Protocol

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

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

R10933-10987-COV-2067

This supplement contains the following items:

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, REGN10989
Clinical Phase:	1/2/3
Protocol Number:	R10933-10987-COV-2067
Protocol Version:	Original
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[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
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
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
MERS-CoV	Middle East respiratory syndrome coronavirus
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NLR	Neutrophil-lymphocyte ratio
PK	Pharmacokinetic
PT	Prothrombin time
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN10933+REGN10987	Co-administered REGN10933+REGN10987 combination therapy
REGN10989	REGN10989 monotherapy
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
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19
Site Locations	The study will be conducted in up to approximately 100 sites in the United States.
Principal Investigator	To be determined

Objectives

Primary

Phase 1

Part A

- 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 shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

Secondary

Phase 1

Part A

- 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 characterize the pharmacokinetic (PK) profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Part B

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10989 compared to placebo
- To characterize the PK profile of REGN10989 in serum
- To assess the immunogenicity of REGN10989

Phase 2

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo

To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum

- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

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 and REGN10989 monotherapy in adult outpatients (ie, ambulatory patients) with COVID-19.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 and COVID-19 symptoms but must not have been previously hospitalized or currently hospitalized.

Sentinel Safety Group

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

Patients in this sentinel safety group can be derived from either of 2 concurrent first-in-human (FIH) phase 1 studies (R10933-10987-COV-2067 in ambulatory patients, and R10933-10987-COV-2066 in hospitalized patients), where the safety and tolerability of REGN10933+REGN10987 (in part A) and REGN10989 (in part B) will be evaluated.

- Part A review: Patients will be pooled together from the phase 1 part A portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.
- Part B review: Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 20 patients (from one or both of the studies combined), the IDMC will review the data.

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. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment will not require the completion of phase 1 enrollment.

Phase 1

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo.

Patients will then be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for serious adverse events (SAEs) and adverse events of special interest (AESIs). On day 3, patients can return home, if medically appropriate, after completing the day's assessments. After completing assessments on day 7, all patients will be sent home, if medically appropriate.

Throughout the study, safety information (SAEs and AESIs) will be collected, as will information about any medically-attended visits related to COVID-19. Nasopharyngeal (NP swab), nasal swab, and saliva samples will be collected to assess viral shedding.

	The study will end on day 29, when patients will have final assessments conducted in person including NP swab, nasal swab, and/or saliva sample collection (as feasible) and blood draws for PK, anti-drug antibody (ADA), and exploratory analyses. **Phase 2** On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home. Nasal swab and saliva samples will be collected every other day for the first 2 weeks and then twice weekly thereafter. Information regarding SAEs, AESIs, and medically-attended related to COVID-19 will be recorded throughout the study. On day 29, patients will have final assessments conducted in clinic, including nasal swab and saliva sample collection and blood draws for PK, ADA, and exploratory analysis.
Study Duration	The duration of the study is 30 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	Phase 1 will continue to enroll until up to 100 patients are randomized. Phase 2 will continue to enroll until up to 250 patients are randomized. It is estimated that 704 patients (176 patients per arm) will be required for phase 3.
Target Population	This study will enroll adult, non-hospitalized patients who have a positive RT-PCR test for SARS-CoV-2 and recent COVID-19 symptoms. A patient must meet the following key criteria to be eligible for inclusion in the study. Other inclusion criteria apply: • Has laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) ≤72 hours of randomization • Is experiencing ≥1 of the following symptoms at randomization: fever, cough, shortness of breath • Has experienced COVID-19 symptoms for <7 days A patient who meets any of the following key criteria will be excluded from the study. Other exclusion criteria apply: • Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19 • Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit • Has a history of COVID-19 investigational or Emergency Use Authorization (EUA)-approved treatments in the past 30 days or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit. This includes, but is not limited to: remdesivir, hydroxychloroquine, tocilizumab, sarilumab, and other immunomodulatory agents • Current use of any COVID-19 investigational or EUA-approved treatment
Treatments	
Study Drug	• Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose

- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose

Placebo
- Placebo IV single dose

Endpoints

Primary

Phase 1

Part A and B

- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in NP swab samples.

Phase 2

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

Phase 3

Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.

Secondary

Phase 1

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, saliva, or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum and corresponding PK parameters

- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Phase 2

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Phase 3

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva or nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

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 with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29

- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients 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
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Procedures and Assessments

Procedures and assessments will include the following:

Efficacy

- NP, saliva, and/or nasal swabs for SARS-CoV-2 RT-qPCR
- Medically-Attended COVID-19 Visit Details

Safety

- Serious adverse events and adverse events of special interest

Statistical Plan

Statistical Hypothesis

The primary statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference.

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

Justification of Sample Size

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

Assuming a standard deviation of 2.1 log_{10} copies/mL, 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.

Assuming a 10% dropout rate and standard deviation of 2.1 log_{10} copies/mL, a sample size of 50 patients per arm in phase 2 will have at least 80% power to detect a difference of 1.25 log_{10} copies/mL. If a standard deviation of 3.8 log_{10} copies/mL is assumed, the detectable difference would be 2.27 log_{10} copies/mL. A total sample size of up to 250 patients are needed including 150 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies when phase 2 starts, and up to 100 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available.

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a

	10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.
Statistical Analysis	**Primary Efficacy Analysis** The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22. The estimand for the primary hypothesis is the difference in means between each of the anti-S SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the FAS. The primary efficacy variable will be calculated using trapezoidal rule based on observed data and is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate. The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented. **Safety Analysis** Safety data including serious adverse events and adverse events of special interest, vital signs, and laboratory tests will be listed and summarized by treatment group.

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, 2020b) (Zhu, 2020). As of May 2020, more than 5.5 million confirmed cases of COVID-19 have been reported globally (WHO, 2020a). 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, 2020b). 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, 2020b). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Richardson, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support(Chen, 2020b) (Huang, 2020)

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

In contrast to hospital cases, published data for COVID-19 cases seen at emergency departments, urgent care centers, outpatient care or non-hospitalized settings are relatively limited. However, guidance has been provided by the Centers for Disease Control and Prevention (CDC) and other organizations for managing ambulatory patients and monitoring them for respiratory or other complications, indicating that some outpatient diagnoses may require subsequent hospitalization (CDC, 2020a). An anti-viral therapeutic that could be administered to ambulatory

(non-hospitalized) patients with COVID-19 has the potential to significantly reduce COVID-19 hospitalization and ICU admissions. Currently, there is a great need for therapies capable of reducing SARS-CoV-2 viral shedding and slowing or preventing COVID-19 disease progression.

1.4. 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 (Li, 2016). 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 of S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.5. REGN10933+REGN10987 and REGN10989: Fully Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing fully human, neutralizing mAbs directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933, REGN10987, and REGN10989 are fully human, IgG1 monoclonal antibodies (mAbs) that bind the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 treatment is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. REGN10989 exhibits exceptionally potent neutralization, suggesting potential use in a monotherapy setting. Importantly, all three mAbs retain neutralization potency against multiple SARS-CoV-2 S protein variants identified through clinical isolates. REGN10933+REGN10987 combination therapy and REGN10989 monotherapy thus represent promising therapeutic strategies to reduce SARS-CoV-2 viral shedding and COVID-19 disease progression.

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

Several therapeutic agents have been previously studied in the context of other coronaviruses (SARS-CoV and MERS-CoV), including corticosteroids, type 1 interferons, convalescent plasma, ribavirin, lopinavir/ritonavir, proteases, and agents targeting viral entry proteins, with generally inconsistent findings of efficacy (Sanders, 2020). Many of these therapies, as well as a number of novel treatments and vaccines, are under investigation for the treatment of COVID-19. Currently,

however, there is no approved treatment for use in ambulatory patients with COVID-19, and additional controlled trials are needed.

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") and REGN10989 monotherapy ("REGN10989") in adult outpatients (ie, ambulatory patients) 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 Brochures.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Phase 1

The primary objectives of phase 1 are:

Part A

- 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 shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

The primary objective of phase 2 is to evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

The primary objective of phase 3 is to evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

2.2. Secondary Objectives

Phase 1

The secondary objectives of phase 1 are:

Part A

- 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 characterize the PK profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Part B

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10989 compared to placebo
- To characterize the PK profile of REGN10989 in serum

- To assess the immunogenicity of REGN10989

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 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

The secondary objectives of phase 3 are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

2.3. Exploratory Objectives

The exploratory objectives in all phases of the study are:

- To evaluate the development of treatment resistance to REGN10933+REGN10987 and/or REGN10989
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 and/or REGN10989 compared to placebo
- To explore the potential association of baseline humoral immune activity to SARS-CoV-2 on response to REGN10933+REGN10987 and/or REGN10989
- To evaluate the effects of REGN10933+REGN10987 and/or REGN10989 as compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To investigate the development of SARS-CoV-2 genetic variants resistant to REGN10933+REGN10987 and/or REGN10989

- To explore the effects of REGN10933+REGN10987 and/or REGN10989 on SARS-CoV-2 in vitro infectivity compared to placebo (as determined by viral culture)
- To explore biomarkers predictive of REGN10933+REGN10987 and/or REGN10989 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To understand the underlying mechanisms of action and biology of REGN10933+REGN10987 and/or REGN10989, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 and/or REGN10989 exposure and selected efficacy and safety endpoints and/or biomarkers

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 1

Treatment of ambulatory patients with COVID-19 with REGN10933+REGN10987 and/or REGN10989 will be tolerated and will reduce viral shedding.

Phase 2

Treatment of outpatients with COVID-19 with REGN10933+REGN10987 and/or with REGN10989 will reduce viral RNA shedding.

Phase 3

Treatment of outpatients with COVID-19 with REGN10933+REGN10987 and/or with REGN10989 will improve clinical outcomes.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

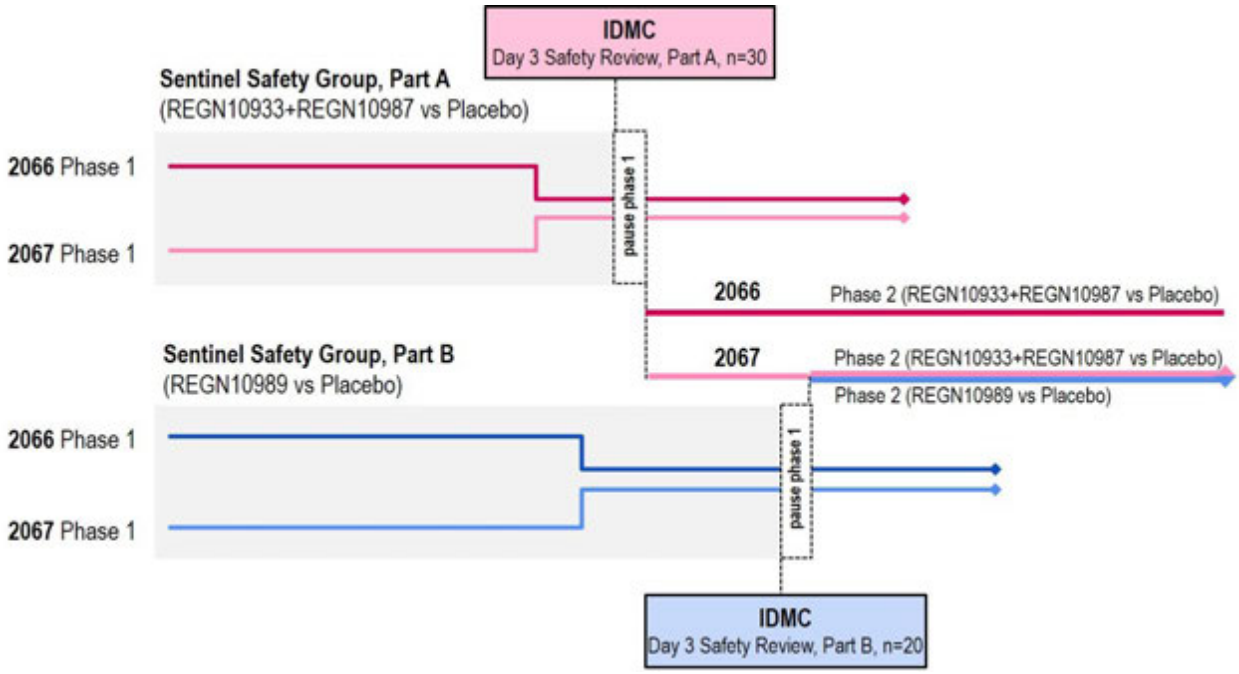
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in hospitalized patients with COVID-19. The safety and tolerability of REGN10989 will also be evaluated in the phase 1 portion of the study to enable investigation of REGN10989 in other clinical settings. The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of these investigational mAbs for COVID-19.

3.2.1.1. Phase 1 Sentinel Safety Group

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

Phase 1 will include a sentinel safety group (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 (in part A) and REGN10989 (in part B) 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

Two separate IDMC reviews will occur: one to assess REGN10933+REGN10987 (part A), and one to assess REGN10989 (part B).

- **Part A review:** Patients will be pooled together from the phase 1 part A 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.
- **Part B review:** Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 20 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. After IDMC reviews and provides a positive recommendation for phase 1 part A, enrollment of studies assessing REGN10933+REGN10987 (including REGN10933+REGN10987 treatment arms in phase 2 of this study and R10933-10987-COV-2066) may begin. After IDMC reviews and provides a positive recommendation for phase 1 part B, enrollment of studies assessing REGN10989 (including the REGN10989 treatment arm in this study) 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.

3.2.1.2. Adaptive Master Protocol Design

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

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

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

The design will allow for the addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing (umbrella design), refinement of disease characteristics of eligible study populations (basket design), as well as other multiple adaptations, including dropping of a treatment arm, determination of phase 3 primary endpoints, and phase 3 sample size estimation.

3.2.1.3. Rationale for Primary 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 adverse events of special interest (AESIs) through day 29.

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 treatment-emergent adverse event (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.

As such, evaluating targeted treatment-emergent SAEs and AESIs (≥grade 2 hypersensitivity reactions including infusion-related reactions) will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987 and/or REGN10989. This subset of treatment-emergent SAEs and AESIs encompasses the key safety concern that would be expected for mAbs targeting an exogenous target (see Section 3.3) and help evaluate unexpected serious adverse events.

Virologic Efficacy

The primary mechanism of action of REGN10933+REGN10987 and REGN10989 is blockade of the S protein RBD interaction with ACE2, leading to decreased infectivity of host cells. Blocking viral entry would result in reductions in SARS-CoV-2 RNA replication, and corresponding viral

shedding 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 and REGN10989 to reduce viral shedding 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) (Cao, 2020) (Wang, 2020c).

Clinical Efficacy

Clinical efficacy will also be evaluated. Patients will be enrolled in this study at or near their initial diagnosis of COVID-19 and are therefore expected to have comparatively mild or less advanced disease. By directly targeting host entry by SARS-CoV-2, REGN10933+REGN10987 REGN10989 may impact the early stages of the disease course, 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. The study will therefore assess the proportion of patients requiring COVID-19 related medically-attended visits (defined in Section 9.3.3.2) subsequent to their initial disease diagnosis and release to home quarantine.

3.2.1.4. Stratification According to Risk of Hospitalization Due to COVID-19

In phase 2 and phase 3, randomization will be stratified based on risk factors for hospitalization due to COVID-19 (refer to Section 8.6 for complete definition of risks factors).

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), cancer, and chronic kidney disease (CDC, 2020b) (Lighter, 2020) (Wu, 2020b) (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) 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).

3.2.2. Rationale for Dose Selection

This study will assess a single IV dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio as well as IV administration of REGN10989 as a single agent. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are non-competing mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure[s]). The study will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2.4 g (1.2 g per mAb), which is expected to be an efficacious dose (see below). The study will also evaluate REGN10933+REGN10987 at a higher dose, 8.0 g (4.0 g per mAb), in the event that a higher dose is required for efficacy.

The study will also assess single dose, intravenous REGN10989, a mAb that has at least 5-fold greater in vitro neutralization potency (EC50) than either REGN10933 or REGN10987. Based on this difference in potency, REGN10989 will be tested at 1.2 g; a dose equivalent to the initial dose level for each of the individual mAbs in the combination therapy REGN10933+REGN10987. Although the primary goal is to assess safety and tolerability of REGN10989 in this study, the use of a lower dose will allow a greater ability to discriminate the potential superior activity of this antibody as monotherapy for use in other studies. REGN10989 will not be further assessed in this protocol after Phase 1.

Cellular entry of coronaviruses depends on binding of the S protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. ACE2 is the receptor for cellular entry of SARS-CoV-2 and its gene expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Wu, 2020a) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration of 99% viral neutralization (EC99) observed against live virus in vitro and to then identify a dose that will meet or exceed this concentration in lung ELF. The effective concentration for 99% of neutralization (EC99) against live virus is 0.14 µg/mL (REGN10933), 0.80 µg/mL (REGN10987), and 0.01 µg/mL (REGN10989).

An average lung ELF-to-serum mean Cmax 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 Cmax 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. Based on healthy subject human PK data for six Regeneron mAbs directed against an exogenous target (N=6 to 12 subjects per mAb), a single IV combination dose of 1.2 g per mAb is predicted to result in ≥95% of patients exceeding the target serum concentration for 28 days after dosing.

A 4-week Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys is currently ongoing and assessing once-weekly dosing of up to REGN10933+REGN10987 (at 150 mg/kg per antibody) and REGN10989 (150 mg/kg) is being conducted to support safety of these mAbs.

3.3. Risk-Benefit

An assessment of risks and benefits is provided in the Investigator's Brochure(s).

4. ENDPOINTS

4.1. Primary Endpoint

Phase 1

The primary endpoints for phase 1 are:

Part A and B

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

  Note: Time-weighted average of change from baseline viral shedding from day 1 to day 22 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 shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples.

Phase 3

The primary endpoint for phase 3 is proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.

