) diagnosed after randomization will be recorded. Refer to Section 9.2.12 for additional information regarding collection and reporting.

9.1.2. Early Termination from the Study

Patients who are withdrawn from the study **before day 29** will be asked to allow an early termination visit consisting of day 29 assessments and sample collections. Patients who are withdrawn from the study **after day 29** will be asked to allow an early termination visit consisting of end-of-study assessments and sample collections.

9.1.3. 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 collection of NP swabs, blood, serum, or plasma, for follow-up of treatment-emergent SAEs, treatment-emergent AESIs, 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 (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 (and assent, as applicable) must be obtained according to the requirements described in Section 13.2. Optional informed consent/assent may be obtained for participation in the pharmacogenomics sub-study (Section 9.2.14) and immunoprofiling sub-study (Section 9.2.13).

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.

9.2.1.3. Demographics

Refer to Section 5.1.

9.2.1.4. Medical History

Medical history will include the following:

- COVID-19 with start date as the date of onset of first symptoms related to COVID-19
- Risk factors for severe COVID-19/hospitalization due to COVID-19, as defined in Section 7.2.1
- Whether the patient is receiving oxygen at home by nasal cannula

- Menopausal history
- Pregnancy or breastfeeding status, if applicable

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. Efficacy Procedures

9.2.3.1. Nasopharyngeal Swab Collection

Nasopharyngeal (NP) swab samples will be collected from patients to determine presence or absence of SARS-CoV-2 virus, including at baseline, and to measure viral load. Samples will be used for RT-qPCR analysis. Samples collected from patients may additionally be used for exploratory viral RNA sequencing, plaque forming unit assays (PFU) assays and/or viral culture. Additional details regarding sample collection and analysis can be found in the laboratory manual.

9.2.3.2. COVID-19-Related Medically-Attended Visit Details

A COVID-19-related medically-attended visit will be defined as follows: hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

Medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. During each indicated collection visit in the Schedule of Events, all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection.

Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit
- If hospitalized due to COVID-19, length of visit
- Reason (list all COVID-19-related symptom[s] or clinical manifestation[s]) that prompted medically-attended visit)
- If hospitalized due to COVID-19, whether ICU care was given
- If hospitalized due to COVID-19, whether mechanical ventilation was required
- Treatments given for COVID-19 (including, but not limited to supplemental oxygen, corticosteroids, COVID-19 convalescent plasma, remdesivir, bamlanivimab, etc)

9.2.4. Safety Procedures

9.2.4.1. Vital Signs

Vital signs will include temperature, blood pressure, heart rate (per minute), SpO₂. For phase 1, respiratory rate (per minute) will also be assessed.

Temperature may be measured using the following methods: axilla, oral, tympanic, or temporal. 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).

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.

SpO₂ 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 SpO₂ wave form.

9.2.4.2. Adverse Event Monitoring

Targeted TEAEs (as defined in Section 10.1.1) will be recorded.

9.2.4.3. Record Targeted Concomitant Medications and Concomitant Procedures

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

- Putative COVID-19 treatments (eg, remdesivir, bamlanivimab, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- Oxygen
- SARS-CoV-2 vaccinations
- Influenza vaccinations
- Any other 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, antibacterials, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)

- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril)
- Any medication used to treat an adverse event

In addition, any concomitant procedures used to treat an adverse event will be recorded in the eCRF.

For more information on concomitant medications and procedures, refer to Section 8.10.

9.2.5. Post-Day 29 Follow-Up

In phase 3, patients (and/or their parent or legal guardian) will be contacted for the post-day 29 safety assessments described below at the time points listed in the respective schedules of events. These assessments will include vital status, pregnancy status, and targeted safety information. If no in-person procedures (eg, sample collections) are required, visit may occur remotely. Phone or telemedicine are the preferred methods of remote contact, but other modes of communication (eg, email) are acceptable if a patient cannot be contacted through other methods.

Vital Status. Record vital status (whether the patient is dead or alive) and record the date of death, when applicable.

Pregnancy Status. Record pregnancy status and date of pregnancy, when applicable. Refer to Section 10.1.3 for reporting requirements.

Targeted Safety Information. Refer to Section 10 for more information on reporting and recording requirements.

Safety Information in Newborns of Study Participants. The incidence and outcome of any SARS-CoV-2 infection will be collected for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study. Note that this information is in addition to outcome reporting of all pregnancies (Section 10.1.3).

9.2.6. Pregnancy Test 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 and should be completed regardless of pregnancy status. Pregnancy test will be performed at the local laboratory.

WOCBP are defined as females 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 is not required for women with documented hysterectomy or tubal ligation.

Information about pregnancy will be recorded as described in Section 10.1.3.

9.2.7. Laboratory Testing

Hematology and blood chemistry will be analyzed by a central laboratory. Detailed instructions are provided in the laboratory manual.

Note that the laboratory tests listed below will only be performed based on samples that are collected according to the corresponding Schedules of Events.

Blood Chemistry

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

Hematology

Tests will include:

Hemoglobin	<i>Differential:</i>	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 are provided in Section [10.1.1](#).

9.2.8. Drug Concentration Measurements and Samples

Note: As of protocol amendment 9 US, the PK sub-study is no longer enrolling new participants.

Samples for assessment of drug concentration will be collected at the timepoints indicated in the schedule of events. For information concerning unused samples and exploratory research, refer to Section 9.2.10.

In phase 3 cohort 1, approximately 600 patients will be enrolled in a PK sub-study (refer to Table 5). This sub-study will only be enrolled at a select number of participating sites. In cohort 1, only patients who are enrolled in the PK sub-study will have samples collected for drug concentrations. Additional samples for immunogenicity assessment will be also collected in these patients.

9.2.9. Immunogenicity Measurements and Samples

Samples for immunogenicity assessment will be collected for adult patients at the timepoints listed in the relevant schedule of events. For pediatric patients, samples may be assessed for ADA and NAb, if feasible. For information concerning unused samples and exploratory research, refer to Section 9.2.10.

9.2.10. Exploratory Pharmacodynamic/Biomarker Analyses

This section describes planned exploratory pharmacodynamic/biomarker analyses, some of which may not be reported in the CSR. Note that, in this adaptive master protocol, the analyses described in this section may be limited to particular or study phases or time periods during a study phase.