4.2. Secondary Endpoints

Phase 1

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, saliva, or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples

- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29

  Note: COVID-19 related medically-attended visits are defined in Section 9.3.3.2.
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum and corresponding PK parameters
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989 over time

Phase 2

The secondary endpoints for phase 2 are:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

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 ICU due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989 over time

Phase 3

The secondary endpoints for phase 3 are:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva or nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

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 with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies to REGN10933, REGN10987, and REGN10989 over time

4.3. Exploratory Endpoints

The exploratory endpoints for phase 1 and phase 2 are:

- Development of resistance to SARS-CoV-2 in NP, saliva, or nasal samples through day 29
- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29
- Change in SE-C19 item scores over time
- Change in PGIS score over time
- PGIC score at day 29

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.3.

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

Efficacy variables include viral shedding (log_{10} copies/mL), number of COVID-19 related medically-attended visits, 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 treatment-emergent SAEs and incidence of AESIs Section 10.1.3.

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point, and select PK parameters. For phase 2, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point The PK sampling time points are specified in the schedule of events (Table 1 and Table 2).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples will be collected at the visits specified in the schedule of events (Table 1 and Table 2).

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, per-symptom SE-C19 score, PGIS score and PGIC score.

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 and REGN10989 monotherapy in outpatient (ie, ambulatory) adults with COVID-19.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 and COVID-19 symptoms but must not have been previously hospitalized or currently hospitalized (refer to Section 7.2 for study inclusion and exclusion criteria).

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

The schedule of events can be found in Table 1 (phase 1) and Table 2 (phase 2). See Figure 2 (phase 1) and Figure 3 (phase 2) for study flow diagrams. Additional information on study procedures can be found in Section 9.3.

Phase 1

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN1098 (high dose), REGN10989, 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.

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo (refer to Section 8.6 for more information on treatment arms and dosing). Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

Patients in phase 1 will be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for SAEs and AESIs (Section 10). On day 3, patients can return home, if medically appropriate, after completing the day's assessments. Patients will have the option, if they choose, to remain sequestered until day 7. After completing assessments on day 7, all patients will be sent home, if medically appropriate.

Since patients will be sequestered and/or home quarantined for the duration of the study, assessments and sample collections may occur through a variety of 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 nurses, 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.

Saliva and/or nasal samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Nasopharyngeal swab samples will be collected on a similar, but less frequent, schedule. 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 conducted in person including NP swab, nasal swab, and saliva sample collections and blood draws for PK, ADA, and exploratory analyses.

Phase 2

On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo. Patients will also have saliva and/or nasal samples taken, and have 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.

Since patients will be quarantined at home, subsequent assessments and sample collections will potentially occur through a variety of in-person, home-based, and/or remote methods as described in phase 1.

Saliva and nasal samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Information regarding SAEs, 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 conducted in clinic, including saliva and nasal sample collection and blood draws for PK, ADA, and exploratory analysis.

Phase 3

The clinical efficacy endpoints, treatment arms, and final sample size for phase 3 are subject to change and will be informed by phase 2 data.

Prior to initiation of phase 3, enrollment may pause for IDMC review of phase 2.

Figure 2: Study Flow Diagram, Phase 1

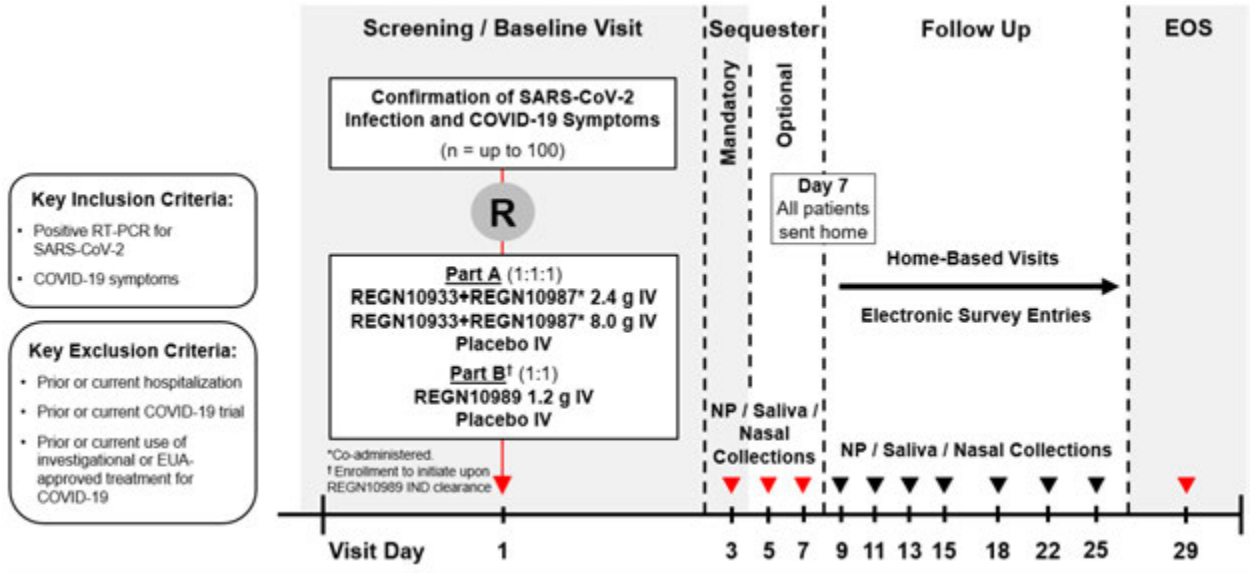
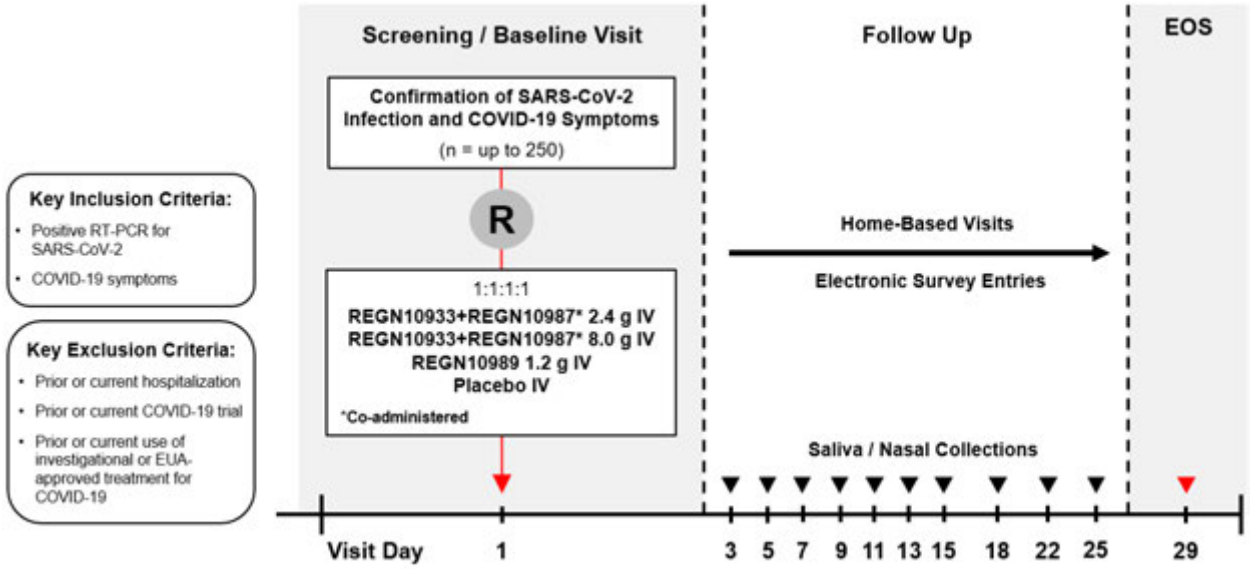


Figure 3: Study Flow Diagram, Phase 2



6.1.1. Study Stopping Rules

6.1.1.1. 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.

Patients stopping rules from the study include withdrawal of consent.

6.1.1.2. Study Stopping Criteria

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

6.1.2. 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 safety of patients. The IDMC can make recommendations about early study closure or changes to the study conduct. Members of the IDMC will include 3 physicians with relevant medical specialty training and 1 statistician. 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 3.2.1.1. In addition, the IDMC will conduct periodic data reviews, for instance, after all patients are enrolled into phase 1. Additional periodic reviews will be conducted during phase 2 and 3 of this study as detailed in the IDMC charter. These data reviews will include all available efficacy and safety data, including deaths, from all enrolled study participants up to the data cut point for the analysis. The IDMC will meet regularly throughout the course of the study to review safety data and make recommendations on study conduct.

6.2.2. Sponsor Review Committee

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

6.3. Planned Interim Analysis

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

Phase 1

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 visit. Safety and efficacy analysis for phase 1 will be performed when all randomized patients have completed the day 29 visit.

Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

Phase 2

An interim analysis is planned when at least 50% of the randomized patients have completed the day 29 visit. The primary efficacy analysis for phase 2 will be performed when all randomized patients have completed the day 22 visit.

Phase 3

An interim analysis plan for phase 3 will be specified when adaptations for phase 3 are implemented in the study.

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 up to 100 patients are randomized. Phase 2 will continue to enroll until up to 250 patients are randomized.

It is estimated that 704 patients (176 patients per arm) will be required for phase 3.

For information on the timing of enrollment, refer to Section 3.2.1.1. For treatment allocation and randomization, refer to Section 8.6.

7.2. Study Population

This study will enroll adult, non-hospitalized patients who have a positive RT-PCR test for SARS-CoV-2 and recent COVID-19 symptoms.

7.2.1. Inclusion Criteria

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

1. Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization
2. Has laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) ≤72 hours of randomization
3. Is experiencing ≥1 of the following symptoms at randomization: fever, cough, shortness of breath
4. Has experienced COVID-19 symptoms for <7 days
5. Maintains O_2 saturation ≥93% on room air
6. Is willing and able to provide informed consent signed by study patient or legally acceptable representative
7. Is willing and able to comply with study procedures, including providing samples for viral shedding testing after discharge

7.2.2. Exclusion Criteria

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

1. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19
2. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Has a history of COVID-19 investigational or Emergency Use Authorization (EUA)-approved treatments in the past 30 days or less than 5 half-lives of the investigational

product (whichever is longer) prior to the screening visit. This includes, but is not limited to: remdesivir, hydroxychloroquine, tocilizumab, sarilumab, and other immunomodulatory agents

4. Current use of any COVID-19 investigational or EUA-approved treatment
5. Requires IVIG for medical condition other than COVID-19
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. Pregnant or breastfeeding women
9. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

   Highly effective contraceptive measures in women include:

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

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

   * WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

   Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

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

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 9.1.2.

7.4. Replacement of Patients

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 the method of treatment allocation for each phase of the study.

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose
- 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. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if required for treatment. All grade ≥2 hypersensitivity reactions including infusion-related reactions (using the CTCAE severity scale specified in Section 10.2.4) must be reported as AESIs (see Section 10.2.2).

8.5.1.1. Interruption of the Intravenous Infusion

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

- Sustained/severe cough
- Rigors/chills

- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

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

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

8.5.1.2. Termination of the Intravenous Infusion

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

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

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

In part A, 60 patients will be randomized in a 1:1:1 allocation ratio to one of the following:

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

In part B, 40 patients will be randomized in a 1:1 allocation ratio to one of the following:

- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

In phase 1, randomization will not be stratified.

Phase 2

Patients will be randomized in a 1:1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS).

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

Randomization will be stratified by risk factors for hospitalization due to COVID-19:

- No risk factors for hospitalization due to COVID-19
- ≥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 3.2.1.4):

- 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 corticosteroids or other immune-weakening medications)

Phase 3

The treatment arms, patient cohorts, sample size, and treatment allocation scheme for phase 3 will be finalized after review of phase 2 data.

8.7. Blinding

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

Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments in phase 2 and phase 3.

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

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

8.8. Emergency Unblinding

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

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patients will be unblinded
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

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

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

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

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

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

8.9.4. Treatment Compliance

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

8.10. Concomitant Medications

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

For more information on recording of concomitant medications, refer to Section 9.3.4.3.

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

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Table 1: Schedule of Events: Phase 1

Day	Screening/Baseline Visit[1]				Mandatory Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1				2	3	4	5	6	7[2]	8	9	11	13	15	18	22	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
Visit Location: Place of Infusion (I), Place of Sequester (S), Home Based (H), Phone (P)[3]	*I*				*S*		*S or H*				*P*	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]												±1	±1	±1	±1	±1	±1	±1	±3
Screening/Baseline																			
Informed Consent	X																		
[redacted]	X																		
Inclusion/Exclusion	X																		
RT-PCR test for SARS-CoV-2[7]	X																		
Demographics	X																		
Medical History (incl. 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
Saliva Sample for SARS-CoV-2 RT-qPCR		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
Safety																			
Vital Signs		X		X															
Treatment-emergent SAEs[8]			X	X	X	X	X	X	X	X	X				X		X		X
Grade ≥2 Hypersensitivity Reactions[8]			X	X	X	X	X	X	X	X	X				X		X		X
Grade ≥2 IRRs[8]			X	X	X	X	X												
Targeted Concomitant Medications[9]	X		X	X	X	X	X	X	X	X	X				X		X		X
Pregnancy Test (WOCBP)[10]	X																		X
Central Laboratory Testing																			
Hematology[11]	X[11]									X									X

Day	Screening/Baseline Visit[1]				Mandatory Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1				2	3	4	5	6	7[2]	8	9	11	13	15	18	22	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
Visit Location: Place of Infusion (I), Place of Sequester (S), Home Based (H), Phone (P)[3]	*I*				*S*		*S or H*				*P*	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]												±1	±1	±1	±1	±1	±1	±1	±3
Blood Chemistry[11]	X[11]									X									X
Coagulation Tests[11]	X[11]									X									X
Central PK and Immunogenicity Testing																			
Serum for PK[12]		X[13]		X[13]		X		X		X					X				X
Serum for ADA[14]		X[14]																	X
Central Biomarker Testing																			
Serum for Serology		X				X				X									X
Serum for Cytokines		X				X				X									X
Serum for Research		X				X				X									X
Plasma for Complement		X				X				X									X
Plasma for Research		X				X				X									X
Exploratory Patient-reported Symptoms																			
SE-C19[15]		X		X	Daily														X
PGIS[15]		X		X	Daily														X
PGIC[15]																			X
[redacted]																			
[redacted]		[redacted]																	
[redacted]		[redacted]																	

ADA, anti-drug antibodies; EOS, end of study; IRR, infusion-related reaction; PGIC; Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; NP, nasopharyngeal; [redacted] PK, pharmacokinetics; 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 2: Schedule of Events: Phase 2

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1				2	3	4	5	7	8	9	11	13	15	18	22	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
Visit Location: Place of Infusion (I), Home Based (H), Phone (P)[3]	*I*				*P*[4]	*H*	*H*	*H*	*H*	*P*[4]	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]	X									±1				±1		±1		±3
Screening/Baseline (in Person)																		
Informed Consent	X																	
[redacted]	X																	
Inclusion/Exclusion	X																	
RT-PCR test for SARS-CoV-2[7]	X																	
Demographics	X																	
Medical History (incl. COVID-19 illness)	X																	
Weight and Height	X																	
Randomization		X																
Treatment (in Person)																		
Study Drug Administration			X															
Efficacy (in Person or Telemedicine)																		
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
Nasal Swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X
Safety (in Person or Telemedicine)																		
Vital Signs		X		X														
Treatment-Emergent SAEs[8]			X	X	X	X	X			X				X		X		X
Grade ≥2 Hypersensitivity Reactions[8]			X	X	X	X	X			X				X		X		X
Grade ≥2 IRRs[8]			X	X	X	X	X											
Targeted Concomitant Medications[9]	X		X	X	X	X	X			X				X		X		X
Pregnancy Test (WOCBP)[10]	X																	X
Central Laboratory Testing (in Person)																		
Hematology[11]	X																	X
Blood Chemistry[11]	X																	X

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8	9	11	13	15	18	22	25	29
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Visit Location: Place of Infusion (I), Home Based (H), Phone (P)[3]	*I*				*P*[4]	*H*	*H*	*H*	*H*	*P*[4]	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]	X									±1				±1		±1		±3
Coagulation tests[11]	X																	X
Central PK and Immunogenicity Testing (in Person)																		
Serum for PK[12]		X[13]		X[13]														X
Serum for ADA[14]		X[14]																X
Central Biomarker Testing (in Person)																		
Serum for Serology		X																X
Serum for Research		X																X
Plasma for Research		X																X
Exploratory Patient-reported Symptoms (Electronic)																		
SE-C19[15]		X		X	Daily													X
PGIS[15]		X		X	Daily													X
PGIC[15]																		X
[redacted]																		
[redacted]		[redacted]																
[redacted]		[redacted]																

ADA, anti-drug antibodies; ALT, alanine transaminase; AST, aspartate transaminase; CRP, c-reactive protein; CT, computed tomography EOI, end of infusion; EOS, end of study; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NLR, neutrophil–lymphocyte ratio; PGIC; Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; [redacted] PK, pharmacokinetics; SAE, serious adverse event; 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.

9.1.1. Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2)

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. **Phase 1 only:** Patients will be sequestered up to and including day 3. Patients have the option to leave sequester on day 4, or continue to remain sequestered until day 7. If medically appropriate, patients will be discharged on day 7 after indicated assessments have been completed. All samples and assessments indicated will be collected, regardless of location.
3. For a given day, the visit may occur at the place of infusion, place of sequester, as a home-based visit (defined as visits by home health nurses, at mobile units, and/or testing centers), or by phone/telemedicine as indicated.
4. **Phase 1:** On days 15, and 22 both home-based and phone visits will occur.