Also 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 to 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.

9.2.10.1. Neutrophil–Lymphocyte Ratio

Exploratory biomarkers, including the neutrophil-lymphocyte ratio (NLR), will be assessed. Neutrophil-lymphocyte ratio is as an inflammatory biomarker and is suggested to be an independent risk factor of the in-hospital mortality for COVID-19 patients. Assessment of NLR trends may help identify individuals with COVID-19 at higher risk of complications (Liu, 2020) (Qin, 2020). We will measure NLR as an exploratory endpoint and, as compared to placebo, and association with clinical endpoints will be evaluated.

9.2.10.2. Serum and Plasma Biomarkers

Changes in circulating concentrations of serum/plasma biomarkers associated with inflammation, coagulation, and disease progression will be assessed in REGN10933+REGN10987 group compared to the placebo group in phase 1 and phase 2. The association between changes in disease related biomarkers with clinical endpoints may be evaluated.

Biomarkers may include (but are not limited to) CRP, LDH, D-dimer, and ferritin. CRP is a general inflammation marker that correlates with severity of COVID-19 including lung lesions, supplemental O₂ requirements, and death (Luo, 2020) (Qin, 2020). LDH was identified as a predictive factor for early recognition of lung injury and advanced COVID-19 cases (Ruan, 2020) (Wang, 2020b) (Young, 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).

9.2.10.3. 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 may be performed on viral nucleic acid isolated from nasopharyngeal swab, 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 viral sequencing will be reported separately from the CSR.

Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use PFU, viral culture or viral subgenomic mRNA 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 may be an indicator of actively-infected cells. These data may be associated with RT-qPCR measuring viral load.

The results of the viral infectivity assays may not be included in the clinical study report.

9.2.10.4. 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 effect the endogenous humoral immune response to SARS-CoV-2.

9.2.10.5. Serum and Plasma for Exploratory 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. These serum and plasma samples may be used for complement and/or cytokine analysis (described below), as well as other analyses.

9.2.10.6. 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 therefore 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.

9.2.10.7. 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-1 β , IFN γ , TNF α , IL-10 and MIP-1 β may be measured. Additional cytokines may be interrogated through the use of cytokine panels.

9.2.10.8. 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.

9.2.11. Monitoring for SARS-CoV-2 Reinfection

Patients in phase 3 cohort 1 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 protocol amendment 9 US. Test results obtained prior to the date of consent will not be collected. Positive results will be reported as an AESI, but will not require expedited reporting (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.

9.2.12. Recording New Medical Diagnoses or Conditions

In phase 3 cohort 1, 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 protocol amendment 9 US 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.

9.2.13. Immunoprofiling Sub-Study (Optional)

Up to 300 patients (cohort 1; cohort 3 ≥ 18 years old) may be enrolled at selected sites in an optional immunoprofiling sub-study to collect whole blood to isolate peripheral blood mononuclear cells (PBMCs) for immunoprofiling. Patients who agree to participate will be required to consent to this optional sub-study before collection of the samples. PBMCs from participants in this sub-study will be isolated from the whole blood at a central lab and stored for analysis. PBMCs will be used to characterize the cellular and humoral immune response to SARS-CoV-2 in REGN10933+REGN10987 treated patients as compared to placebo and as compared to baseline. Both B cell and T cell immune responses may be studied. Assays for B cell responses may include, but will not necessarily be limited to, quantification of spike subdomain specific B cells and plasma cells by antigen specific flow cytometry, and quantification of SARS-CoV-2 specific antibody responses in either primary ELISPOT assays or re-stimulation assays followed by ELISPOT. Studies focused on T cell responses may include, but may not be limited to, flow cytometry with isolated PBMCs to characterize immune subsets, quantify SARS-CoV-2 specific T cell responses via ex vivo peptide stimulation assays with downstream flow cytometry, or ELISPOT and/or cytokine measurements. Cell profiling may include bulk RNA (transcriptome) sequencing, T-cell receptor or B-cell receptor RNA or DNA sequencing.

9.2.14. Pharmacogenomics Sub-Study (Optional)

Eligible patients (≥ 18 years of age) who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of samples. Newly-enrolled patients will have blood samples collected for both DNA and RNA; patients who were previously 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 targeted TEAEs. 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.

9.2.15. Exploratory Patient-Reported Symptoms

This section describes planned patient-reported symptom analyses, some of which may not be reported in the CSR. Note that, in this adaptive master protocol, the analyses described in this section may be limited to particular or study phases or time periods during a study phase. Note that any symptoms collected by the instruments described below will not be considered AEs and will not be reconciled with any AEs.

SE-C19, PGIS, and PGIC

The Symptom Evolution of COVID-19 (SE-C19) instrument was developed de novo by Regeneron with the aim to better understand the symptomatic course of COVID-19 infection over time and is based on current available evidence on symptoms of COVID-19 ([Arentz, 2020](#)) ([Chen, 2020a](#)) ([Chen, 2020b](#)) ([Huang, 2020](#)) ([Lapostolle, 2020](#)) ([Mizrahi, 2020](#)) ([Song, 2020](#)) ([Wang, 2020a](#)). Patients self-report symptoms using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer). Patients are presented with a list of symptoms and are asked to identify all those that they are experiencing.

Patients rate each identified symptom as mild, moderate, or severe at the worst moment within the last 24 hours. An ‘other’ category is also available, where a free text field allows the addition of any symptom that is not on the list. Each score is assigned a numeric value: 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). [Table 9](#) provides the symptoms evaluated in the SE-C19.

Table 9: Symptoms Evaluated in the Symptom Evolution of COVID-19 (SE-C19) Instrument

SE-C19 Symptoms Recorded and Planned for Analysis		
• Body aches such as muscle pain or joint pain	• Chest pain	• Chills
• Confusion ¹	• Cough	• Diarrhea
• Dizziness	• Fatigue	• Feverish
• Headache	• Loss of appetite	• Loss of taste / smell
• Nausea	• Pressure / tight chest	• Rash ¹
• Red or watery eyes	• Runny nose	• Shortness of breath / difficulty breathing
• Sneezing ¹	• Sore throat	• Sputum / phlegm
• Stomachache	• Vomiting ¹	

¹ Not included in the phase 3 key secondary analysis (Section [11.4.3.2](#))

To aid interpretation, the SE-C19 is supplemented by the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS), which assess the overall subjective experience of symptom severity and change in symptoms over time.