   Phase 2: On days 15 and 22, both home-based and phone visits will occur. Phone visit on day 8 is only required if patient returns home after mandatory sequester.
5. Visit windows are applicable only for visits in which samples are collected. Visits to collect information (eg, phone visits) will occur on the scheduled visit day.

[redacted]

7. Positive RT-PCR test will be obtained prior to randomization. Either rapid test (provided by Sponsor or locally) or prior documentation of positive test (≤72 hours) is acceptable. If prior test was conducted >72 hours from screening, RT-PCR must be repeated.
8. Only treatment-emergent SAEs and AESIs will be recorded in the eCRF.
9. Medications will be reviewed and recorded. Only the targeted medications listed in Section 9.3.4.3 will be recorded in the eCRF.
10. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.3.4.4 for more information on pregnancy testing and contraceptive measures.
11. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization. See Section 9.3.5 for details.
12. Actual dosing time and PK sample collection times will be recorded. Note that samples collected for PK can be analyzed, regardless of whether they are collected within the specified window.
13. At the screening/baseline visit, blood samples for PK assessment will be taken pre-dose 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.

14. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
15. Patients will self-report symptoms using the SE-C19, PGIS, and PGIC electronic surveys. Order of completion will be as follows: SE-C19, PGIS, and PGIC (when applicable).

9.1.2. Early Termination: Early Termination Visit and Follow-up Contact

Patients who are withdrawn from the study will be asked to provide a final blood draw sample for PK analysis and to have a follow-up contact by phone at the end of study.

9.2. Unscheduled Visits

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

9.3. 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 (Table 1 and Table 2).

9.3.1. 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.

9.3.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. [redacted]

9.3.1.2. RT-PCR Test for SARS-CoV-2

The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2 by RT-PCR and record the local testing result, specimen type, assay type, and date of the test in the eCRF. If local RT-PCR testing was performed >72 hours prior to screening, a new test is required for study inclusion

9.3.1.3. Demographics

Refer to Section 5.1.

9.3.1.4. Medical History

Medical history will include the following:

- Prior and current symptoms related to COVID-19
- Risk factors for hospitalization due to COVID-19, as defined in Section 8.6
- Whether the patient will be receiving oxygen at home by nasal cannula
- Menopausal history

9.3.1.5. Weight and Height

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

9.3.2. Treatment

See Section 8.1.

9.3.3. Efficacy Procedures

9.3.3.1. Nasopharyngeal, Nasal Swab, and Saliva Sample Collection

Nasal swab, saliva samples, and will be used to collect secretions from patients to determine presence or absence of SARS-CoV-2 virus and to measure viral shedding. In phase 1, NP samples will also be collected.

Samples will be used for RT-qPCR analysis. Samples may additionally be used for exploratory viral RNA sequencing (NP, nasal swab, saliva) and/or viral culture (NP, nasal swab).

Additional details regarding sample collection and analysis can be found in the laboratory manual.

9.3.3.2. Medically-Attended COVID-19 Visit Details

Details associated with any medically-attended visit will be recorded in the eCRF. This will include at minimum:

- Nature of the visit (telemedicine, urgent care, other outpatient, hospital, EC, ICU)
- Date and length of visit
- If hospitalized, whether the primary reason for hospitalization is related to COVID-19
- If outpatient medically-attended visit, whether the primary reason for the visit is related to COVID-19

COVID-19 related medically-attended visit will be defined as: hospitalization with the primary reason for hospitalization being COVID-19, or an outpatient visit (including a visit to the ER, UCC, doctor's office, or telemedicine visit) with the primary reason for the visit being COVID-19.

During the 48-hour sequestration period (phase 1 only), medically-attended visits will include any transfer of a patient from the phase 1 clinic/research unit/quarantine site to a setting indicative of worsening COVID-19 (eg, admission to an ER or hospital).

9.3.4. Safety Procedures

9.3.4.1. Vital Signs

Vital signs will include blood pressure, heart rate, respiration rate, and temperature.

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

9.3.4.2. Serious Adverse Events and Adverse Events of Special Interest

Serious adverse events (as defined in Section 10.2.1) and AESIs (as defined in Section 10.2.2) will be recorded.

Note that any symptoms collected by SE-C19, PGIC, or PGIS (Section 9.3.9) will not be considered adverse events.

9.3.4.3. Record Targeted Concomitant Medications

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

- Putative COVID-19 treatment
- Antipyretics, such as aspirin, acetaminophen, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs)
- Warfarin or other anti-thrombotic drugs
- Cyclosporine A
- Theophylline
- Digoxin
- Antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), valproic acid (Depakene®);
- Antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), quinidine (Quinidex®, Quin Release Quin-G®)
- Antivirals, antibacterial, and antifungals
- Anti-parasitics
- Interferon beta
- Corticosteroids
- Angiotensin receptor blockers, such as Azilsartan (Edarbi®), Candesartan (Atacand®), Eprosartan (Teveten®), Irbesartan (Avapro®), Losartan (Cozaar®), Olmesartan (Benicar®), Telmisartan (Micardis®), Valsartan (Diovan®)
- Angiotensin converting enzyme inhibitors: benazepril (Lotensin®), captopril (Capoten®), enalapril (Vasotec®), fosinopril (Monopril®), lisinopril (Prinivil®, Zestril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®)

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

9.3.4.4. 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. Pregnancy test will be performed at the local laboratory.

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

9.3.5. Laboratory Testing

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

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
D-dimer	Ferritin	

Hematology

Tests will include:

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

Other Laboratory Tests

Coagulation tests: Prothrombin time (PT/INR), partial thromboplastin time (PTT)

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

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

9.3.6. Drug Concentration and Measurements

Samples for PK assessment will be collected at the timepoints indicated in the schedule of events.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.3.7. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at the timepoints listed in the schedule of events.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.3.8. Exploratory Pharmacodynamic/Biomarker Analyses

9.3.8.1. Hematology for Complete Blood Count and Differential

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.

9.3.8.2. Serum and Plasma Biomarkers

Changes in circulating concentrations of serum/plasma biomarkers associated with inflammation and disease progression will be assessed in REGN10933+REGN10987 and/or REGN10989 groups as compared to the placebo group in phase 1 and phase 2. The association between changes in disease related biomarkers with clinical endpoints will be evaluated.

Biomarkers to be assessed may include, but not be limited to, the following:

C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer, and ferritin will be assessed as exploratory endpoints. CRP is a general inflammation marker that is increased and tracks with severity of COVID-19 and lung lesions. CRP is associated with adverse outcomes including supplemental O_2 requirement and death (Luo, 2020) (Qin, 2020) (Ruan, 2020) (Wang, 2020b) (Young, 2020). LDH was identified as a predictive factor for early recognition of lung injury and advanced COVID-19 cases (Han, 2020) and will be assessed as part of the clinical chemistry panel. Ferritin is a general inflammation marker that is associated with severity of COVID-19 (Qin, 2020). D-dimer levels greater than 1 µg/mL have been reported to identify patients with poor prognosis at an early stage (Zhou, 2020).

9.3.8.3. 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 will be performed on viral nucleic acid isolated from nasopharyngeal, nasal swab, and/or saliva samples.

Viral Resistance

Patients will be assessed for virologic resistance, defined as a positive RT-qPCR test at the EOS visit, an inability to reach 2 consecutive negative RT-qPCR assessments by day 29, or 2 consecutive negative RT-qPCR tests with subsequent viral load at detectable limits with positive RT-qPCR at the EOS visit. For patients who exhibit viral resistance, viral sequencing will be assessed to understand the potential relationship between genetic mutations and mAb functional activity.

Viral Infectivity

In vitro SARS-CoV-2 infectivity of cultured cells will be explored using NP and/or nasal swab samples. Infectivity of cells grown in culture will be assessed by plaque forming unit (PFU) assays and/or immunofluorescence assays. We may also use sub-genomic viral RNA transcript assays or

other measures of in vivo infectivity. Viral sub genomic mRNA is transcribed only in infected cells and is not packaged into virions, and is therefore an indicator of actively-infected cells. These various infectivity data may be associated with RT-qPCR data.

9.3.8.4. Serological Immunoassays for Anti-SARS-CoV2 Antibodies

In order to explore the impact of a baseline humoral activity SARS-CoV2 on the response to REGN10933+REGN10987, and/or REGN10989, anti-SARS-CoV2 antibodies in serum will be assayed in serological immunoassays detecting antibodies against the S protein and/or the N protein will be measured. Association of baseline serology results with clinical endpoints will be evaluated. To evaluate the effects of REGN10933+REGN10987, and/or REGN10989, on generation of a humoral immune response to SARS-CoV2, anti-SARS-CoV2 N antibodies in serum will be measured.

9.3.8.5. Serum and Plasma for Research

COVID-19, SARS-CoV-2, REGN10933+REGN10987, REGN10989, host and viral biological pathways and mechanisms related disease activity and clinical outcomes. Analyses on serum and plasma for research may include but are not limited to the following analyses.

Complement

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

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-1β and IFNγ may be measured in phase 2. Additional cytokines may be interrogated by use of cytokine panels.

The data from these exploratory analyses of complement and cytokines may not be included in the CSR.

9.3.9. Exploratory Patient-Reported Symptoms

Patients will provide self-reported symptoms using the Symptom Evolution of COVID-19 (SE-C19) instrument. This electronic survey was developed de novo by Regeneron as a means to better understand the symptomatic course of COVID-19 infection over time and is based on the current available evidence on symptoms of COVID-19 (CEBM) (Arentz, 2020) (Chen, 2020a) (Chen, 2020b) (Huang, 2020) (Song, 2020) (Wang, 2020a). Patients will self-report symptoms using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer). For each symptom, patients will be asked to rate their experience as mild, moderate, or severe at the worst moment within the last 24 hours.

To aid interpretation, the SE-C19 will be supplemented by 2 brief scales, the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS) scales, 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 will be confirmed by an interview-based study of patients and clinicians.

Note that any symptoms collected by SE-C19, PGIS, or PGIC will not be considered adverse events and will not be reconciled with any adverse events.

[redacted]

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record treatment-emergent SAEs and AESIs (as defined in Section 10.1.3) occurring during the study data collection, beginning from the pretreatment period until the end of the observation period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Throughout the study, the investigator will determine whether any treatment-emergent SAEs and AESIs have occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all serious TEAEs and AESIs 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 treatment-emergent SAEs and AESIs until they have resolved or are considered clinically stable.

Always report the diagnosis as the SAE or AESI term. When a diagnosis is unavailable, report the primary sign or symptom as the SAE or AESI 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 of SAE or AESI.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance and whether they fulfil the criteria of SAEs and AESIs and will need to be reported.

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 SAE, but the reason for the procedure may be an 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 that may occur subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should also be reported.

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

10.1.2. Reporting Procedure

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

10.2. Definitions

10.2.1. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an adverse event that had occurred in a more severe form, might have caused death.
- Requires in-patient **re-hospitalization** (readmission after discharge) or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new adverse event as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.2. Adverse Events of Special Interest

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

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

10.2.3. Infusion 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.

10.2.4. Severity

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (Division of Cancer Treatment and Diagnosis [DCTD], 2020).

Treatment-emergent SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 3.

Table 3: NCI-CTCAE General Grading System (v5.0)

not bedridden.

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

Grade	Severity	Description
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

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

10.2.5. Causality

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

The following factors should be considered when assessing causality:

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

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

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

  or

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

Causality to the study conduct (protocol specified procedure):

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

10.3. Safety Monitoring

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

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

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

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

Event expectedness for study drug is assessed against the Reference Safety Information section of the Investigator's Brochure 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 (SAP) 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 final SAPs will be issued before the first 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-2S 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 the phase 3 portion will depend on the final endpoints and treatment groups selected based on phase 2 results.

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

Endpoints are listed in Section 3.2.2. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference.

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

11.2. Justification of Sample Size

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

Due to lack of published data on the variation of time-weighted average change from baseline in viral shedding in COVID-19, the standard deviation of actual viral shedding values at a timepoint from the literature was used for sample size calculation. Blinded sample size re-estimation will be performed to assess the assumed standard deviation of primary virologic endpoint.

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 100 patients is planned for phase 1 including 60 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies and 40 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available.

Assuming a 10% dropout rate and standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 50 patients per arm in phase 2 will have at least 80% power to detect a difference of 1.25 $\log_{10}$ copies/mL. If a standard deviation of 3.8 $\log_{10}$ copies/mL is assumed (Wang, 2020c), the detectable difference would be 2.27 $\log_{10}$ copies/mL. A total sample size of up to 250 patients are needed including 150 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies when phase 2 starts, and up to 100 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available. 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 17%.

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a 10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients and is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

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. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had a 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 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.

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.

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- 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

The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22. The estimand for the primary hypothesis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the FAS. 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.

Before calculating the primary efficacy variable, missing viral shedding 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; missing values with negative RNA are imputed with 0 $\log_{10}$ copies/mL. 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 primary efficacy variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate.

The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb

treatment arm and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

Sensitivity analysis may be performed to include all available data including data collected after use of convalescent serum therapy. Other sensitivity analyses may be conducted and will be specified in the SAP.

The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented.

11.4.3.2. Secondary Efficacy Analysis

For phase 1 and phase 2, time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in other type of samples such as nasal samples, will be analyzed using the same method as the primary efficacy endpoint.

Time to event endpoints including time to negative PCR results will be analyzed using the stratified log-rank test with randomization strata as a stratification factor. Estimates of difference in median times and associated 95% confidence intervals using Kaplan-Meier method will be reported. The hazard ratio and its 95% CI will be estimated by Cox regression model with terms for treatment group and randomization strata. P-value from the stratified log-rank test will be reported.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 1 will be summarized descriptively. Difference in proportions between each anti-spike mAb treatment arm and placebo will be presented descriptively along with 95% confidence interval.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 2 will be compared between groups using stratified Cochran-Mantel-Haenszel (CMH) test at two-sided 0.05 level. P-values and 95% stratified Newcombe confidence intervals with CMH weights for the treatment difference will be presented.

The total number of COVID-19 related medically-attended visits and days of hospitalization due to COVID-19 will be summarized descriptively. To assess the time course of treatment effect in viral shedding, the change from baseline in viral shedding at each visit will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline, randomization strata, treatment, visit, 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 each anti-S mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval.

Other continuous variables including change from baseline in SE-C19 score will be analyzed using the similar MMRM method.

Subgroup analysis for the primary efficacy endpoint and selected secondary endpoints for phase 2 may be performed by randomization strata and other factors if deemed appropriate.

11.4.4. Control of Multiplicity

There will be no control for multiplicity for phase 1 data analyses. Appropriate multiplicity adjustment will be applied to control for multiple comparisons and maintain study-wise Type I error rate at a two-sided 0.05 level for the phase 2 and phase 3 portions of the study and detailed in the SAP.

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 SAEs and AESIs 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 SAEs and AESIs 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.

Phase 1 primary safety analysis

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 of SAEs and AESIs 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 10.2.4), 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

Deaths, SAEs and AESIs will also be listed.

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, REGN10987, and REGN10989 in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Phase 2 (Sparse Sampling)

The concentrations of REGN10933, REGN10987, and REGN10989 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 responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA 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 ≤ titer ≤10,000)
- High (titer >10,000)

The following analysis will be provided:

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

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

11.5. Interim Analysis

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 in-clinic visit. Safety and efficacy analyses for phase 1 will be performed when all randomized patients have completed the day 29 visit.

For phase 2, an interim analysis is planned when at least 50% of the randomized patients have completed the day 29 visit. Non-binding O'Brien-Fleming boundaries for efficacy and futility will be used as a guide to monitor the primary efficacy endpoint at an overall two-sided type-I error rate of 0.05. Bayesian predictive probability based on non-informative prior will be provided as

an additional guide for futility monitoring. Bayesian predictive probability allows computation of the probability of obtaining a positive result by the end of the trial given observed data. If the predictive probability is less than 10%, it suggests a low probability of having a positive result for the dose arm at the end of the study. The primary efficacy analysis for phase 2 will be performed when all randomized patients have completed the day 22 visit. Based on the interim and phase 2 analyses, 1 or 2 dose arms may be dropped. The interim analysis will be detailed in the SAP.

Timing and details of interim analysis for phase 3 will be provided and appropriate Type I error control will be applied once phase 3 study design is determined based on review of phase 2 data. Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

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

The study monitor and/or designee will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the monitoring strategy for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

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

12.2.2. Source Document Requirements

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

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

12.2.3. Case Report Form Requirements

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

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

12.3. Audits and Inspections

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

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

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

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

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

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

13.3. 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.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of 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

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-00112977 v1.0

ESig Approval	[redacted]
ESig Approval	[redacted]
ESig Approval	[redacted]
ESig Approval	[redacted]

Signature Page for VV-RIM-00112977 v1.0 Approved

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, REGN10989
Clinical Phase:	1/2/3
Protocol Number:	R10933-10987-COV-2067
Protocol Version:	Amendment 5
Amendment 5 Date of Issue	*See appended electronic signature page*
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
Medical/Study Director:	[redacted] Early Clinical Development and Experimental Sciences [redacted] Early Clinical Development and Experimental Sciences [redacted], Clinical Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

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 3.2.1.4 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 2 Schedule of Events: Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2

Description of Change	Brief Rationale	Section(s)
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 2 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #10 Section 9.2.5 Laboratory Tests Section 9.2.8.8 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 2 Schedule of Events: Phase 2
Minor clarifications were made to descriptions of other biomarker analyses.	To better describe planned analyses	Section 9.2.8.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.8.5 Serum and Plasma for Research Section 9.2.8.7 Cytokines
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

Description of Change	Brief Rationale	Section(s)
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	Synopsis, Target Population 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 2 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

Description of Change	Brief Rationale	Section(s)
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: • 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 2 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 2 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 1 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 9.2.8.3 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 1 Schedule of Events: Phase 1 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2

Description of Change	Brief Rationale	Section(s)
Study will be conducted in the US and other countries	To broaden reach of study	Section 6.1 Study Description and Duration
Added country as a stratification factor for randomization in phase 2	To ensure balance in study populations	Section 8.6. Method of Treatment Assignment Section 11.4 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 1 Schedule of Events: Phase 1 Table 2 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 and efficacy data during the study	To clarify the planned IDMC review process	Section 6.2.1 Independent Data Monitoring Committee
Any unused or leftover biological samples collected during the study may be used for exploratory research; maximum time period of allowable storage (for [redacted] exploratory research samples [redacted]) may be shorter per regional laws and regulations	To clarify the intended use and storage of samples	Section 9.2.6 Drug Concentration Measurements and Samples Section 9.2.7 Immunogenicity Measurements and Samples Section 9.2.8 Exploratory Pharmacodynamic/Biomarker Analyses [redacted]
The following operational changes and clarifications have been made: • 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 1 Schedule of Events: Phase 1 Table 2 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 9.1.2 Early Termination from the Study

Description of Change	Brief Rationale	Section(s)
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with eCRF	Section 9.2.4.3 Record Targeted Concomitant Medications
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 9.2.8.8 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 1 Schedule of Events: Phase 1 Table 2 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 9.2.5 Laboratory Testing Section 9.2.8.2 Serum and Plasma Biomarkers Section 9.2.8.4 Serological Immunoassays for Anti-SARS CoV 2 Antibodies Section 9.2.8.5 Serum and Plasma for Research Section 9.2.8.6 Complement Section 9.2.8.7 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 1 Schedule of Events: Phase 1 Table 2 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 Medically-Attended COVID-19 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 1 Schedule of Events: Phase 1 Table 2 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

Description of Change	Brief Rationale	Section(s)
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
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
MERS-CoV	Middle East respiratory syndrome coronavirus
mFAS	Modified full analysis set
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
REGN10989	REGN10989 monotherapy
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
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19
Site Locations	The study will be conducted in approximately 100 sites in the United States and other countries.
Principal Investigator	To be determined

Objectives

Primary

Phase 1

Part A

- 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 shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

Secondary

Phase 1

Part A

- 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 pharmacokinetic (PK) profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Part B

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To estimate the clinical efficacy of REGN10989 compared to placebo
- To compare RT-qPCR results acquired with different sample types (NP, nasal, and saliva)
- To characterize the PK profile of REGN10989 in serum
- To assess the immunogenicity of REGN10989

Phase 2

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

- To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

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 and REGN10989 monotherapy in adult outpatients (ie, ambulatory patients) with COVID-19, including asymptomatic patients with SARS-CoV-2 infection.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 but must not have been previously hospitalized or currently hospitalized. In phase 1, only patients with COVID-19 symptoms be enrolled. In phase 2, symptomatic patients and asymptomatic patients will be enrolled into separate cohorts.

Sentinel Safety Group

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

Patients in this sentinel safety group can be derived from either of 2 concurrent first-in-human (FIH) phase 1 studies (R10933-10987-COV-2067 in ambulatory patients, and R10933-10987-COV-2066 in hospitalized patients), where the safety and tolerability of REGN10933+REGN10987 (in part A) and REGN10989 (in part B) will be evaluated.

- Part A review: Patients will be pooled together from the phase 1 part A portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.
- Part B review: Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 20 patients (from one or both of the studies combined), the IDMC will review the data.

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. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment will not require the completion of phase 1 enrollment.

Phase 1

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo. Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo.

Patients in the phase 1 sentinel safety group will be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for treatment-emergent serious adverse events

	(SAEs), adverse events of special interest (AESIs), and grade 3 or 4 AEs. 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. Throughout the study, safety information (treatment-emergent SAEs, AESIs, and grade 3 or 4 AEs) will be collected, as will information about any medically-attended visits related to COVID-19. Nasopharyngeal (NP) swabs, nasal swabs, and saliva samples will be collected every other day for the first 2 weeks and then twice weekly thereafter to assess viral shedding. The study will end on day 29, when patients will have final assessments including NP swab, nasal swab, and saliva sample collection and blood draws for PK, anti-drug antibody (ADA), and exploratory analyses. **Phase 2** On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989 (after regulatory clearance), or placebo. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home. NP swabs will be collected every other day for the first 2 weeks and then twice weekly thereafter. Blood samples will also be collected periodically. Information regarding treatment-emergent SAEs, treatment-emergent AESIs, and medically-attended related to COVID-19 will be recorded throughout the study. 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.
Study Duration	The duration of the study is 30 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	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 704 patients (176 patients per arm) will be required for phase 3.
Target Population	This study will enroll adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. A patient must meet the following key criteria to be eligible for inclusion in the study. Other inclusion criteria also apply and are described in the main text: • Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as NP, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable. • Meets one of the following two criteria: a. Symptomatic Cohort (All Phases): Has symptoms consistent with COVID-19, as determined by the investigator, with onset ≤7 days before randomization **or** b. Asymptomatic Cohort (Phase 2): Meets all of the following:

	– Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization – Has had no positive SARS-CoV-2 test results from a sample collected >7 days prior to randomization – Has had no known contact (of any duration) with an individual who has confirmed COVID-19 or confirmed positive SARS-COV-2 test result >14 days prior to randomization. A patient who meets any of the following key criteria will be excluded from the study. Other exclusion criteria also apply and are described in the main text: • Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19 • Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit • Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, intravenous immunoglobulin (IVIG) (any indication), systemic corticosteroids (any indication), or COVID-19 EUA-approved treatments, where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (which is longer) from screening
Treatments	
Study Drug	• Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose • Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose • REGN10989 monotherapy, 1.2 g IV single dose (after regulatory clearance)
Placebo	• Placebo IV single dose
Endpoints	
Primary	**Phase 1** **Part A and B** • Proportion of patients with treatment-emergent SAEs through day 29 • Proportion of patients with infusion-related reactions (grade ≥2) through day 4 • Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29 • Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in NP swab samples **Phase 2** Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in NP swab samples. **Phase 3** Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.
Secondary	**Phase 1** ***Virologic*** • Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, nasal swabs, saliva)
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs
- Correlation and concordance of RT-qPCR results across different sample types (NP, nasal, and saliva)
- Time-weighted average change from baseline in viral shedding (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, REGN10987, and REGN10989 in serum and corresponding PK parameters
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989

Phase 2

Virologic

- Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP samples
- Time-weighted average change from baseline in viral shedding (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 admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only)
- Duration of symptoms consistent with COVID-19
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989

Phase 3

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in NP swabs
- Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to post-baseline study days (eg, day 5, 7, 15, and 29)

Clinical

- 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 with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients 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
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989

Procedures and Assessments

Procedures and assessments will include the following:

Efficacy

- NP swabs (all phases), nasal swabs (phase 1 only), and saliva samples (phase 1 only) for SARS-CoV-2 RT-qPCR
- Medically-attended COVID-19 visit details

Safety

- Treatment-emergent SAEs, treatment-emergent AESIs, and (phase 1 only) treatment-emergent grade 3 or 4 AEs
- Blood collection for safety labs
- Vital signs

Statistical Plan

Statistical Hypothesis

The primary statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference (if REGN10989 is available and added to the study).

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

Justification of Sample Size

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

Assuming a standard deviation of 2.1 log_{10} copies/mL, 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.

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, 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, the detectable difference would be 1.51 log_{10} copies/mL. Based on this per-arm sample size, a total sample size of approximately 1300 patients is needed. This includes 650 patients each in the symptomatic and asymptomatic cohorts (390 randomized to placebo and to the 2 REGN10933+REGN10987 combination therapy doses, as well as 260 randomized to placebo and the REGN10989 monotherapy when it is available).

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a 10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.

Statistical Analysis

Primary Efficacy Analysis

The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22, as measured by RT-qPCR in NP swab samples. The estimand for the primary hypothesis is the difference in means between each of the anti-S SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the modified FAS. The primary efficacy variable will be calculated using trapezoidal rule based on observed data and is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate. For phase 2, analysis will be performed for each cohort separately (symptomatic and asymptomatic) and for both cohorts combined.

The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo (in phase 2, for each cohort separately and for both cohorts combined), will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented.

Safety Analysis

Safety data, including treatment-emergent SAEs, treatment-emergent AESIs, treatment-emergent grade 3 or 4 AEs (phase 1 only), vital signs, and laboratory tests will be listed and summarized by treatment group.

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, 2020b) (Zhu, 2020). As of August 2020, more than 18 million confirmed cases of COVID-19 have been reported globally (WHO, 2020a). 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, 2020b). 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, 2020b). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Richardson, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support(Chen, 2020b) (Huang, 2020).

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

In contrast to hospital cases, published data for COVID-19 cases seen at emergency departments, urgent care centers, outpatient care or non-hospitalized settings are relatively limited. However, guidance has been provided by the Centers for Disease Control and Prevention (CDC) and other organizations for managing ambulatory patients and monitoring them for respiratory or other complications, indicating that some outpatient diagnoses may require subsequent hospitalization (CDC, 2020a). An anti-viral therapeutic that could be administered to ambulatory (non-

hospitalized) patients -has the potential to significantly reduce COVID-19 hospitalization and ICU admissions. Currently, there is a great need for therapies capable of reducing viral shedding and slowing or preventing COVID-19 disease progression.

1.4. 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 (Li, 2016). 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 of S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.5. REGN10933+REGN10987 and REGN10989: Fully Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing fully human, neutralizing monoclonal antibodies (mAb)s directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933, REGN10987, and REGN10989 are fully human, IgG1 mAbs that bind the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 treatment is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. REGN10989 exhibits exceptionally potent neutralization, suggesting potential use in a monotherapy setting. Importantly, all three mAbs retain neutralization potency against multiple SARS-CoV-2 S protein variants identified through clinical isolates. REGN10933+REGN10987 combination therapy and REGN10989 monotherapy thus represent promising therapeutic strategies to reduce SARS-CoV-2 viral shedding and COVID-19 disease progression.

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

Several therapeutic agents have been previously studied in the context of other coronaviruses (SARS-CoV and MERS-CoV), including corticosteroids, type 1 interferons, convalescent plasma, ribavirin, lopinavir/ritonavir, proteases, and agents targeting viral entry proteins, with generally inconsistent findings of efficacy (Sanders, 2020). Many of these therapies, as well as a number of novel treatments and vaccines, are under investigation for the treatment of COVID-19. Currently,

however, there is no approved treatment for use in ambulatory patients-, and additional controlled trials are needed.

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") and REGN10989 monotherapy ("REGN10989") in adult outpatients (ie, ambulatory patients) with COVID-19, including asymptomatic patients with SARS-CoV-2 infection.

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(s).

2. STUDY OBJECTIVES

2.1. Primary Objectives

Phase 1

The primary objectives of phase 1 are:

Part A

- 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 shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

The primary objective of phase 2 is to evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

The primary objective of phase 3 is to evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

2.2. Secondary Objectives

Phase 1

The secondary objectives of phase 1 are:

Part A

- 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

Part B

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

- To estimate the clinical efficacy of REGN10989 compared to placebo
- To compare RT-qPCR results acquired with different sample types (NP, nasal, and saliva)
- To characterize the PK profile of REGN10989 in serum
- To assess the immunogenicity of REGN10989

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 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

The secondary objectives of phase 3 are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

2.3. Exploratory Objectives

The exploratory objectives for phase 1 and phase 2 are:

- To assess viral genetic variation in patients with a positive SARS-CoV-2 RT-qPCR
- To explore the potential association of baseline humoral immune response to SARS-CoV-2 on response to REGN10933+REGN10987 and/or REGN10989
- To evaluate the effects of REGN10933+REGN10987 and/or REGN10989 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 and/or REGN10989 on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays

- To explore biomarkers predictive of REGN10933+REGN10987 and/or REGN10989 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To understand the underlying mechanisms of action and biology of REGN10933+REGN10987 and/or REGN10989, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 and/or REGN10989 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 and/or REGN10989 compared to placebo

Additional exploratory objective for phase 1 only:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 and/or REGN10989 compared to placebo

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 1

Treatment of ambulatory patients with COVID-19 with REGN10933+REGN10987 and/or REGN10989 will be tolerated and will reduce viral shedding.

Phase 2

Treatment of ambulatory patients with SARS-CoV-2 infection-with REGN10933+REGN10987 and/or with REGN10989 will reduce viral RNA shedding.

Phase 3

Treatment of outpatients with COVID-19 with REGN10933+REGN10987 and/or with REGN10989 will improve clinical outcomes.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

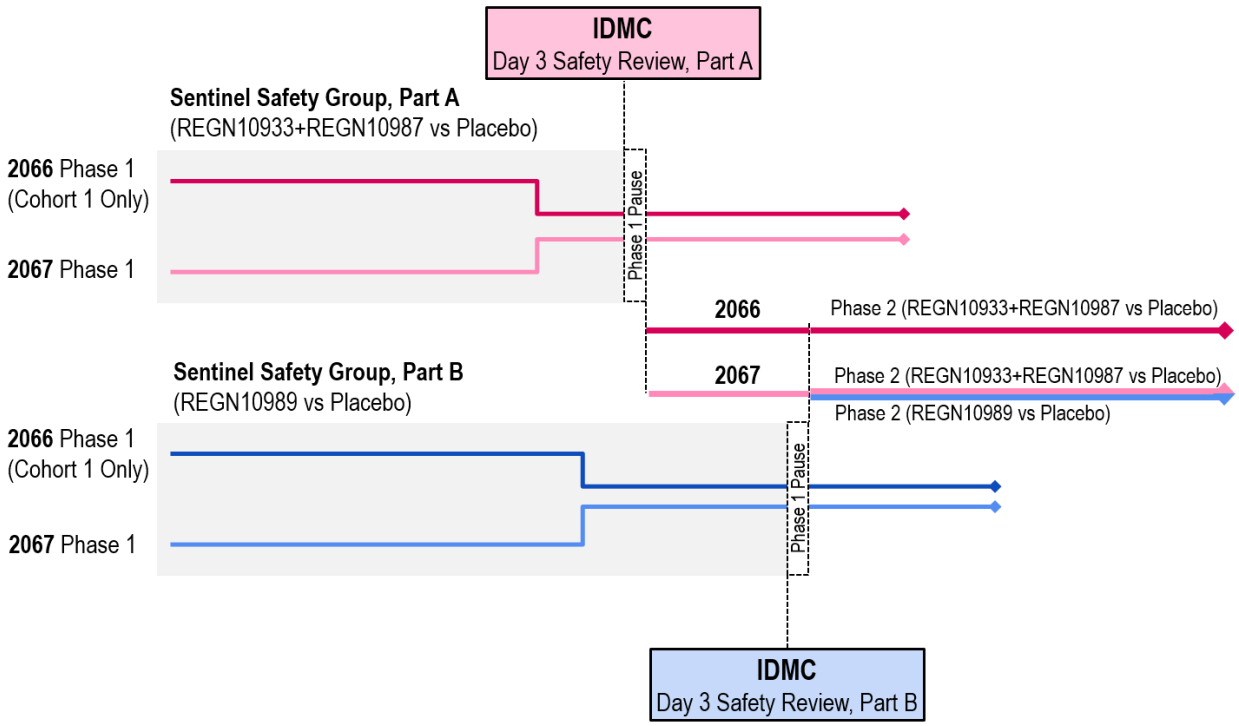
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 and REGN10989 in ambulatory patients with COVID-19 (including those with asymptomatic SARS-CoV-2 infection). The multicenter conduct of this 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 (see Section 3.3).

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 (in part A) and REGN10989 (in part B) 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

Two separate IDMC reviews will occur: one to assess REGN10933+REGN10987 (part A), and one to assess REGN10989 (part B).

- **Part A review:** Patients will be pooled together from the phase 1 part A 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.
- **Part B review:** Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 20 patients (from one or both of the studies combined), the IDMC will review the data.

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

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

After the IDMC reviews and provides a positive recommendation for the phase 1 part A 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. After the IDMC reviews and provides a positive recommendation for the phase

1 part B sentinel safety group, enrollment of studies assessing REGN10989 (including REGN10989 treatment arm in phase 2 of R10933-10987-COV-2067) may begin.

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

Review of Sentinel Safety Group, Part A (information added to protocol in amendment 5)

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

3.2.1.2. Adaptive Master Protocol Design

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

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

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

The design will allow for the addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing (umbrella design), refinement of disease characteristics of eligible study populations (basket design), as well as other multiple adaptations, including dropping of a treatment arm, determination of phase 3 primary endpoints, and phase 3 sample size estimation.

3.2.1.3. Rationale for Primary 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 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 targeted treatment-emergent grade 3 or 4 TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs (grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions) will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987 and/or REGN10989. 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 health care delivery system.

Virologic Efficacy

The primary mechanism of action of REGN10933+REGN10987 and REGN10989 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 shedding 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 and REGN10989 to reduce viral shedding 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) (Cao, 2020) (Wang, 2020c). 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 shedding occurs just before or soon after the onset of COVID-19 symptoms (He, 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 REGN10989 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. The study 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 Due to COVID-19

In phase 2 randomization will be stratified based on risk factors for hospitalization due to COVID-19 (refer to Section 8.6 for complete definition of risks factors; also note that other stratification factors will be used as described in Section 8.6).

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), cancer, and chronic kidney disease (CDC, 2020b) (Lighter, 2020) (Wu, 2020b) (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) 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).

3.2.2. Rationale for Dose Selection

This study will assess a single IV dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio as well as IV administration of REGN10989 as a single agent. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are non-competing mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure[s]). The study will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2.4 g (1.2 g per mAb), which is expected to be an efficacious dose (see below). The study will also evaluate REGN10933+REGN10987 at a higher dose, 8.0 g (4.0 g per mAb), in the event that a higher dose is required for efficacy.