As a representation of the current available evidence of COVID-19 symptoms, the SE-C19 appears to have face validity for tracking symptom onset, severity, and recovery. Content validity was confirmed through an interview-based study of patients and clinicians, separate from this study.

WPAI+CIQ

Acute respiratory illnesses can lead to a significant economic burden owing to absenteeism and loss of workplace productivity ([Li, 2007](#)). 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 COVID-19 pandemic has resulted in a multisectoral global economic burden ([Nicola, 2020](#)), a significant portion of which is likely attributable to indirect costs related to school absenteeism, loss of workspace productivity, as well as health-related quality of life. Assessing the quality of life of individuals with SARS-CoV-2 is important, as it can aid in understanding the potential impact of interventions from the perspective of cost-utility analysis.

The EQ-5D-5L is a validated and extensively published self-reported quality of life scale. 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).

The EQ-5D-Y is a youth version of the adult scale designed and validated for use by children. It includes also 5 domains: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy.

9.2.16. Assessment of Long COVID

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 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 are self-reported using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer).

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, 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.

9.2.16.1. 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](#)).

Participants are presented with a list of symptoms and are asked to identify all those that they are experiencing. Participants rate each symptom as mild, moderate, or severe at the worst moment within the last 24 hours. Each score is assigned a numeric value: 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). [Table 10](#) lists the symptoms evaluated in the SE-LC19.

Table 10: 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	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			Symptoms Included: 22	
Confusion				
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) and Patient Global Impression of Change (PGIC) questionnaires will assess the overall subjective experience of COVID-19 symptom severity and change in symptoms 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).

9.2.16.2. 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 9.2.10.3. Additional details regarding sample collection can be found in the laboratory manual.

In the event of a positive RT-qPCR, the investigator will be notified so that the patient may be informed of the result. Clinical management of a positive test result is deferred to the investigator or caring physician. As central laboratory test results may not be available in real time, any symptoms that may be related to acute COVID-19 infection should be tested and managed according to standard of care.

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 [9.2.10](#).

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

Only **targeted TEAEs** will be recorded:

- **All phases:** Treatment-emergent SAEs, up to day 29
- **Phase 1 and phase 2 only:** Treatment-emergent AESIs, defined as grade ≥ 2 IRRs and grade ≥ 2 hypersensitivity reactions (see Section 10.1.3), up to day 29
- **Phase 1 only:** TEAEs (grade 3 or grade 4 only), up to day 29
- **Phase 3 only, all cohorts:** Treatment-emergent AESIs, defined as grade ≥ 2 IRRs, grade ≥ 2 hypersensitivity reactions, **and** any TEAE that led to a medically-attended visit (see Section 10.1.3), up to day 29
- **Phase 3 only, all cohorts:** Treatment-emergent SAEs from day 30 to day 169
- **Phase 3 only, cohort 2 (and cohort 3 patients <18 years) only:** Grade 3 and grade 4 TEAEs, up to day 29
- **Phase 3 only, cohort 1:** Positive SARS-CoV-2 local test result, from the day of consent to protocol amendment 9 US until day 169
- **Phase 3 only, cohort 1:** Any new medical condition that was diagnosed after randomization, until day 169

The investigator must promptly the above targeted TEAEs occurring during the observation period (see Section 11.4.5.1). Note that the length of this period differs in each study phase, owing to different final study visit days. 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 targeted TEAEs 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 targeted TEAEs 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. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, require corrective treatment, or constitute an AE in the investigator's clinical judgement. 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 SAE occurring subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should be reported. In addition, any SAE resulting in death that occurs prior to study day 169 should also be reported, regardless of patient withdrawal or early termination.

All treatment-emergent SAEs, 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

The targeted treatment-emergent AEs defined in Section 10.1.1 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, 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 AESI (serious and nonserious), defined as:

- Grade ≥ 2 infusion-related reactions
- Grade ≥ 2 hypersensitivity reactions
- **Phase 3 only:** Any treatment-emergent adverse event that led to a medically-attended visit, regardless of whether the visit is related to COVID-19

Note: pre-planned or prescheduled medical appointments will not be considered medically-attended visits

- **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 during the study or existing at the time of signing the informed consent form. A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.

Any complication of pregnancy affecting a female 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, including testing results for SARS-CoV-2 infection in the newborn, if performed.

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. However, these AESIs do not require expedited reporting to the Sponsor:

- **Phase 3 cohort 1 only:** positive SARS-CoV-2 local test result (Section 9.2.11)
- **Phase 3 cohort 1 only:** any new medical condition that was diagnosed after randomization (Section 9.2.12)

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 **hospitalization** (admission 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 (refer to Section [10.1.1](#) Section [10.1.2](#)).

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](#).

10.2.4. Infusion-Related Reactions and Hypersensitivity Reactions

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.

10.2.5. 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).

Treatment-emergent AEs, SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in [Table 11](#).

Table 11: 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) ¹
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ²
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

¹ Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

² Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.6. 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 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. The SAPs may be revised during the study to accommodate amendments to the clinical study protocol, and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The initial phase 1/2 SAP describes the interim descriptive analysis of data from the first 275 symptomatic patients enrolled in this study. The phase 2 SAP describes the primary phase 2 analysis based on data from the first 799 symptomatic patients in the study. A SAP for phase 3 will provide additional details for the analysis of phase 3 data. The final SAPs will be issued before the database lock in each portion of the study.

This master protocol is intended to allow for adaptations, including dropping of a treatment group, addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing, determination of the primary endpoints for phase 3, and sample size re-estimation for phase 2 and 3. Therefore, treatment groups in phase 3 and analyses for phase 3 will depend on the final endpoints and treatment groups selected based on phase 2 results.

Phase 3 will be powered and analyzed independently of phase 2, in order to ensure that phase 3 is confirmatory and to avoid inflating type I error rate in phase 3.