The study will also assess single dose, intravenous REGN10989, a mAb that has at least 5-fold greater in vitro neutralization potency (EC_{50})* than either REGN10933 or REGN10987. Based on this difference in potency, REGN10989 will be tested at 1.2 g; a dose equivalent to the initial dose level for each of the individual mAbs in the combination therapy REGN10933+REGN10987. Although the primary goal is to assess safety and tolerability of REGN10989 in this study, the use of this lower dose will allow a greater ability to discriminate the potential superior activity of this antibody as monotherapy for use in other studies. REGN10989 will not be further assessed in this protocol after Phase 1.

Cellular entry of coronaviruses depends on binding of the S protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. ACE2 is the receptor for cellular entry of SARS-CoV-2 and its gene expression has been reported in the lungs, particularly in type-2 alveolar

epithelial cells and bronchial airway epithelium (Wu, 2020a) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration of 99% viral neutralization (EC_{99})* observed against live virus SARS-CoV-2 and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC_{99} against SARS-CoV-2 is 0.14 µg/mL (REGN10933), 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 1.2 g per mAb is predicted to result in ≥95% of patients exceeding the target serum concentration for 28 days after dosing, for each mAb.

A 4-week Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys assessing once-weekly dosing of up to REGN10933+REGN10987 (at 150 mg/kg per antibody) and REGN10989 (150 mg/kg) is being conducted to support the safety of these mAbs.

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

3.3. Risk-Benefit

An assessment of risks and benefits is provided in the Investigator's Brochure(s).

4. ENDPOINTS

4.1. Primary Endpoint

Phase 1

The primary endpoints for phase 1 are:

Part A and B

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

  Note: Time-weighted average of change from baseline viral shedding from day 1 to day 22 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 shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in NP swab samples.

Phase 3

The primary endpoint for phase 3 is proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.

4.2. Secondary Endpoints

Phase 1

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, nasal swabs, saliva)
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples

- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs
- Correlation and concordance of RT-qPCR results across different sample types (NP, nasal, and saliva)
- Time-weighted average change from baseline in viral shedding (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

  Note: COVID-19 related medically-attended visits are defined in Section 9.2.3.2.
- 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, REGN10987, and REGN10989 in serum and corresponding PK parameters
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989

Phase 2

The secondary endpoints for phase 2 are:

Virologic

- Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP samples
- Time-weighted average change from baseline in viral shedding (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 admitted to an ICU due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only)
- Duration of symptoms consistent with COVID-19
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989

Phase 3

The secondary endpoints for phase 3 are:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in NP swabs
- Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Time-weighted average change from baseline in viral shedding (log10 copies/mL) from day 1 to post-baseline study days (eg, day 5, 7, 15, and 29)

Clinical

- 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 with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29

- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent 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

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies to REGN10933, REGN10987, and REGN10989

4.3. Exploratory Endpoints

The exploratory endpoints for phase 1 and phase 2 are:

- Proportion of patients with treatment failure having mutations in the gene encoding the SARS-CoV-2 S protein through day 29
- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29
- 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 ICU due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.2.

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

Efficacy variables include viral shedding (log_{10} copies/mL), number of COVID-19 related medically-attended visits, 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 TEAEs (grade 3 or 4; phase 1 only), incidence of treatment-emergent SAEs and incidence of treatment-emergent AESIs Section 10.1.3.

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point, and select PK parameters. For phase 2, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point The PK sampling time points are specified in the schedule of events (Table 1 and Table 2).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples will be collected at the visits specified in the schedule of events (Table 1 and Table 2).

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, and PGIC score.

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 and REGN10989 monotherapy in outpatient (ie, ambulatory) adults with COVID-19, including asymptomatic patients with SARS-CoV-2 infection. The study will be conducted in approximately 100 sites, in the US and other countries.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 -but must not have been previously hospitalized or currently hospitalized. 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 (refer to Section 7.2 for study inclusion and exclusion criteria).

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).

The schedule of events can be found in Table 1 (phase 1) and Table 2 (phase 2). See Figure 2 (phase 1) and Figure 3 (phase 2) for study flow diagrams. Additional information on study procedures can be found in Section 9.2.

6.1.1. Phase 1

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, 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.

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo (refer to Section 8.6 for more information on treatment arms and dosing). Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

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

On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989 (after regulatory clearance), 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

The clinical efficacy endpoints, virologic endpoints (including sample types), treatment arms, and final sample size for phase 3 are subject to change and will be informed by phase 2 data.

Prior to initiation of phase 3, enrollment may pause for IDMC review of phase 2.

Figure 2: Study Flow Diagram, Phase 1

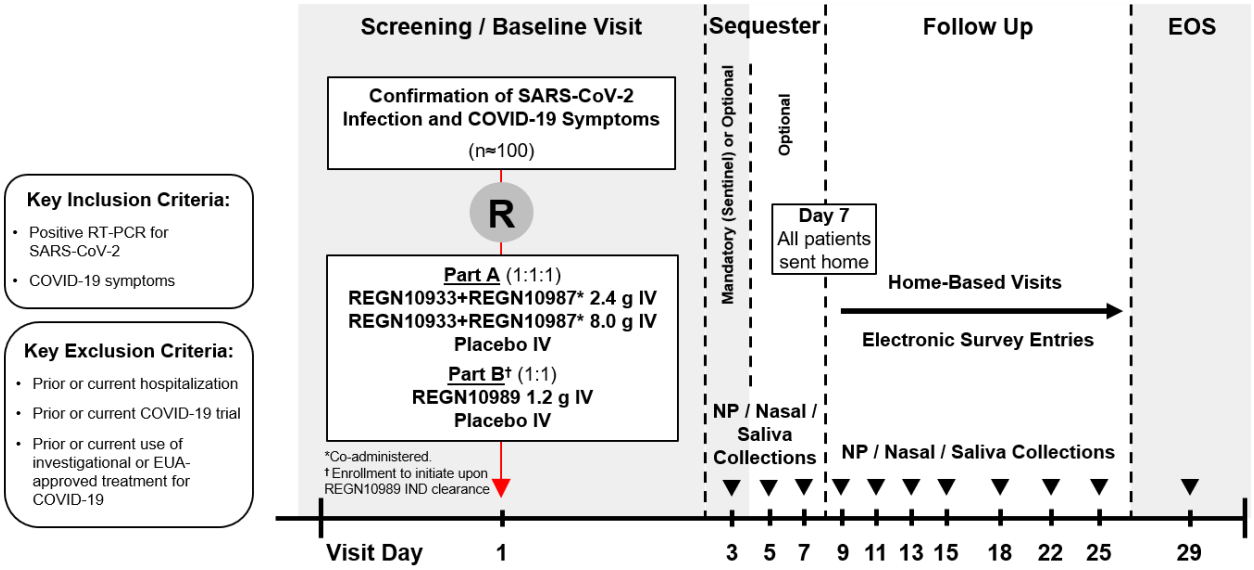
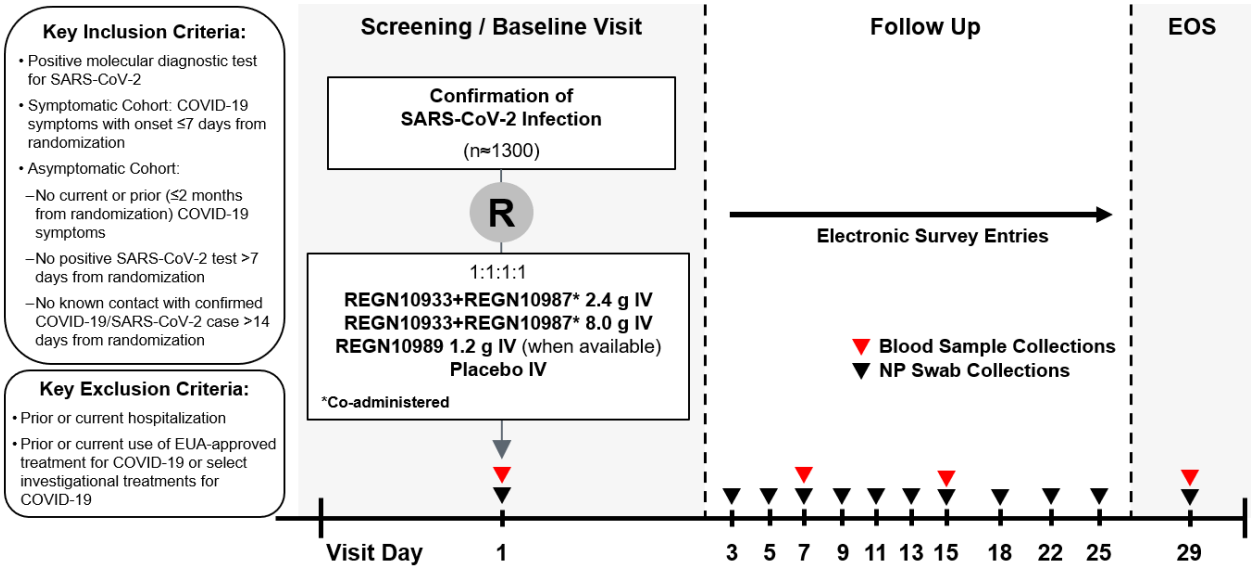


Figure 3: Study Flow Diagram, Phase 2



6.1.4. Study Stopping Rules

6.1.4.1. Individual Patient Stopping Rules

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

Patient stopping rules from the study include withdrawal of consent.

6.1.4.2. Study Stopping Criteria

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

6.1.5. End of Study Definition

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

6.2. 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 in Section 11.5, and blinding implications are discussed in Section 8.7.

Phase 1

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 visit. Safety and efficacy analysis for phase 1 will be performed when all randomized patients have completed the day 29 visit.

Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

Phase 2

Given the context of a public health emergency, interim analyses for phase 1 and phase 2, combined or alone, may be performed at various times at Sponsor's discretion. The primary efficacy analysis for phase 2 will be performed when all randomized patients in each cohort have completed the day 22 visit.

Phase 3

An interim analysis plan for phase 3 will be specified when adaptations for phase 3 are implemented in the study.

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 704 patients (176 patients per arm) will be required for phase 3.

For information on the timing of enrollment, 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 adult, 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. Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization
2. Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as NP, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable.
3. [Criterion removed]
4. Meets 1 of the following 2 criteria:

    a. **Symptomatic Cohort (All Phases):** Has symptoms consistent with COVID-19 as determined by the investigator with onset ≤7 days before randomization

    or

    b. **Asymptomatic Cohort (Phase 2):** Meets all of the following:

    - Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization
    - Has had no positive SARS-CoV-2 test results from a sample collected >7 days prior to randomization
    - Has had no known contact (of any duration) with an individual who has confirmed COVID-19 or confirmed positive SARS-COV-2 test result >14 days prior to randomization.

5. Maintains O_2 saturation ≥93% on room air

6. Is willing and able to provide informed consent signed by study patient or legally acceptable representative
7. Is willing and able to comply with study procedures, including providing samples for viral shedding testing

7.2.2. Exclusion Criteria

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

1. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19
2. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 EUA approved treatments, where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (which 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. Pregnant or breastfeeding women
9. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

   Highly effective contraceptive measures in women include:

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

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

* WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

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

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

7.3. Premature Withdrawal from the Study

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

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

Patient who are withdrawn prematurely from the study will be asked to complete an early termination visit and follow up contact, as described in Section 9.1.2.

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 the method of treatment allocation for each phase of the study.

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose
- 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

In part A, 60 patients will be randomized in a 1:1:1 allocation ratio to one of the following:

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

In part B, 40 patients will be randomized in a 1:1 allocation ratio to one of the following:

- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

In phase 1, randomization will not be stratified.

Phase 2

Patients will be randomized in a 1:1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS):

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose (only after regulatory clearance)
- 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 3.2.1.4):

- 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

The treatment arms, patient cohorts, sample size, and treatment allocation scheme for phase 3 will be finalized after review of phase 2 data.

8.7. Blinding

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

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

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

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

8.8. Emergency Unblinding

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

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patients will be unblinded
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IWRS which will notify Regeneron

- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

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

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

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

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

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

8.9.4. Treatment Compliance

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

8.10. Concomitant Medications

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

For more information on recording of concomitant medications, 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 unless medically indicated (Section 7.2.2). Patients may otherwise continue their normal regimen of medications and procedures.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Table 1: 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	±3
Screening/Baseline Only																			
Informed consent	X																		
[redacted]	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
Nasal swab for SARS-CoV-2 RT-qPCR		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
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																			
Hematology (including differential)	X[10]									X									X

Day	Screening/Baseline Visit[1]				Mandatory / Optional Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1																		
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	6	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
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	±3
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
[redacted]																			
[redacted]		[redacted]																	
[redacted]		[redacted]																	

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; [redacted] 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 2: Schedule of Events: Phase 2

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
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																	
[redacted]	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
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

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
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
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
[redacted]																		
[redacted]		[redacted]																
[redacted]		[redacted]																

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; [redacted] 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.

9.1.1. Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2)

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. **Phase 1 sentinel safety group only:** Patients will be sequestered up to day 3 (mandatory). Patients have the option to leave sequester on day 3 (if medically appropriate) after completing the indicated assessments, or continue to remain sequestered for any period of time up to day 7. After completing assessments on day 7, all patients who are still sequestered in the sentinel safety group will be sent home, if medically appropriate.

   All other patients in phase 1: Optional sequestering is allowed for other patients in phase 1. These patients may choose 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.
3. On days 8, 15, and 22, information will be collected by the site on medically-attended visits, targeted concomitant medications, treatment-emergent SAEs, treatment-emergent AESIs, and (for phase 1 only) treatment-emergent grade 3 or 4 AEs. This information may be collected by phone; however, days 15 and 22 will still require in-person visits for sample collections. Phone visits will have a window of ±1 day.

[redacted]

5. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
6. Vital signs, including temperature, blood pressure, heart rate, SpO_2, and respiratory rate (for phase 1 only), will be collected as described in Section 9.2.4.1.

   For patients in the **phase 1 sentinel safety group only**, vital signs will be taken once before the infusion, every 15 minutes during the infusion, every 30 minutes for the first 2 hours after the infusion is completed, and then once per hour for the following 4 hours.

   For **all other** patients (phase 1 and phase 2), 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 2 hours.
7. Only treatment-emergent SAEs, treatment-emergent AESIs, and (in phase 1 only) treatment-emergent grade 3 or 4 AEs will be recorded. See Section 10.
8. Medications will be reviewed and recorded. Only the targeted medications listed in Section 9.2.4.3 will be recorded in the eCRF.
9. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.4.4 for more information.
10. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization.
11. Actual dosing time and PK sample collection times will be recorded.

12. At the screening/baseline visit, blood samples for PK assessment will be taken pre-dose 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.
13. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
14. Patients will self-report symptoms using the SE-C19, PGIS, and PGIC electronic surveys. Order of completion will be as follows: SE-C19, PGIS, and PGIC (when applicable).

9.1.2. Early Termination from the Study

Patients who are withdrawn from the study will be asked to allow an early termination visit consisting of day 29 (EOS) assessments and sample collections. In addition, patients will be contacted by phone on day 29 to obtain vital status and information on medically-attended visits.

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 follow-up of treatment-emergent SAEs, treatment-emergent AESIs, and (for phase 1) treatment-emergent grade 3 or 4 AEs, 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 (Table 1 and Table 2).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

9.2.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. [redacted]

9.2.1.2. Diagnostic Test for SARS-CoV-2

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

9.2.1.3. Demographics

Refer to Section 5.1.

9.2.1.4. Medical History

Medical history will include the following:

- COVID-19, if applicable, with start date as the date of onset of first symptoms related to COVID-19
- Risk factors for hospitalization due to COVID-19, as defined in Section 8.6
- Whether the patient will be receiving oxygen at home by nasal cannula
- Menopausal history

9.2.1.5. Weight and Height

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

9.2.2. Treatment

See Section 8.1.

9.2.3. Efficacy Procedures

9.2.3.1. Nasopharyngeal Swab, Nasal Swab, and Saliva Collection

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

9.2.3.2. Medically-Attended COVID-19 Visit Details

Details associated with any medically-attended visit will be recorded in the eCRF. This will include at minimum:

- Nature of the visit (telemedicine, urgent care, other outpatient, hospital, EC, ICU)
- Date and length of visit
- If hospitalized, whether the primary reason for hospitalization is related to COVID-19
- If outpatient medically-attended visit, whether the primary reason for the visit is related to COVID-19

COVID-19 related medically-attended visit will be defined as: hospitalization with the primary reason for hospitalization being COVID-19, or an outpatient visit (including a visit to the ER, UCC, doctor's office, or telemedicine visit) with the primary reason for the visit being COVID-19.

For patients undergoing mandatory or optional sequestering, medically-attended visits will include any transfer of a patient from the phase 1 clinic/research unit/quarantine site to a setting indicative of worsening COVID-19 (eg, admission to an ER or hospital).

9.2.4. Safety Procedures

9.2.4.1. Vital Signs

Vital signs will include temperature, blood pressure, heart rate (per minute), SpO_2. 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.

SpO_2 will be measured using a fingertip or similar non-invasive device following 5 minutes of rest (inactivity) while supine, semi-recumbent, or sitting and will only be measured in the presence of a good SpO_2 wave form.

9.2.4.2. Adverse Event Monitoring

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

Note that any symptoms collected by SE-C19, PGIC, or PGIS (Section 9.2.8.8) will not be considered adverse events.

9.2.4.3. Record Targeted Concomitant Medications

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

- Putative COVID-19 treatments (eg, remdesivir, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- Antipyretics (eg, aspirin, acetaminophen, ibuprofen)
- Anticoagulants (eg, enoxaparin, warfarin, rivaroxaban)
- Immunosuppressants (eg, cyclosporine A, corticosteroids)
- Interferon beta
- Theophylline
- Antiepileptics (eg, carbamazepine, divalproex, phenytoin)
- Antiarrhythmics (eg, digoxin, disopyramide, procainamide)
- Antivirals, antibacterial, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)
- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril). For more information on concomitant medications, refer to Section 8.10.

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

9.2.4.4. 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. Pregnancy test will be performed at the local laboratory.

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

9.2.5. Laboratory Testing

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

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
Ferritin		

Hematology

Tests will include:

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

Other Laboratory Tests

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

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

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

9.2.6. Drug Concentration Measurements and Samples

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

9.2.7. Immunogenicity Measurements and Samples

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

9.2.8. Exploratory Pharmacodynamic/Biomarker Analyses

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

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

9.2.8.1. 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.

9.2.8.2. Serum and Plasma Biomarkers

Changes in circulating concentrations of serum/plasma biomarkers associated with inflammation and disease progression will be assessed in REGN10933+REGN10987 and/or REGN10989 groups compared to the placebo group in phase 1 and phase 2. The association between changes in disease related biomarkers with clinical endpoints will be evaluated.

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

9.2.8.3. 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 will be performed on viral nucleic acid isolated from nasopharyngeal, nasal swab, and/or saliva samples at baseline. Sequencing analyses will consist of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

Viral Resistance

Patients will be assessed for virologic resistance if they meet 1 or more of the following criteria:

- An inability to reach 2 consecutive negative RT-qPCR assessments by day 29

  and/or

- 2 consecutive negative RT-qPCR tests with subsequent positive RT-qPCR test result,

and/or

- Any other pattern that suggests an emergence of viral resistance.

For patients whose RT-qPCR findings suggest potential viral resistance, viral sequencing will 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.

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

Viral Infectivity

To explore the effects of REGN10933+REGN10987 or REGN10989 on infectivity of SARS-CoV-2, we may use viral culture or subgenomic viral RT-qPCR assays. In vitro SARS-CoV-2 infectivity of cultured cells may be explored using NP and/or nasal swab samples. Infectivity of cells grown in culture may be assessed by plaque forming unit (PFU) assays and/or immunofluorescence assays. We may also use sub-genomic viral mRNA transcript assays 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 is therefore an indicator of actively-infected cells. These data may be associated with other RT-qPCR measuring viral shedding.

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

To explore the impact of baseline humoral activity against SARS-CoV-2 on the response to REGN10933+REGN10987 and/or REGN10989, 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 and/or REGN10989 effect the endogenous humoral immune response to SARS-CoV-2.

9.2.8.5. Serum and Plasma for Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN10933+REGN10987, REGN10989, 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.

9.2.8.6. Complement

Complement activation has been hypothesized to contribute to the maladaptive inflammatory response seen in some patients with advanced COVID-19. Circulating complement biomarker concentrations may 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.

9.2.8.7. Cytokines

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

9.2.8.8. Serum and Plasma for Cardiac Biomarkers

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

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

9.2.9. Exploratory Patient-Reported Symptoms

Patients will provide self-reported symptoms using the Symptom Evolution of COVID-19 (SE-C19) survey. This electronic survey was developed de novo by Regeneron as a means to better understand the symptomatic course of COVID-19 infection over time and is based on current available evidence on symptoms of COVID-19 (CEBM) (Arentz, 2020) (Chen, 2020a) (Chen, 2020b) (Huang, 2020) (Song, 2020) (Wang, 2020a). Patients will self-report symptoms using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer).

Patients are presented with a list symptoms and are asked to identify all those that they are experiencing. For each symptom they identify, they will be asked to rate their experience 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 item of the SE-C19 is subjectively scored from 0 (no symptom) to 3 (severe symptom).To aid interpretation, the SE-C19 will be supplemented by 2 brief surveys, 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 will be confirmed through an interview-based study of patients and clinicians, separate from this study.

Note that any symptoms collected by SE-C19, PGIS, or PGIC will not be considered AEs and will not be reconciled with any AEs.

[redacted]

[redacted]

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

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

- **All phases:** Treatment-emergent AESI (grade ≥2 hypersensitivity and grade ≥2 IRRs; see Section 10.1.3)
- **All phases:** Treatment-emergent SAEs
- **Phase 1 only:** TEAEs (grade 3 or grade 4 only)

The investigator must promptly record treatment-emergent SAEs, treatment-emergent AESI), and (in phase 1 only) grade 3 or 4 treatment-emergent AEs occurring during the observation period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as TEAE, provided that it fulfills the above criteria.

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

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

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to

signing the informed consent form [ICF]) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

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

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

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

10.1.2. Reporting Procedure

All treatment-emergent SAEs, treatment-emergent AESI, and (in phase 1 only) treatment-emergent grade 3 or 4 AEs must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, 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
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient for up to 6 months after the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor.

10.2. 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.

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

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 3.

Table 3: NCI-CTCAE Severity Grading System for Adverse Events (v5.0)

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

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

10.2.6. 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 final SAPs will be issued before the first 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 the phase 3 portion will depend on the final endpoints and treatment groups selected based on phase 2 results.

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

Endpoints are listed in Section 3.2.2. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference

- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference (if REGN10989 is available and added to the study).

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

11.2. Justification of Sample Size

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

Due to lack of published data on the variation of time-weighted average change from baseline in viral shedding in COVID-19, the standard deviation of actual viral shedding 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 100 patients is planned for phase 1 including 60 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies and 40 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available and added to the study.

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 1300 patients is needed. This includes 650 patients each in the symptomatic and asymptomatic cohorts (390 randomized to placebo and to the 2 REGN10933+REGN10987 combination therapy doses, as well as 260 randomized to placebo and the REGN10989 monotherapy when it is available). 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%.

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a 10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients 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).

Efficacy endpoints will be analyzed using the FAS and/or mFAS.

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. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had a 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 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.

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 8.6.

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- 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

The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22, as measured by RT-qPCR in NP swab samples. The estimand for the primary hypothesis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the mFAS. 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.

Before calculating the primary efficacy variable, uncertain viral shedding 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 primary efficacy variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate. For phase 2, analysis will be performed for each cohort separately (symptomatic and asymptomatic) and for both cohorts combined.

The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo (in phase 2, for each cohort separately and for both cohorts combined), will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

Sensitivity analysis may be performed to include all available data including data collected after use of convalescent serum therapy. Other sensitivity analyses may be conducted for FAS for each cohort separately and for both cohorts combined and will be specified in the SAP.

The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented.

11.4.3.2. Secondary Efficacy Analysis

For phase 1 time-weighted average change from baseline in viral shedding ($\log_{10}$ copies/mL) from day 1 to day 22 as measured by RT-qPCR in other sample types (nasal swabs and saliva), will be

analyzed using the same method as the primary efficacy endpoint based on mFAS and FAS. The same method will be used to analyze the time-weighted average change from baseline in viral shedding (log10 copies/mL) from day 1 to other post-baseline visit timepoints for phase 1 and phase 2. Time to event endpoints including time to negative PCR results for phase 1 will be analyzed using Kaplan-Meier method based on mFAS and FAS. Estimates of median times and associated 95% confidence intervals will be reported. The hazard ratio and its 95% CI will be estimated by Cox regression model with terms for treatment group.

Time to event endpoints including time to negative PCR results for phase 2 will be analyzed using the stratified log-rank test with randomization strata as a stratification factor based on mFAS and FAS for each cohort separately and for both cohorts combined. Estimates of median times and associated 95% confidence intervals using Kaplan-Meier method will be reported. The hazard ratio and its 95% CI will be estimated by Cox regression model with terms for treatment group and randomization strata. P-value from the stratified log-rank test will be reported. Time to onset of symptoms consistent with COVID-19 will be analyzed using the similar method for the asymptomatic cohort.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 1 will be summarized descriptively based on FAS. Difference in proportions between each anti-spike mAb treatment arm and placebo will be presented descriptively along with 95% confidence interval.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 2 will be compared between groups using stratified Cochran-Mantel-Haenszel (CMH) test at two-sided 0.05 level based on FAS for each cohort separately. P-values and 95% stratified Newcombe confidence intervals with CMH weights for the treatment difference will be presented.

The total number of COVID-19 related medically-attended visits, days of hospitalization due to COVID-19, and duration of symptoms consistent with COVID-19 will be summarized descriptively based on FAS for each cohort separately.

To assess the time course of treatment effect in viral shedding, the change from baseline in viral shedding at each visit will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline, randomization strata, treatment, visit, and treatment-by-visit interaction based on mFAS and FAS for each cohort separately and for both cohorts combined. 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 each anti-S mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval.

Other continuous variables including change from baseline in SE-C19 score for each cohort will be summarized descriptively.

The phase 1 comparison between NP swab, nasal swab and saliva RT-qPCR results (in $\log_{10}$ copies/mL) or the qualitative results (positive, negative) will be analyzed using the following methods. Scatter plots will be generated to show the correlation pattern between different samples at each study day, if data is available. Bland-Altman plots will be generated and Lin's concordance

correlation coefficient, Spearman rank coefficient, and Cohen's kappa coefficient will be estimated by treatment group as well as for pooled treatment groups, to show pairwise comparisons between the various sample types (NP swab, nasal swab and saliva swab) (Altman, 1983) (Lin, 1989). No statistical testing will be performed.

Subgroup analysis for the primary efficacy endpoint and selected secondary endpoints for phase 2 may be performed by randomization strata and other factors if deemed appropriate.

11.4.4. Control of Multiplicity

For phase 1 primary analysis of safety endpoints, no multiplicity adjustment will be applied. The primary virologic efficacy endpoint will be tested at α=0.05 for part A and part B, separately.

Appropriate multiplicity adjustment will be applied for the phase 2 and phase 3 portions of the study and detailed in the SAP.

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.

Phase 1 primary safety analysis

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 of SAEs and AESIs 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 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, REGN10987, and REGN10989 in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Phase 2 (Sparse Sampling)

The concentrations of REGN10933, REGN10987, and REGN10989 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 responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA 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 ≤ titer ≤10,000)
- High (titer >10,000)

The following analysis will be provided:

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

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

11.5. Interim Analysis

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 in-clinic visit. Safety and efficacy analyses for phase 1 will be performed when all randomized patients have completed the day 29 visit.

Given the context of a public health emergency, interim analyses for phase 1 and phase 2 combined or alone, may be performed at various times at the sponsor's discretion. Non-binding O'Brien-Fleming boundaries for efficacy will be used as a guide to monitor the primary efficacy endpoint. Details will be specified prior to conducting the interim analyses. Bayesian predictive probability based on non-informative prior will be provided as a guide for futility monitoring. Bayesian predictive probability allows computation of the probability of obtaining a positive result by the end of the trial given observed data. If the predictive probability is less than 10%, it suggests a low probability of having a positive result for the dose arm at the end of the study. The primary efficacy analysis for phase 2 will be performed when all randomized patients have completed the day 22 visit. Based on the interim and phase 2 analyses, 1 or 2 dose arms may be dropped. The interim analyses will be detailed in the SAP.

Timing and details of interim analysis for phase 3 will be provided and appropriate Type I error control will be applied once phase 3 study design is determined based on review of phase 2 data. Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

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

The study monitor and/or designee will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the monitoring strategy for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

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

12.2.2. Source Document Requirements

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

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

12.2.3. Case Report Form Requirements

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

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

12.3. Audits and Inspections

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

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

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

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

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

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

13.3. 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.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of 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 5

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-00121100 v1.0

ESig Approval	[redacted]
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ESig Approval	[redacted]

Signature Page for VV-RIM-00121100 v1.0 Approved

AMENDMENT HISTORY

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 3.2.1.4 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 2 Schedule of Events: Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2

Description of Change	Brief Rationale	Section(s)
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 2 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #10 Section 9.2.5 Laboratory Tests Section 9.2.8.8 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 2 Schedule of Events: Phase 2
Minor clarifications were made to descriptions of other biomarker analyses.	To better describe planned analyses	Section 9.2.8.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.8.5 Serum and Plasma for Research Section 9.2.8.7 Cytokines
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

Description of Change	Brief Rationale	Section(s)
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	Synopsis, Target Population 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 2 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

Description of Change	Brief Rationale	Section(s)
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: • 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 2 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 2 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 1 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 9.2.8.3 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 1 Schedule of Events: Phase 1 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2

Description of Change	Brief Rationale	Section(s)
Study will be conducted in the US and other countries	To broaden reach of study	Section 6.1 Study Description and Duration
Added country as a stratification factor for randomization in phase 2	To ensure balance in study populations	Section 8.6. Method of Treatment Assignment Section 11.4 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 1 Schedule of Events: Phase 1 Table 2 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 and efficacy data during the study	To clarify the planned IDMC review process	Section 6.2.1 Independent Data Monitoring Committee
Any unused or leftover biological samples collected during the study may be used for exploratory research; maximum time period of allowable storage (for [redacted] exploratory research samples [redacted]) may be shorter per regional laws and regulations	To clarify the intended use and storage of samples	Section 9.2.6 Drug Concentration Measurements and Samples Section 9.2.7 Immunogenicity Measurements and Samples Section 9.2.8 Exploratory Pharmacodynamic/Biomarker Analyses [redacted]
The following operational changes and clarifications have been made: • 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 1 Schedule of Events: Phase 1 Table 2 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 9.1.2 Early Termination from the Study

Description of Change	Brief Rationale	Section(s)
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with eCRF	Section 9.2.4.3 Record Targeted Concomitant Medications
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 9.2.8.8 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 1 Schedule of Events: Phase 1 Table 2 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 9.2.5 Laboratory Testing Section 9.2.8.2 Serum and Plasma Biomarkers Section 9.2.8.4 Serological Immunoassays for Anti-SARS CoV 2 Antibodies Section 9.2.8.5 Serum and Plasma for Research Section 9.2.8.6 Complement Section 9.2.8.7 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 1 Schedule of Events: Phase 1 Table 2 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 Medically-Attended COVID-19 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 1 Schedule of Events: Phase 1 Table 2 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

Description of Change	Brief Rationale	Section(s)
Editorial updates implemented	To ensure clarity, accuracy, and consistency	Section 8.7 Blinding

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
INITIAL PHASE 1 / 2 PORTION OF THE STUDY
VERSION: FINAL V1.0

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 (REGN-CoV2)
Protocol Number:	R10933-10987-COV-2067
Clinical Phase:	Phase 1/2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatisticians:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Directors:	[redacted]
Version/Date:	Original (Version 1.0) / 23 SEP 2020

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Study Biostatisticians [redacted]

See appended electronic signature page

Study Clinical Pharmacologist [redacted]

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Study Medical Directors [redacted]

See appended electronic signature page

Project Biostatistician [redacted]

See appended electronic signature page

Head of BDM [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
ECG	Electrocardiogram
ICH	International Council for Harmonisation
IWRS	Interactive Web Response System
IV	Intravenous
mFAS	Modified full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OP	Oropharyngeal
NP	Nasopharyngeal
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cell
RNA	Ribonucleic Acid
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set

Abbreviation	Definition
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper Limit Normal
US	United States (of America)
WBC	White blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the integrity of the study results by pre-specifying the statistical approaches for the analysis of study data prior to a database lock of this phase 1/2/3 adaptive study R10933-10987-COV-2067 of anti-Spike SARS-CoV-2 monoclonal antibodies in ambulatory patients with COVID-19. This version of the SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for the first 275 subjects randomized between a combined phase 1/2 portion of the study based on the Protocol Amendment 5 (dated 08-AUG-2020). A separate SAP will be written for the subsequent portion(s) of the study.

Based on blinded review of virologic data from the study, it became apparent that the primary virologic endpoint of the study should have been limited to approximately the first week on study and prioritized to evaluation of patients who were seronegative at baseline. However, because some individuals in the company (Sponsor) had been unblinded to portions of the virologic data at an earlier timepoint, the Sponsor has decided that this first analysis of the study will be descriptive only without specific statistical hypotheses and will provide data from the first 275 patients enrolled in phases 1 and 2 combined.

Plans for subsequent analyses may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The plan will be issued prior to the phase 1/2 data lock and before code breaking.

1.1. Background/Rationale

This study is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in outpatient (ie, ambulatory) adults with COVID-19 (Coronavirus Disease 2019 (COVID-19) Situation Report) (World Health Organization 2020b) (Zhu 2020). Treatments referenced in the protocol that will not be in the study will not be analyzed. Any new treatments added will be analyzed per the SAP.

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 2020b). Due to the novel nature of COVID-19, efficacy endpoints are not well established, and the standard of care is expected to evolve over time. The adaptive design allows for the assessment of virologic and clinical efficacy endpoints in phase 2, which are then seamlessly confirmed in the phase 3 portion of the study, as well as evaluating the benefit risk of the different treatment groups. This study is therefore intended to allow for multiple adaptations, including dropping of treatment arm(s), addition of new treatment arms, modification of the primary endpoint for phase 2/3 including the primary populations for analyses and sample size re-estimation for phase 2/3.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objectives of the combined phase 1/2 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.

1.2.2. Secondary Objectives

The secondary objectives of the combined phase 1/2 are:

- To estimate the clinical efficacy of REGN-CoV-2 compared to Placebo, primarily based on a reduction in proportion of patients with medically attended visits
- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933, and REGN10987, in serum
- To assess the immunogenicity of REGN10933, and REGN10987

1.2.3. Exploratory Objectives

The exploratory objectives in the combined phase 1/2 of the study are:

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

1.2.4. Modifications from the Statistical Section in the Final Protocol

The key descriptive virologic endpoint analysis is revised from time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 22 as measured by RT-PCR in nasopharyngeal (NP) swab samples in all patients as defined in the protocol, to time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in NP swab samples for seronegative patients.

No multiplicity adjustment will be applied for pooled phase 1 and 2 efficacy analyses and O'Brien-Fleming boundaries and Bayesian predictive probabilities will not be calculated. All statistical tests will be performed at nominal significance level of 0.05 (two-sided).