Endpoints are listed in Section 3.2.1.6. Analysis variables are summarized in Section 5.

11.1. Statistical Hypothesis

Phase 1

The safety and tolerability objectives of phase 1 will be evaluated by estimating the proportion of patients with treatment-emergent SAEs through day 29, hypersensitivity reactions (grade ≥ 2) through day 29, and infusion-related reactions through day 4.

Phase 2

The statistical hypotheses for the primary virologic efficacy endpoint for the phase 2 symptomatic cohort portion of the study are as follows:

- H_0 : There is no treatment difference between REGN10933+REGN10987 2400 mg and 8000 mg combined group and placebo in terms of time weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7
- H_1 : There is treatment difference between REGN10933+REGN10987 2400 mg and 8000 mg combined group and placebo in terms of time weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to day 7

Phase 3

The statistical hypotheses for the primary clinical efficacy endpoint for the phase 3 cohort 1 portion of the study are as follows:

- H_0 : The risk of a patient having ≥ 1 COVID-19-related hospitalization, or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo
- H_1 : The risk of a patient having ≥ 1 COVID-19-related hospitalization, or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo

11.2. Justification of Sample Size

Phase 2

The sample size for phase 2 is 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 7, using a two-sample t-test at a two-sided significance of $\alpha=0.05$.

Due to lack of published data 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 sample size 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. The smallest treatment difference that will result in $p<0.05$ is approximately 1.34 \log_{10} copies/mL. A total sample size of 60 patients is planned for phase 1 including patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapy arms.

Assuming that 23% of the patients may have missing baseline values or drop out early, and assuming a standard deviation of 2.1 \log_{10} copies/mL (Cao, 2020), a sample size of 130 patients per arm per cohort in phase 2 will have at least 80% power to detect a difference of 0.84 \log_{10} copies/mL. If a standard deviation of 3.8 \log_{10} copies/mL is assumed (Wang, 2020c), the detectable difference would be 1.51 \log_{10} copies/mL. Based on this per-arm per cohort sample size calculation, a total sample size of approximately 780 patients is needed. This includes 390 patients in the symptomatic and asymptomatic cohorts (randomized to placebo and to the 2 REGN10933+REGN10987 combination therapy doses). For the clinical endpoint of proportion of patients with ≥ 1 COVID-19-related medically-attended visit, assuming a 30% rate in the control arm, the smallest treatment difference that will result in $p<0.05$ is approximately 11%.

Phase 3 Cohort 1

The sample size of phase 3 cohort 1 is based on having sufficient power to analyze the primary endpoint (Section 4.1) in the modified full analysis set (mFAS; Section 11.3.1).

Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled, as well as blinded phase 3 data, the Sponsor assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS (patients with at least 1

risk factor for severe COVID-19 and a positive SARS-CoV-2 RT-qPCR test at baseline), and that 83% of randomized patients will have a positive SARS-CoV-2 RT-qPCR test at baseline.

Table 12 presents estimated number of randomized patients with at least 1 risk factor for severe COVID-19 at each analysis time point for cohort 1 efficacy analysis.

Table 12: Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with ≥ 1 Risk Factor for Severe COVID-19

	Placebo FAS (mFAS) ¹	1200 mg FAS (mFAS) ¹	2400 mg FAS (mFAS) ¹	8000 mg FAS (mFAS) ¹	Total FAS (mFAS) ¹
Pre-Amendment 6 patients	662 (550)	Not applicable	662 (550)	662 (550)	1986 (1650)
Amendment 6/7 randomized by 17 January 2021	841 (698)	841 (698)	841 (698)	N/A	2523 (2094)
Final analysis, 2400 mg vs. placebo (randomized by 17 January 2021)	1503 (1248)		1503 (1248)		
Interim analysis, 1200 mg vs. placebo (randomized by 17 January 2021)	841 (698)	841 (698)			
Amendment 6/7 randomized by 24 February 2021	1352 (1122)	1352 (1122)	1352 (1122)	N/A	4056 (3366)
Final analysis, 1200 mg vs. placebo (randomized by 24 February 2021)	1352 (1122)	1352 (1122)			

¹ FAS estimates only include those in FAS with ≥ 1 risk factor for severe COVID-19.

The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in the mFAS). With this sample size, the study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with REGN10933+REGN10987 treatment). If there is a greater treatment difference, such as a 60% reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death.

The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in the mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (ie, when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (ie, a 50% reduction). If there is a greater treatment

difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death.

From 25 February 2021 onward, the Sponsor plans to randomize up to 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group, in addition to the patients already enrolled under protocol amendment 6 and protocol amendment 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the observed difference. Blinded sample size re-estimation may be performed based on the pooled observed event rates.

EAST v6.0 software was used for sample size calculation.

Phase 3 Cohort 2 and Cohort 3

Up to approximately 180 pediatric patients in cohort 2 is planned with a goal of approximately 52 patients exposed to each dose of study drug, which is considered adequate to describe the drug concentrations over time. In cohort 2, there will be an enrollment of approximately 20 patients < 10 kg (10 per treatment group) and 20 patients between ≥ 10 kg and < 40 kg (10 per treatment group).

In cohort 3, no minimum or maximum enrollment is planned. Cohort 3 will be analyzed descriptively for safety and may be analyzed descriptively for clinical and virologic outcomes.

Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

Phase 1/2 (Symptomatic)

The phase 1/2 portion of the study includes all symptomatic patients up to the 799th randomized symptomatic patient. The full analysis set (FAS) includes all randomized symptomatic patients in phase 1/2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). The seronegative FAS or seronegative mFAS are defined as all randomized patients with documented seronegative status at baseline in FAS or mFAS, respectively. Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. 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 will be used for the analysis of certain virologic endpoints and in descriptive analyses of certain clinical endpoints.

Phase 2 (Asymptomatic)

Full analysis set (FAS), mFAS, and seronegative mFAS for asymptomatic patients are defined similarly as above.

Phase 3 (Cohort 1)

Only patients with COVID-19 symptoms will be included in phase 3. All symptomatic patients from the 800th randomized symptomatic patient will be included in phase 3. For phase 3 cohort 1, the full analysis set (FAS) includes all randomized symptomatic patients and is based on the treatment allocated (as randomized). The FAS includes patients with and without risk factors for severe COVID-19.

The definition of the modified full analysis set (mFAS) for phase 3 is different from phase 2. In phase 3, the mFAS includes all randomized patients with a positive SARS-CoV-2 central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and with at least one risk factor for severe COVID-19 at baseline. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics. The mFAS will be used for the analysis of clinical, symptoms, and virologic endpoints. The seronegative mFAS will be used for the analysis of certain virologic endpoints and in analyses of certain clinical endpoints. Data from patients with no risk factors will be summarized descriptively.

For the analyses of the 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after protocol amendment 6 is implemented) will be included in the above analysis sets.

Phase 3 (Cohort 2)

The FAS includes all randomized patients in phase 3 cohort 2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). If pre-dose results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Phase 3 (Cohort 3)

Data on all patients in cohort 3 will be utilized in the analyses.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of “as treated” will be based on the

actual study drug received on day 1. Demographic and baseline characteristics, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all patients who received study drug and had at least 1 non-missing ADA result from the ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

Samples positive in the ADA assay will be characterized further for ADA titers and for the presence of neutralizing antibody (Nab). The NAb analysis set (NAS) includes all patients who received any study drug and who are negative in the ADA assay or with at least one non-missing result in the NAb assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Stratification factors are provided in Section 8.5.1.

Statistical analyses will be performed using Statistical Analysis System (SAS) Version 9.4 or higher.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: informed consent was signed (by the patient if at or above the country's age of legal adulthood, or by patient's parent[s] or legal guardian[s] if below the country's age of legal adulthood)
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized

- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics including medical history will be summarized descriptively for each phase by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

Phase 2

The primary virologic efficacy variable for phase 2 is time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples for the symptomatic cohort. The estimand for the primary hypothesis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatments and placebo (as well as pooled doses and placebo). Data collected after use of convalescent serum therapy 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. Analysis will be performed for patients with baseline viral load $>10^7$ copies/mL in the mFAS, for patients with baseline viral load $>10^6$ copies/mL in the mFAS, seronegative mFAS and for mFAS (with serostatus added to the ANCOVA model as a factor).

The analyses will be based on the observed data with no imputation for missing data except the following cases: uncertain viral load values with less than the lower limit of quantification of the PCR assay but with positive qualitative results are imputed with half of lower limit of quantification of the PCR assay; uncertain values with negative RNA are imputed with $0 \log_{10}$ copies/mL if the reason for the uncertain values is not a failed test. The primary efficacy variable will be calculated using trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. The variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, country, and risk factor (no risk factor versus at least 1 risk factor) based on clinical database data as fixed effects and baseline viral load and treatment by baseline interaction as covariates.

The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo as well as between combined dose group and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Accompanying descriptive analyses will be provided at the individual timepoints used to calculate the TWA.

At time of writing of protocol amendment 6, phase 2 analyses were complete and the protocol has been updated for consistency with the SAP for phase 2.

Phase 3 Cohort 1

The primary efficacy endpoint for phase 3 cohort 1 is the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29, which will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The primary analysis will be performed based on mFAS. As key secondary analyses, the same analyses will be performed for patients with high baseline viral load ($>10^6$ copies/mL) in the mFAS and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity and supportive analyses will be described in the SAP.

11.4.3.2. Secondary Efficacy Analysis

Phase 3

The following section describes analyses planned for phase 3 cohort 1. Analysis of asymptomatic patients (phase 2), pediatric patients (phase 3 cohort 2), and pregnant patients (phase 3 cohort 3) will be descriptive and detailed in the SAP.

Phase 3, Cohort 1 Patient-Reported Symptoms Endpoint

Time to COVID-19 symptoms resolution will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed in the mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and 95% CI for time to COVID-19 symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group and randomization strata. The P-value from the stratified log-rank test will be reported. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤ 3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

COVID-19 symptoms included in the analysis are as follows: Body aches such as muscle pain or joint pain, Chest pain, Chills, Cough, Diarrhea, Dizziness, Fatigue, Feverish, Headache, Loss of appetite, Loss of taste/smell, Nausea, pressure/tight chest, Red or watery eyes, Runny nose, Shortness of breath/difficulty breathing, Sore throat, Sputum/Phlegm, and Stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except Cough, Fatigue, and Headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

Additional information regarding the SE-C19 scoring instrument is provided in Section [9.2.15](#).

Phase 3 Cohort 1 Clinical Endpoints

Proportion endpoints such as proportion of patients with a COVID-19-related hospitalization, ER visit, or all-cause death and proportion of patients with a COVID-related MAV or all-cause death will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The analyses will be performed based on observed data for the mFAS for secondary analyses, and for seronegative mFAS and FAS as additional analyses. Similar analysis will be performed for the proportion of patients with a COVID-19-related hospitalization, ER visit, or urgent care visit as well as proportions of patients with each type of COVID-19-related MAV. Risk difference and its 95% confidence interval based on stratified Newcombe method for the proportion endpoints between 1200 mg and 2400 mg dose groups will be calculated based on patients concurrently randomized, ie, under protocol amendments 6/7/8, for the mFAS.

Analyses will be performed for the cumulative incidence of patients having a COVID-19-related hospitalization or all-cause death through day 29 based on the time to first COVID-19-related hospitalization or all-cause death using the stratified log-rank test with randomization strata as stratification factor for mFAS. Estimates of cumulative event rate at different time points and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for patients having event will be estimated by the Cox regression model with terms for treatment group (2400 mg dose groups versus placebo), and randomization strata. The p-value from the stratified log-rank test for risk of having events will be reported. Similar analysis will be performed comparing 1200 mg dose group to placebo including only the subset of patients concurrently randomized. A patient who has no COVID-19-related hospitalization will be censored at last known date of contact up to day 29. A patient who dies on or before day 29 will be considered as having an event at the date of death. A patient with multiple COVID-19 related hospitalizations and/or who dies will be counted as having one event. Similar secondary analyses will be performed for cumulative incidence of COVID-19-related hospitalization, ER visit, or all-cause death and cumulative incidence of patients having a COVID-19-related MAV or all cause death through day 29 for the mFAS. Additional landmark analysis for time to event endpoint such as cumulative incidence of COVID-19 related hospitalization or death may be performed if the proportional hazard assumption is considered not valid. Sensitivity analyses will be performed using FAS.