1.2.5. Revision History for SAP Amendments

Analyses described in this phase 1/2 SAP supersede analyses described in any prior SAPs for this study. Analyses of phase 1 data not specified in this phase 1/2 SAP will be based on phase 1 SAP version 1.0. The original version of the phase 1 SAP was based on protocol amendment 3 and was approved on 25Jun2020.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is the phase 1/2 portion of an adaptive, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, and efficacy of REGN10933+REGN10987 in outpatient (ie, ambulatory) adults with early-stage COVID-19.

Patients will be randomized in a 1:1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS):

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 1.2 g IV single dose (when available)
- Placebo IV single dose

REGN10989 is not being studied in clinical trials at the time of finalization of this SAP version.

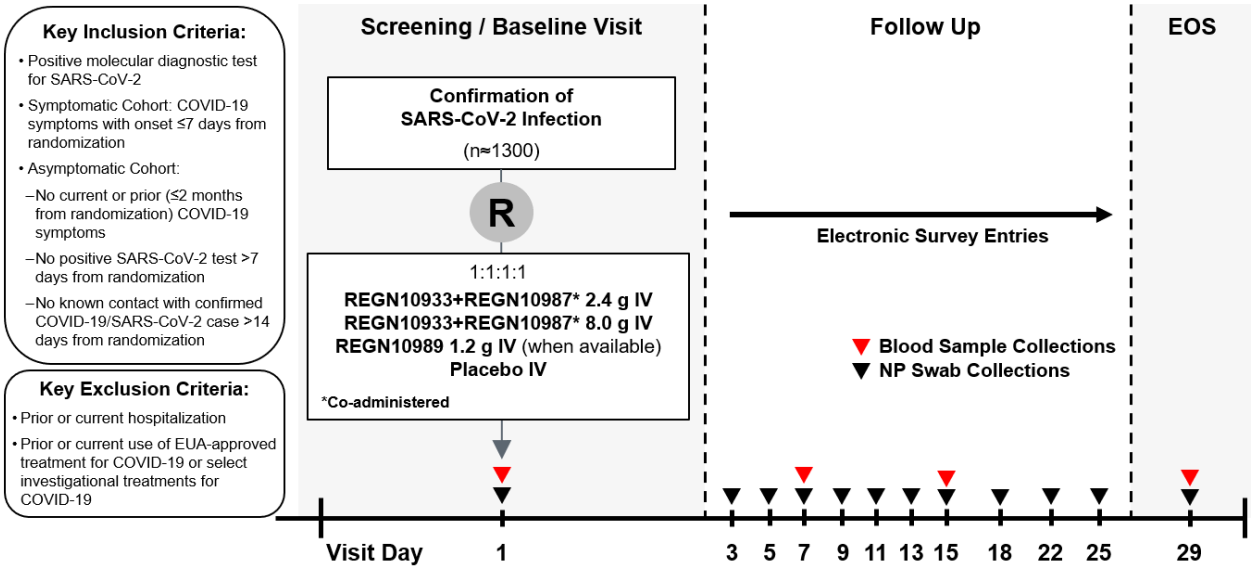
In phase 2, for presence/absence of COVID-19 symptoms (ie, symptomatic versus asymptomatic) cohort, randomization will be stratified by:

- 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 study event table is presented in Section 10.1.

At the time of this SAP version, only patients from the United States are enrolled in the study. All 275 randomized patients in this phase 1/2 analysis are in the symptomatic cohort.

Figure 1: Study Flow Diagram, Phase 2



2.2. Sample Size and Power Considerations for Phase 2

Details for sample size calculations are in Section 11.2 of the protocol.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH 1998), the following population of analysis will be used for all statistical analyses in the phase 1/2 portion of this study.

3.1. Full Analysis Sets

The full analysis set (FAS) includes all randomized patients 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. FAS will be used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. Both mFAS and FAS will be used for the analysis of virologic endpoints for phase 1 and phase 2. The seronegative FAS and seronegative mFAS will be used for the analysis of efficacy endpoints for phase 1 and phase 2.

3.2. Safety (SAF) population

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. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. Pharmacokinetics Analysis Sets

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

3.4. Immunogenicity Analysis Sets

The immunogenicity analysis set is dependent on assay availability.

The anti-drug antibody (ADA) analysis set (AAS) includes all subjects who received any study drug (safety population) and had at least one non-missing ADA result from the ADA assay after first dose of the study drug(s). Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic variables include the following:

- Age at screening (years)
- Age group (18 to <45, 45<65, 65<85, >=85 years)
- Sex (Male, Female)
- Race (Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not-Hispanic or Latino)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m^2) calculated from weight and height
- Baseline SARS-CoV-2 results from central lab (excluding assessment at screening visit)
- Baseline serostatus (positive, negative, other)

  A patient's serostatus is considered to be positive if any of the tests (Anti-SARS-CoV-2 Antibodies, eg, IgA or IgG) is positive, while serostatus is consided to be negative if all tests are negative, and other if serostatus is not positive or negative.
- Baseline C-Reactive Protein (mg/L)
- Time from symptom onset to randomization

4.2. Medical History

Medical history will include the following:

- Prior and current symptoms related to COVID-19
- Risk factors for hospitalization due to COVID-19
- Whether the patient will be receiving oxygen at home by nasal cannula
- Menopausal history

The following are considered risk factors:

- Age >50 years
- Obesity, defined as BMI >30 kg/m^2
- 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

4.3. Prior / Concomitant Medications or Procedures

Medications/Procedures will be recorded from the day of informed consent until the final study assessment (Day 29 or early study discontinuation or death). Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to WHO Drug Dictionary (WHODD) version 202003. Patients will be counted once in all ATC categories linked to the medication.

Prior medications/procedures are: medications taken or procedures performed prior to administration of the study drug.

Concomitant medications/procedures are: medications taken or procedures performed following the first dose of study drug through the final study assessment (Day 29 or early study discontinuation or death). This includes medications taken that started before the study and are ongoing during the study.

Only select concomitant medications will be captured in this trial. The select list of medications include corticosteroids, remdesivir, lopinavir-ritonavir, chloroquine, hydroxychloroquine, interferon beta, and convalescent serum.

Analysis of medications data will be focused on the targeted medications (specified in the protocol) that are expected to be reviewed and recorded by sites. Targeted medications include but are not limited to:

- Putative COVID-19 treatments (eg, remdesivir, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- Antipyretics (eg, aspirin, acetaminophen, ibuprofen)
- Anticoagulants (eg, enoxaparin, warfarin, rivaroxaban)
- Immunosuppressants (eg, cyclosporine A, corticosteroids)
- Interferon beta
- Theophylline
- Antiepileptics (eg, carbamazepine, divalproex, phenytoin)
- Antiarrhythmics (eg, digoxin, disopyramide, procainamide)
- Antivirals, antibacterial, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)
- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril).

4.4. Rescue Medication/or Prohibited Medication During Study

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatments are not provided as part of the study.

Patients are not permitted to receive any medication specified in the exclusion criteria (of the protocol) for study enrollment unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures. All data collected on medications/procedures (pre-treatment and concomitant) will be summarized.

4.5. Efficacy Endpoints

4.5.1. Key Descriptive Efficacy Endpoints

The key descriptive virologic efficacy endpoint for combined phase 1/2 is:

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

Time-weighted average of change from baseline viral load in the nasopharyngeal (NP) swab samples from day 1 through day 7 will be calculated for each patient using the linear 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.

For example, the time-weighted average (TWA) change from baseline in viral load in the nasopharyngeal (NP) swab samples till the last observation day t_k will be calculated using formula

$$TWA_{[0-k]} = [\sum_{i=1}^{k}(t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_k - t_0)$$

Where

- $k=11$ refers to 11 post-baseline assessments
- D_i is the change from baseline in viral load value (log10 copies/mL) obtained at time t_i, D_0 =0
- t_i is the time (day) for which D_i is measured, such as t_0 = 1 (day) for baseline and $\{t_i\}$ = 3, 5, 7, 9, 11, 13, 15, 18, 22, 25, 29, for i=1 to 11 where the postbaseline assessment is taken.
- If the D_i is not available per protocol or missing due to failed test or other reasons, only the time points with non-missing values will be included into the calculation. For example, we will calculate the TWA till day 7. In this case, data is not available at day 1, 2, 4, and 6 per the protocol schedule of events. Suppose the scheduled assessment result is missing at day 5 due to a failed test but non-missing at day 3 and day 7, then

$$TWA_{[0-7]} = [(t_3 - t_0) * (D_3 + D_0)/2 + (t_7 - t_3) * (D_7 + D_3)/2]/(t_7 - t_0)$$

Baseline is defined as the last non-missing values prior to the study drug infusion. Patients with missing baseline will be excluded from the analysis.

The key descriptive clinical efficacy endpoint for combined phase 1 / 2 is

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29 for both seronegative FAS and FAS.

4.5.2. Additional Descriptive Endpoints

The additional descriptive efficacy endpoints are listed in Table 1 below.

Table 1: Additional Endpoints and Populations for the first Phase 1/2 analysis

Endpoint	Category	Timepoint	Population
Time-weighted average change from baseline, and percent change in viral load	Virologic	Through each post-baseline timepoint	Seronegative mFAS
Proportion of patients with high viral titers (>10^4 copies/mL)	Virologic	At Day 9 and at all other timepoints	Seronegative mFAS Overall mFAS
Proportion of patients with low titers below limit of detection	Virologic	At Day 9 and at all other timepoints	Seronegative mFAS Overall mFAS
Proportion of patients with low titers below lower limit of quantitation	Virologic	At Day 9 and at all other timepoints	Seronegative mFAS Overall mFAS
Time to sustained negative PCR	Virologic	Through Day 15	Seronegative mFAS Overall mFAS
Time-weighted average change from baseline in viral load	Virologic	Through Day 7	Overall mFAS
Time-weighted average change from baseline in viral load	Virologic	Through Day 7	Seropositive mFAS
Time-weighted average change from baseline in viral load	Virologic	Through Day 11	Seronegative mFAS
Time-weighted average change from baseline in viral load	Virologic	Through Day 11	Overall mFAS

Time to symptom resolution	Symptom	Through Day 11	Seronegative FAS
Time to fatigue resolution	Symptom	Through Day 11	Seronegative FAS
Time to symptom alleviation (all symptoms)	Symptom	Through Day 11	Overall FAS Seronegative FAS
Time to sustained alleviation (all symptoms)	Symptom	Through Day 22	Overall FAS Seronegative FAS
Time to sustained resolution (all symptoms)	Symptom	Through Day 22	Overall FAS Seronegative FAS
Time to resolution of each individual symptom	Symptom	Through Day 22	Overall FAS Seronegative FAS
Percent change in CRP from baseline	Biomarker	At Day 7 (phase 1 only) At Day 29 (phase 1 / 2)	Overall FAS Seronegative FAS

Based on the 23-item patient-reported diary SE-C19 for COVID-19 symptoms, the following symptom endpoints are defined:

- For asymptomatic cohort,
  - Time to first onset of symptoms consistent with COVID-19 is defined as the days from the first dose date to the earliest date among any symptom that is reported as present. For patients without any symptom consistent with COVID-19 in the study period, the time to onset will be censored at day 29.
  - If a patient developed any symptom consistent with COVID-19 during the study period, duration of symptoms consistent with COVID-19 will be defined as the days from the date of first onset of any symptom consistent with COVID-19 to the last date when at least one symptom consistent with COVID-19 is rated at least mild by the patient, or to Day 29, whichever is later if the subject still has symptoms consistent with COVID-19 at the end of study (EOS). If a patient does not have any symptom consistent with COVID-19 during the study period, duration of symptoms consistent with COVID-19 will be 0.

- For symptomatic cohort,
  - Time to first day of symptom alleviation for all symptoms will be defined as the days from first dose date to the first day when all symptoms were rated by patients to be absent or mild. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. Patients who died or had medically attended visits will be censored at day 29. For patients with no baseline symptoms data or no reported symptoms at baseline, all symptoms have to be rated as absent in order to be considered as having symptom alleviation. Patients with all mild baseline symptoms will have to have at least one symptom rated as absent post-baseline to be considered as having symptom alleviation.
  - Time to sustained symptom alleviation for all symptoms will be defined as the days from first dose date to the first day when all symptoms were rated by patients to be absent or mild with no symptom recurrence or new symptoms. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. Patients who died or had medically attended visits will be censored at day 29. For patients with no baseline symptoms data or no reported symptoms at baseline, all symptoms have to be rated as absent in order to be considered as having symptom alleviation. Patients with all mild baseline symptoms will have to have at least one symptom rated as absent post-baseline to be considered as having symptom alleviation.
  - Time to first day of symptom resolution for all symptoms will be defined as the days from first dose date to the first day when all symptoms were rated by patients to be absent. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had medically attended visits will be censored at day 29.
  - Time to sustained symptom resolution for all symptoms will be defined as the days from first dose date to the first day when all symptoms were rated by patients to be absent with no symptom recurrence or new symptoms. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had medically attended visits will be censored at day 29.
  - Time to alleviation of symptoms excluding cough is defined similarly as above.
  - Time to alleviation of baseline symptoms (i.e., duration of symptoms) will be defined as the days from first dose date to the first day when all baseline symptoms were rated by patients to be improved to absent or mild. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. Patients who died or had medically attended visits will be censored at day 29.
  - Time to alleviation of respiratory symptoms (Cough, Shortness of breath, Sore throat, Sneezing, Sputum/phlegm production, Runny nose) will be defined as the days from first dose date to the first day when the baseline respiratory symptoms was rated by patients as absent or mild.

- Time to alleviation of respiratory symptoms excluding cough (Shortness of breath, Sore throat, Sneezing, Sputum/phlegm production, Runny nose) will be defined as the days from first dose date to the first day when the baseline selected respiratory symptoms was rated by patients as absent or mild.
- Time to alleviation of non-respiratory symptoms (Body aches, Chest pain, Chills, Confusion, Diarrhea, Fatigue, Feverish, Hearache, Loss of smell/taste, Nausea, Pressure/tightness in chest, Rash, Red or watery eyes, Stomach ache, vomiting) will be defined as the days from first dose date to the first day when the baseline non-respiratory symptoms was rated by patients as absent or mild.
- Time to alleviation of each individual symptom at baseline will be defined as the days from first dose date to the first day when the symptom was rated by patients as absent or mild. Patients whose symptom at baseline is assessed as 0 (None) or missing will be excluded from the analysis.
- Time to resolution of each individual symptom at baseline will be defined as the days from first dose date to the first day when the symptom was rated by patients as absent. Patients whose symptom at baseline is assessed as 0 (None) or missing will be excluded from the analysis.

- For both cohorts:
  - Proportion of patients who develop new predefined COVID symptoms not present at baseline by Day 29 of any severity
  - Proportion of patients with any predefined COVID symptoms at Day 29 that is moderate or severe. If a patient died or had medically attended visits on or before day 29, the patient will be counted as having symptoms.

4.5.3 Pharmacokinetics

- Concentrations of REGN10933 and REGN10987 in serum and select PK parameters

4.5.4 Immunogenicity

- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933 and REGN10987

4.5.5. Exploratory Endpoints

The exploratory endpoints for phase 1/2 are:

- Proportion of patients with treatment failure having mutations in the gene encoding the SARS-CoV-2 S protein through day 29
- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29

- Change and percentage change in 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

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Serious adverse events and AESIs will be collected according to the Schedule of Events (Section 10.1). All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.0).

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed.

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.

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 SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 2.

Table 2: NCI-CTCAE Severity Grading System for Adverse Events

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

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

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) of scientific and medical interest specific to this drug program, for which ongoing monitoring and rapid communication by the investigator to the sponsor will be appropriate.

Adverse events of special interest for this study are grade ≥2 hypersensitivity and grade ≥2 infusion-related reactions.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of blood chemistry (including C-Reactive Protein, liver function tests, creatinine and other), hematology, urinalysis, infection testing, SARS-Cov-2 RT-PCR, serum, and other (as specified in the protocol).

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Liver function including ALT, AST, alkaline phosphatase, total bilirubin,
- Renal function including creatinine, uric acid,
- Electrolytes including sodium, potassium,
- C-Reactive Protein (CRP),
- Creatine Phosphokinase (CPK)
- Metabolic parameters including total proteins, albumin,
- White blood cells (WBCs) including WBCs count and differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes),
- Red blood cells (RBCs) and platelets including red blood cells count, hemoglobin, hematocrit and platelets count,
- Other

4.6.4. Vital Signs

Vital signs, including blood pressure, pulse, and respiratory rate, are recorded at multiple time points according to Schedule of Time and Events table (See Section 10.1). Temperature is also recorded at multiple time points.

4.6.5. Physical Examination Variables

A targeted physical examination including lung auscultation will be performed at time point according to Schedule of Time and Events table (See Section 10.1).

During screening period, if any existing clinically significant abnormalities are present, these will be recorded in the Medical History CRF. Post-screening period, if any new clinically significant abnormalities are present (per investigator discretion), the relevant event will be recorded in the Adverse Event CRF, if applicable

4.7. Pharmacokinetic Variables

The PK variables are the concentration of REGN10933, REGN10987 in serum at each time point as specified in the Schedule of Events table (please refer to table 10.1 in the appendix). (See Section 10.1).

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples will be collected at the visits as specified in Section 10.1.

4.9. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables may be reported outside of the clinical study report (CSR).

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics variables given in Section 4.1 will be summarized descriptively by treatment group, and all groups combined using full analysis set (FAS).

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined using FAS.

5.3. Prior / Concomitant Medications or Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups using FAS. Summaries will present patient counts (and percentages) for all medications, dictionary coded by WHODRUG, by decreasing frequency of the overall group incidence (or high dose group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and preferred term. Focus of the results will be on the list of targeted medications (Section 4.3).

5.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be medications/procedures will be summarized by treatment groups in the FAS population, similar to the concomitant medications.

5.5. Subject Disposition

The following will be provided using FAS:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- 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 summary of analysis sets including FAS, mFAS, SAF, PK, immunogenicity (ADA), and exploratory biomarkers (Section 3).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Proportion of patients with fully completed infusions of study drug will be reported as the treatment compliance since the patients will only receive one infusion during the study. Treatment compliance and proportion of patients with infusion interruptions will be summarized by treatment group using descriptive statistics based on the SAF population.