Additional analyses will be performed to examine the relationship between viral load and COVID-19-related MAVs in patients who underwent an intensive sampling schedule. For example, viral load over time will be compared between patients with and without a COVID-19-related MAV.

Virologic Endpoints

For phase 3 cohort 1, virologic analyses will be descriptive. The time-weighted average change from baseline in viral load (\log_{10} copies/mL) from day 1 to post-baseline visit timepoints will be analyzed using the same method as the phase 2 primary virologic endpoint based on mFAS for seronegative patients and seropositive patients separately. In cohort 1, the TWA analysis will be

limited to patients who were randomized prior to protocol amendment 6. A similar analysis will be performed for mFAS with baseline serostatus as an additional term to the ANCOVA model. The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference comparing each anti-spike mAb treatment arm versus placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Subgroup analysis of the TWA change from baseline in viral load at each visit will also be performed by baseline viral load categories ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL).

For phase 2, time to negative RT-PCR results through day 15 for seronegative mFAS will be analyzed using the stratified log-rank test with randomization strata as a stratification factor. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to negative RT-PCR results through day 15 will be estimated by the Cox regression model with terms for treatment group, baseline viral load, treatment by baseline interaction, randomization strata. P-value from the stratified log-rank test for time to negative RT-PCR results through day 15 will be reported. Similar analysis will be performed for the mFAS with baseline serostatus as an additional term to the model.

Proportion endpoints based on observed virologic data will be compared between groups using similar method as the proportion clinical endpoints. The analyses will be performed for seronegative mFAS as well as for mFAS.

To assess the time course of treatment effect in viral load, the change from baseline in viral load (\log_{10} copies/mL) at each visit for seronegative mFAS and mFAS will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline viral load, randomization strata, treatment, visit, treatment by baseline viral load interaction, baseline viral load by visit interaction, and treatment-by-visit interaction. Within-patient errors will be modeled with an unstructured, heterogeneous autoregressive (1), or compound symmetry covariance matrix in that order if a model does not converge. The least squares means estimates for the mean at each visit and mean change from baseline to each visit as well as the difference of these estimates between treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. Subgroup analysis of the change from baseline in viral load at each visit will also be performed by baseline viral load categories ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL).

11.4.3.3. Exploratory Analysis

Phase 2 Patient-Reported Symptom Endpoints (Exploratory)

Time to alleviation or resolution of COVID-19 symptoms endpoints for the symptomatic patients will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed for seronegative mFAS as well as for mFAS with baseline serostatus as an additional term to the model. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to alleviation or improvement of COVID-19 symptoms endpoints will be estimated by the Cox regression model with terms for treatment group, randomization strata. P-value from the

stratified log-rank test will be reported. Subgroup analysis may be performed for patients with more than one risk factor, with high baseline viral load, or are seronegative at baseline.

Analysis for data from asymptomatic patients, pediatric patients, and pregnant patients will be descriptive and detailed in the SAP.

Long COVID

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.

11.4.4. Control of Multiplicity

Phase 1

For phase 1 primary analysis of safety endpoints, no multiplicity adjustment will be applied. The primary virologic efficacy endpoint will be tested at $\alpha = 0.05$.

Primary Phase 2 Analysis of Virologic and Clinical Endpoints

The primary analysis of virologic and clinical endpoints will be conducted at $\alpha = 0.05$ (Table 13). Eight virologic endpoints and 2 clinical endpoints will be tested hierarchically in the following order:

Table 13: Statistical Testing Hierarchy, Primary Phase 2 Analysis

Hierarchy Number	Description
1	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁷ copies/mL for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (descriptive analysis will be provided for individual timepoints comprising the time-weighted average for this and all subsequent endpoints)
2	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁶ copies/mL for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
3	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the Seronegative mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
4	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
5	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁷ copies/mL for REGN10933+REGN10987 8000 mg group versus placebo

Hierarchy Number	Description
6	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁷ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
7	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁶ copies/mL for REGN10933+REGN10987 8000 mg group versus placebo
8	Time-weighted average change from baseline in viral load (log ₁₀ copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load >10 ⁶ copies/mL for REGN10933+REGN10987 2400 mg versus placebo.
9	Proportion of patients with MAVs through day 29 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (patients 1 through 799)
10	Proportion of patients with subset of MAVs consisting only of hospitalization or ER visit or urgent care visit through day 29 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (patients 1 through 799)

Phase 3

Cohort 1

The primary endpoint and key secondary endpoint will be tested hierarchically ([Table 14](#)), adjusting for interim analysis as described below.

Table 14: Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load >10 ⁶ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 2400 mg group versus placebo

Hierarchy Number	Description
5	Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 1200 mg group versus placebo
6	Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 1200 mg group versus placebo
7	Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
8	Proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo

The final analysis of the primary efficacy endpoint, ie, proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021 in the mFAS, at α level of 0.05.

If the 2400 mg group versus placebo comparison for the primary endpoint is positive, an interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (2 in [Table 14](#)) will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021 in the mFAS. If the comparison is positive, this analysis will be considered as the final analysis of the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison. Final analysis of the primary and key endpoints for comparisons 3 to 10 ([Table 14](#)) will then be performed based on patients randomized on or before 17 January 2021 in the mFAS in the hierarchical order above at α level of 0.05.

If the interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison is negative at α level of 0.01, no tests will be performed for the primary and key endpoints for comparisons 3 to 10 based on patients randomized on or before 17 January 2021. Final analysis of the proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison (2 in [Table 14](#)) and other comparisons 3 to 10 will be performed based on all patients randomized on or before 24 February 2021 and tested hierarchically at an alpha level adjusted based on the information fraction at the interim analysis using Gamma family alpha spending function, eg, at 0.047 level as illustrated in the example in [Table 15](#).

The Gamma family alpha spending function based on the primary endpoint of proportion of patients with ≥ 1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg versus placebo comparison will be used to control for type I error for the planned interim and final analyses. The parameter for the Gamma family spending function will be calculated based on the information fraction of the interim analysis, such that the alpha level at the interim analysis is equal to 0.01 and the remaining alpha level is calculated based on the gamma parameter. The information fraction will be determined based on the sample size in the mFAS at the interim analysis and at the final analysis of the primary endpoint for the 1200 mg group versus placebo comparison.

Table 15 provides an example alpha spending boundary for the interim analysis and final analysis of the primary and key secondary endpoints. Under protocol amendment 6 and protocol amendment 7 combined, a total of 2524 patients were randomized to the 1200 mg, 2400 mg, and placebo groups on or before 17 January 2021 for the planned interim analysis, and 4056 patients were randomized on or before 24 February 2021 for the final analysis of 1200 mg versus placebo comparisons. With these sample sizes utilized in each analysis, the information fraction is approximately 62% ($\gamma = -4$), assuming the proportions of RT-qPCR-positive patients in the FAS are the same at the interim and final analysis. The resulting overall alpha for the final analysis would then be 0.047.

Table 15: Example Alpha Spending Function for Analysis of Primary Endpoint

Information Time	Value	Overall α for Proportion Analysis = 0.05
62% of the mFAS patients completing day 29	α (2-sided)	0.01
Final analysis	α (2-sided)	0.047

Cohort 2 and Cohort 3

Analysis of cohort 2 and cohort 3 will be descriptive. No multiplicity adjustment will be applied.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before 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

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 preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse events (SAEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reactions (grade ≥ 2), through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reactions (grade ≥ 2), through day 29 by PT

For each phase, summaries by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 event by SOC and PT
- SAEs and AESIs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- SAEs and AESIs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs and AESIs
- Treatment-emergent grade 3 or 4 AEs (phase 1, phase 3 cohort 2, and phase 3 cohort 3 <18 years only) by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment arm.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

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.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The number and percentage of patients randomized and exposed to double-blind study drug, and duration of exposure to treatment during the study will be presented by treatment group.

11.4.5.4. Treatment Compliance

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Phase 1 (Dense Sampling)

The PK parameters may include, but are not limited to C_{max} , $C_{max}/dose$, t_{max} , and AUC_{last} .

The concentrations of REGN10933 and REGN10987 in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Phase 2 and Phase 3 (Sparse Sampling)

The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate.

11.4.8. Analysis of Immunogenicity Data

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

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA assays for all time points regardless of any missing samples
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay response at baseline with all post first dose ADA results negative, or a positive assay response at baseline with all post first dose ADA assay 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.
- Treatment boosted ADA 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 ($1,000 \leq \text{titer} \leq 10,000$)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories and at the
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

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

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

11.5. Interim Analysis

Phase 1/2

An initial phase 1/2 descriptive analysis of data from the first 275 symptomatic patients enrolled in this study was conducted based on a database lock on 23 Sep 2020.

Phase 3

Cohort 1

An interim analysis of the primary and key secondary endpoints for the 1200 mg treatment group will be performed when the final analysis of the primary efficacy endpoint for the 2400 mg treatment group is conducted. Refer to Section 11.4.4 for more information regarding these analyses.

Cohort 2 and 3

An interim descriptive analysis of phase 3 cohort 2 and 3 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.

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
- Electronic Clinical Outcome Assessment (eCOA) system – electronic patient diary and patient reported outcomes

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 investigator must allow study related monitoring activities to occur. 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.

Adult Patients

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.

For patients at or above the legal age of adulthood, it is the responsibility of the investigator or authorized 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 the 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.

Patients Under 18 Years of Age (or Under Country's Legal Age of Adulthood)

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.

For patients under the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain written informed consent from the patient's parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient's parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and by the same investigator or designee who explained the ICF.

Local law and site policies must be observed by the investigator in deciding whether the consent of 1 or both parents/guardians is required. If only 1 parent or guardian signs the ICF, the investigator must document the reason the other parent or guardian did not sign.

The investigator (or authorized designee) may also be required to obtain assent from the patient,, as determined by the IRB/EC and in accordance with the local regulations and requirements:

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form
- Patients who can understand but who can neither write nor read will have the assent form read to them by the person obtaining assent, who will sign and date the ICF to confirm that assent 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's parent(s) or legal guardian(s).

13.3. Patient 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.

19. REFERENCES

Alwan NA, Attree E, Blair JM, Bogaert D, Bowen MA, Boyle J, et al. From doctors as patients: a manifesto for tackling persisting symptoms of covid-19. *Bmj* 2020; 370:m3565.

Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *Jama* 2020; 323(16):1612-1614.

Burke MJ, del Rio C. Long COVID has exposed medicine's blind-spot. *The Lancet Infectious Diseases* 2021.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; 382(19):1787-1799.

CDC. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States. Centers for Disease Control and Prevention. <https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html>. Published 2020a. Accessed 26 Jan 2021.

CDC. Post-COVID Conditions. CDC. <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html>. Published 2021. Updated 8 Apr 2021. Accessed 20 Jun 2021.

CDC. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. *Morbidity and Mortality Weekly Report* 2020b; 69(13).

CDC. Prevalence of Obesity Among Adults, by Household Income and Education — United States, 2011–2014. *Morbidity and Mortality Weekly Report* 2017; 66(50).

CDC. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *Morbidity and Mortality Weekly Report* 2020c; 69(12).

Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020a; 43(0):E005.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020b; 395(10223):507-513.

Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. *Cell* 2021.

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019; 17(3):181-192.

Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic and research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. *Theranostics* 2020; 10(16):7448-7464.

del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. *JAMA* 2020; 324(17):1723-1724.

Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(25):769-775.

EMA. Treatments and Vaccines for COVID-19: Authorised Medicines. 2021.

FDA. Casirivimab and Imdevimab EUA Letter of Authorization. Food and Drug Administration (FDA). <https://www.fda.gov/media/143891/download>. Published 2020. Accessed 17 Jun 2021.

FDA. Coronavirus Disease 2019 (COVID-19). FDA. <https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19>. Published 2021.

Fehr AR, Perlman S. *Coronaviruses: an overview of their replication and pathogenesis*. *Methods Mol Biol*. 2015: 1-23.

Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020; 370:m3026.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382(18):1708-1720.

He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; 26(5):672-675.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; 181(2):271-280.e278.

Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, Spata E, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2021:2021.2006.2015.21258542.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223):497-506.

Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol* 2020;1-3.

Jiang S, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. *Trends Immunol* 2020; 41(5):355-359.

Kam YW, Kien F, Roberts A, Cheung YC, Lamirande EW, Vogel L, et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcγR2-dependent entry into B cells in vitro. *Vaccine* 2007; 25(4):729-740.

Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(32):1081-1088.

Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *Bmj* 2020; 369:m2107.

Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, Berdah J, et al. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. *Intern Emerg Med* 2020; 15(5):813-817.

Lewis NM, Chu VT, Ye D, Connors EE, Gharpure R, Laws RL, et al. Household Transmission of SARS-CoV-2 in the United States. *Clinical Infectious Diseases* 2020.

Li S, Leader S. Economic burden and absenteeism from influenza-like illness in healthy households with children (5-17 years) in the US. *Respir Med* 2007; 101(6):1244-1250.

Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. *Clin Infect Dis* 2020.

Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. *JAMA Cardiology* 2020.

Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019; 4(4).

Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020; 20(6):656-657.

Luo F, Liao FL, Wang H, Tang HB, Yang ZQ, Hou W. Evaluation of Antibody-Dependent Enhancement of SARS-CoV Infection in Rhesus Macaques Immunized with an Inactivated SARS-CoV Vaccine. *Virol Sin* 2018; 33(2):201-204.

Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with COVID-19. medRxiv 2020:2020.2003.2021.20040360.

Magyarics Z, Leslie F, Bartko J, Rouha H, Luperchio S, Schörghofer C, et al. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother 2019; 63(8):e00350-00319.

Mizrahi B, Shilo S, Rossman H, Kalkstein N, Marcus K, Barer Y, et al. Longitudinal symptom dynamics of COVID-19 infection. Nat Commun 2020; 11(1):6208.

Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nature Medicine 2021; 27(4):601-615.

NHS. Long-term effects of coronavirus (long COVID). <https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/>. Published 2021. Accessed 28 Jun 2021.

NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. <https://www.nice.org.uk/guidance/ng188>. Published 2021. Updated 18 Dec 2020. Accessed 21 Jun 2021.

Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. Int J Surg 2020; 78:185-193.

O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. Subcutaneous REGEN-COV Antibody Combination in Early SARS-CoV-2 Infection. medRxiv 2021a:2021.2006.2014.21258569.

O'Brien MP, Forleo Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention. medRxiv 2021b:2021.2006.2014.21258567.

Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020; 11(1):1620.

Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology 2020.

Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.

REGEN-COV™ (casirivimab with imdevimab) [HCP Fact Sheet]. 2021; Regeneron Pharmaceuticals, Inc., Tarrytown, NY. <https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf>.

Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; 323(20):2052-2059.

Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrob Agents Chemother* 2012; 56(9):4927-4936.

Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020:1-3.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006; 47(4):373-380.

Sandoval Y, Januzzi JL, Jr., Jaffe AS. Cardiac Troponin for the Diagnosis and Risk-Stratification of Myocardial Injury in COVID-19: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020.

Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr* 2020; 174(9):868-873.

Shi L, Wang Y, Wang Y, Duan G, Yang H. Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients. *Am J Cardiol* 2020.

Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology* 2020; 295(1):210-217.

Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(24):759-765.

Szablewski C, Chang K, Brown M, et al. SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp — Georgia, June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(31):1023-1025.

Talla A, Vasaikar SV, Lemos MP, Moodie Z, Pebworth M-PL, Henderson KE, et al. Longitudinal immune dynamics of mild COVID-19 define signatures of recovery and persistence. *bioRxiv* 2021:2021.2005.2026.442666.

Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69(30):993-998.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veessler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; 181(2):281-292.e286.

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 2020a; 323(11):1061-1069.

Wang L. C-reactive protein levels in the early stage of COVID-19. *Med Mal Infect* 2020b; 50(4):332-334.

Wang Q, Zhang L, Kuwahara K, Li L, Liu Z, Li T, et al. Immunodominant SARS Coronavirus Epitopes in Humans Elicited both Enhancing and Neutralizing Effects on Infection in Non-human Primates. *ACS Infect Dis* 2016; 2(5):361-376.

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020c; 395(10236):1569-1578.

Weingartl H, Czub M, Czub S, Neufeld J, Marszal P, Gren J, et al. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *J Virol* 2004; 78(22):12672-12676.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail in Outpatients with Covid-19. *medRxiv* 2021a:2021.2006.2009.21257915.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med* 2020.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients. *medRxiv* 2021b:2021.2005.2019.21257469.

WHO. Novel Coronavirus (2019-nCoV) Situation Report – 22. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>. Published 2020. Accessed 24 Apr 2020.

WHO. Update on Clinical long-term effects of COVID-19. https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update54_clinical_long_term_effects.pdf?sfvrsn=3e63eee5_8. Published 2021. Accessed 28 Jun 2021.

Wu Z,McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12(1):8.

Yasui F, Kohara M, Kitabatake M, Nishiwaki T, Fujii H, Tateno C, et al. Phagocytic cells contribute to the antibody-mediated elimination of pulmonary-infected SARS coronavirus. Virology 2014; 454-455:157-168.

Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020; 323(15):1488-1494.

Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(44):1641-1647.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054-1062.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382(8):727-733.

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 Ambulatory 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 Ambulatory Patients with COVID-19

Protocol Number: R10933-10987-COV-2067

Protocol Version: Amendment 10 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

Signature Page for VV-RIM-00163381 v1.0

ESig Approval	PPD [redacted] PPD [redacted] PPD [redacted] 13-Aug-2021 17:17:10 GMT+0000
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ESig Approval	PPD [redacted] PPD [redacted] PPD [redacted] 14-Aug-2021 13:09:48 GMT+0000
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ESig Approval	PPD [redacted] PPD [redacted] PPD [redacted] 16-Aug-2021 00:55:01 GMT+0000
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ESig Approval	PPD [redacted] PPD [redacted] PPD [redacted] 16-Aug-2021 11:56:21 GMT+0000
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