5.6.2. Exposure to Investigational Product

Exposure to study drug will be examined for each patient as recorded on the Study Drug Administration-IV CRF. The following variables will be analyzed by treatment group:

- Duration of intravenous infusion
- Total volume of drug administered (units: mL)
- Number of patients with total planned dose administered (yes/no)
  - If no, reason for not administration of total planned dose (equipment failure, adverse event, other)
- Number of patients with infusion interruptions

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

5.7. Analyses of Efficacy Variables

For efficacy analyses, pairwise comparisons will be made as follows:

- Low dose (REGN10933+REGN10987 2.4 g) versus Placebo,
- High dose (REGN10933+REGN10987 8.0 g) versus Placebo, and
- Pooled doses of REGN10933+REGN10987 versus Placebo

5.7.1. Analysis of Key Descriptive Efficacy Variables

The key descriptive virologic efficacy variable for phase 1/2 is the time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 as measured in NP samples based on data from both phase 1 and 2 of the study. The estimand for the analysis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatment and placebo (as well as pooled doses and placebo) in the key descriptive efficacy variable for seronegative patients in the mFAS. Data collected after use of convalescent plasma 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, i.e., treatment policy approach.

Before calculating the key descriptive virologic efficacy variable, 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 log10 copies/mL (i.e., 1 copy/mL) if the reason for the uncertain values is not a failed test. This variable will be calculated using the trapezoidal rule, i.e., 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 the Day of the last observation. The variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, country and risk factor (no risk factor vs. at least 1 risk factor) based on EDC data as fixed effects and baseline viral load as covariate. Analysis will be performed for seronegative mFAS and for mFAS (with serostatus added to the ANCOVA model as a factor).

The least squares mean 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, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

The key descriptive clinical endpoint, proportion of patients with medically attended visits due to worsening COVID-19, will be compared between groups using stratified Cochran-Mantel-Haenszel (CMH) test at two-sided 0.05 level. P-values and 95% exact confidence intervals for the treatment difference will be presented. The analyses will be performed for the seronegative FAS and FAS with baseline serostatus as an additional term to the model. COVID-19 related medically-attended visit will be defined as: hospitalization with the primary reason for hospitalization being COVID-19, or an outpatient visit (including a visit to the ER, UCC, doctor's office, or telemedicine visit) with the primary reason for the visit being COVID-19.

5.7.2. Analysis of Additional Efficacy Variables

Virologic endpoints

For phase 1/2 the time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline visit timepoints will be analyzed using the same method as the key descriptive virologic efficacy endpoint based on mFAS and FAS for seronegative patients and seropositive patients separately. Similar analysis will be performed for the overall population 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 and for both anti-spike mAb treatment arms pooled, as well as the difference comparing each anti-spike mAb treatment arm and both anti-spike mAb treatment arms pooled versus placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

Time-weighted average percentage change from baseline in viral load from day 1 to post-baseline visits will be analyzed using a similar ANCOVA approach. Additional sensitivity analysis will be performed using the same method excluding patients with baseline viral load below the lower limit of quantification.

Time to negative PCR results through day 15 for Seronegative mFAS will be analyzed using the stratified log-rank test with country and risk factor (no risk factor vs. at least 1 risk factor) based on EDC data 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 PCR results through day 15 will be estimated by the Cox regression model with terms for treatment group, country and risk factor (no risk factor vs. at least 1 risk factor) based on EDC data. P-value from the stratified log-rank test for time to negative 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. Additional analysis will be performed using Restricted Mean Survival Time (RMST) computed at Day 7, 9, 11, 15, and 22 (Kim, 2017). Two-sided confidence intervals and p-values will be computed for differences and ratios in RMST based on asymptotic normal distribution.

Proportion endpoints based on virologic data will be compared between groups using stratified Cochran-Mantel-Haenszel (CMH) test at two-sided 0.05 level based on mFAS. P-values and 95% exact confidence intervals for the treatment difference will be presented. The analyses will be performed for seronegative mFAS as well as for mFAS with baseline serostatus as an additional term to the model.

To assess the time course of treatment effect in viral load, the change from baseline in viral load (log10 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, country, risk factor (no risk factor vs. at least 1 risk factor) based on EDC data, treatment, visit, 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 each anti-S mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. The percentage change from baseline in viral load in raw

scale at each visit for seronegative patients and overall will be back-transformed from the log10-transformed viral load and presented along with the change from baseline in viral load (log10 copies/mL).

Clinical endpoints

The total number of COVID-19 related medically-attended visits, and days of hospitalization due to COVID-19, will be summarized descriptively based on FAS.

Patient-reported Symptom endpoints

Time to onset of symptoms consistent with COVID-19 for asymptomatic cohort and time to alleviation or resolution of COVID-19 symptoms endpoints for symptomatic cohort will be analyzed using the similar method as for time to negative PCR. The analyses will be performed for seronegative FAS as well as for FAS with baseline serostatus as an additional term to the model. P-values and hazard ratio for time to alleviation or resolution of COVID-19 symptoms endpoints through the cutoff day specified in Table 1 will be reported. Additional analysis will be performed using Restricted Mean Survival Time computed at Day 7, 9, 11, 15, and 22 (Kim, 2017). Two-sided confidence intervals and p-values will be computed for differences and ratios in RMST based on asymptotic normal distribution.

Other exploratory variables including change from baseline in SE-C19 score will be summarized descriptively based on observed data using FAS.

Biomarker endpoints

Change from baseline in CRP (log-scale) will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, country and risk factor (no risk factor vs. at least 1 risk factor) based on EDC data as fixed effects and baseline CRP (log-scale) as covariate using seronegative FAS and FAS. The least squares means estimates for the mean change from baseline in CRP (log-scale) for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. The percentage change from baseline in CRP in raw scale at each visit will be back-transformed from the log-transformed CRP and presented along with the change from baseline in CRP.

Other biomarker variables such as neutrophil-lymphocyte ratio, D-dimer, ferritin, and LDH will be descriptively analyzed.

5.7.3. Adjustment for Multiple Comparison

No multiplicity adjustment will be applied for the combined Phase 1/2 efficacy analyses. All statistical testing will be performed at 0.05 (2-sided) level.

5.8. Analysis of Safety Data

The analysis of safety data will be performed on the SAF, as defined in Section 3.2.

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

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.2.

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

5.8.1. 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 SAEs and AESIs 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 SAEs and AESIs 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

Summaries of SAEs and AESIs 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 4.6.1), 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
- The number (n) and percentage (%) of patients with Grade 3 or Grade 4 treatment-emergent adverse events.

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

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry and hematology results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline to Day 29. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum.
- 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 parameters of interest.

Listing of all laboratory parameters normal range and abnormal flag by patient and visit will be provided.

5.8.3. Analysis of Vital Signs

Vital signs (including temperature, blood pressure, pulse, and respiration) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

5.8.4. Physical Exams

The number (n) and percentage (%) of patients with abnormal physical exams will be summarized at baseline and end of study. A summary of treatment emergent abnormal findings will be provided.

5.9. Analysis of Pharmacokinetics, Pharmacodynamics and Biomarker Data

5.9.1. Analysis of Drug Concentration Data

The concentrations of REGN10933, and REGN10987, in serum over time will be summarized descriptively for each of the treatment groups. Selected PK parameters will be determined by non-compartmental analysis (NCA). No formal statistical hypothesis testing will be performed. PK parameters may include but not limited to:

Phase 1 (Dense Sampling)

The PK parameters to be determined by non-compartmental analysis may include, but are not limited to C_{max}, C_{max}/dose, t_{max}, $AUC_{last,}$ and AUC_{last}/dose. 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 (Sparse Sampling)

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

For Phase 1 and Phase 2 analyses, no formal statistical hypothesis testing will be performed.

5.9.2. Analysis of Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

At a minimum, exposure-response analyses for viral load will be explored. Additional exposure-response analyses for other select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate.

5.9.3. Analysis of Immunogenicity Data

Immunogenicity variables will be summarized using descriptive statistics.

Immunogenicity will be characterized by the ADA responses and titers observed in subjects in the ADA analysis set.

ADA response categories and titer categories are defined as follows:

ADA response categories:

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

Titer categeories (Maximum titer values)

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

The following analysis will be provided:

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

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

5.10. Association of Immunogenicity with Exposure and Safety

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN10933, and REGN10987 will be explored by treatment groups. Plots of drug concentration time profiles may be provided to examine the potential impact of ADA response status, and titer on these profiles.

5.10.2. Immunogenicity and Safety

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow]).

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Definitions of baseline for efficacy variables are defined in Section 4.5.

For safety variables, baseline will be the latest available valid measurement taken prior to the administration of study drug.

6.2. Data Handling Convention for Efficacy Variables

Not applicable.

6.3. Data Handling Convention for Missing Data

Missing data in SE-C19 between Day 22 and 29 will be not imputed.

For categorical variables, patients with missing data will be included in calculations of percentages. Number of patients with missing data will be presented.

Handling of Medications with missing/partial dates

To determine whether a medication is prior or concomitant medication, the missing medication start date is estimated as early as possible up to first dose date, and the missing medication end date is estimated as late as possible up to Day 29. If the medication start date is missing, the onset day will not be imputed in medication listings.

Handling of Adverse events Severity and Relatedness

If the intensity of a SAE, AESI and grade 3 or 4 AEs is missing, it will be classified as “Grade 3” in the frequency tables by CTC grade of SAE and AESIs. If the assessment of relationship of the investigational product is missing, it will be classified as related to the investigational product.

Date of infusions

Date of infusion is the non-missing administration date filled in the Study Drug Administration-IV CRF. If the first dose of study drug administration date is missing (even after site is queried), then the dosing date will be imputed with the randomization date. If any subsequent study drug administration date is missing, the date of dispensation of study drug from IRT will be used.

6.4. Visit Windows

Data analyzed by-visit-analysis will be summarized by the study scheduled visits described Appendix 10.1, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits nor for drug concentration/immunogenicity data.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for NP Swab for SARS-CoV-2 RT-qPCR, based on the study day during the double blind period:

Table 3: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 3	3	[2, 3]
Day 5	5	[4, 5]
Day 7	7	[6, 7]
Day 9	9	[8, 9]
Day 11	11	[10, 11]
Day 13	13	[12, 13]
Day 15	15	[14, 16]
Day 18	18	[17, 20]
Day 22	22	[21, 23]
Day 25	25	[24, 27]
Day 29	29	[28, 32]

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for laboratory and biomarker variables based on the study day during the double blind period:

Table 4: Time Window for Summary of Laboratory and Biomarker Variables

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 11]
Day 15	15	[12, 22]
Day 29	29	[23, 32]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is scheduled, early termination visit then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

6.5. Pooling of Centers for Statistical Analyses

Not applicable.

7. INTERIM ANALYSIS

In order to determine the optimal patient populations and timing of analysis to achieve the study objectives, a series of endpoints (Section 4.5 and 4.6) will be descriptively analyzed in the first 275 patients in the combined Phase 1/2 portions of the study. All statistical tests will be performed at 0.05 level without adjustment for multiplicity. Data from these first 275 patients will not be reused for inferential analyses of the remainder of the study.

8. SOFTWARE

All analyses will be done using SAS Version 9.4.

9. REFERENCES

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10. APPENDIX

10.1. Schedule of Time and Events

Day	Screening/Baseline Visit[1]				Follow Up												EOS
	-1 to 1																
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[2]	9	11	13	15[2]	18	22[2]	25	29
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																	
[redacted]	X																	
Inclusion/exclusion	X																	
Antigen or molecular diagnostic test for SARS-CoV-2[4]	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[5]		X[5]														
Treatment-emergent grade ≥2 IRRs[6]			← continuous monitoring →															
Treatment-emergent SAEs[6]			← continuous monitoring →															
Treatment-emergent grade ≥2 hypersensitivity[6]			← continuous monitoring →															
Targeted concomitant medications[7]	X		← continuous monitoring →															
Pregnancy test (WOCBP)[8]	X																	X
Central Laboratory Testing																		
Hematology (including differential)	X[9]								X					X				X
Blood chemistry (including AST, ALT, CRP ferritin, LDH)	X[9]								X					X				X
Coagulation tests (D-dimer, PT/INR, aPTT)	X[9]								X					X				X
Central PK and Immunogenicity Testing																		
Serum for PK[10]		X[11]		X[11]														X
Serum for ADA[12]		X[12]																X
Central Biomarker Testing																		

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[2]	9	11	13	15[2]	18	22[2]	25	29
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
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[13]		X							X					X				X
Exploratory Patient-reported Symptoms																		
SE-C19[13]		X			Daily													
PGIS[13]		X			Daily													
PGIC[13]																		X
[redacted]																		
[redacted]		[redacted]																
[redacted]		[redacted]																

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; [redacted] 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.

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. On days 8, 15, and 22, information will be collected by the site on medically-attended visits, targeted concomitant medications, treatment-emergent SAEs, treatment-emergent AESIs, and (for phase 1 only) treatment-emergent grade 3 or 4 AEs. This information may be collected by phone; however, days 15 and 22 will still require in-person visits for sample collections. Phone visits will have a window of ±1 day.

[redacted]

4. Refer to Section 4.1 for diagnostic test requirements during screening.
5. Vital signs, including temperature, blood pressure, heart rate, SpO_2, and respiratory rate (for phase 1 only), will be collected as described in Section 4.6.4.

For **all other** patients (phase 1 and phase 2), 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 2 hours.

6. Only treatment-emergent SAEs, treatment-emergent AESIs, and (in phase 1 only) treatment-emergent grade 3 or 4 AEs will be recorded. See Section 5.8.1.
7. Medications will be reviewed and recorded. Only the targeted medications listed in Section 4.3 will be recorded in the eCRF.
8. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable.
9. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization.
10. Actual dosing time and PK sample collection times will be recorded.
11. At the screening/baseline visit, blood samples for PK assessment will be taken pre-dose 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.
12. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
13. Patients will self-report symptoms using the SE-C19, PGIS, and PGIC electronic surveys. Order of completion will be as follows: SE-C19, PGIS, and PGIC (when applicable).

10.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.

Parameter	PCSV	Comments
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN, and baseline Total Bilirubin ≤ 35% or TBILI ≤1.5 ULN	Conjugated bilirubin determined on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤ 3 ULN or TBILI ≤ 2ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) or ≥ULN (if ULN≥150 µmol/L) and baseline < 150 µmol/L or <ULN (if ULN≥150 µmol/L) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria

Parameter	PCSV	Comments
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Use is optional. FDA draft guidance 2010 Four independent criteria, will provide additional shift table if needed
Uric Acid Hyperuricemia: Hypouricemia:	>408 μmol/L or >ULN (if ULN≥408 μmol/L) and baseline ≤408 μmol/L or ≤ULN (if ULN≥408 μmol/L) <120 μmol/L or <LLN (if LLN≤120 μmol/L) and baseline ≥ 120 μmol/L or ≥LLN (if LLN≤120 μmol/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	<80 mmol/L or <LLN (if LLN≤80 mmol/L) and baseline ≥ 80 mmol/L or ≥LLN (if LLN≤80 mmol/L) >115 mmol/L or >ULN (if ULN≥115 mmol/L) and baseline ≤ 115 mmol/L or ≤ULN (if ULN≥115 mmol/L)	Two independent criteria
Sodium Hyponatremia: Hypernatremia:	≤129 mmol/L or ≤LLN (if LLN≤129 mmol/L) and baseline > 129 mmol/L or >LLN (if LLN≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L or <LLN (if LLN≤3 mmol/L) and baseline ≥ 3 mmol/L or ≥LLN (if LLN≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN≥5.5 mmol/L)	FDA Feb 2005. Two independent criteria

Parameter	**PCSV**	**Comments**
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN≥7.74 mmol/L) and baseline < 7.74 mmol/L or <ULN (if ULN≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN≥4.6 mmol/L) and baseline < 4.6 mmol/L or <ULN (if ULN≥4.6 mmol/L)	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN and baseline < 3 ULN	
Amylasemia	≥3 ULN and baseline < 3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black)* ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L or >ULN (if ULN≥4.0 Giga/L) and baseline ≤ 4.0 Giga/L or ≤ULN (if ULN≥4.0 Giga/L)	

Parameter	PCSV	Comments
Neutrophils	<1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) for Non-Black or <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) for Black and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) for Non-Black or ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) for Black* <1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) (Black) <0.5 Giga/L regardless of baseline value or racce	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.
Monocytes	>0.7 Giga/L or >ULN (if ULN≥0.7 Giga/L) and baseline ≤ 0.7 Giga/L or ≤ULN (if ULN≥0.7 Giga/L)	
Basophils	>0.1 Giga/L or >ULN (if ULN≥0.1 Giga/L) and baseline ≤ 0.1 Giga/L or ≤ULN (if ULN≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008.

Parameter	PCSV	Comments
Hemoglobin	≤115 g/L or ≤LLN (if LLN≤115 g/L) for male or ≤95 g/L or ≤LLN (if LLN≤95 g/L) for female and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male or > 95 g/L or >LLN (if LLN≤95 g/L) for Female* ≤115 g/L or ≤LLN (if LLN≤115 g/L) and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN≤95 g/L) and baseline > 95 g/L or >LLN (if LLN≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN≥185 g/L) for male or ≥165 g/L or ≥ULN (if ULN≥165 g/L) for female and baseline <185 g/L or <ULN (if ULN≥185 g/L) for male or <165 g/L or <ULN (if ULN≥165 g/L) for Female* ≥185 g/L or ≥ULN (if ULN≥185 g/L) and baseline <185 g/L or <ULN (if ULN≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN≥165 g/L) and baseline < 165 g/L or <ULN (if ULN≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	PCSV	Comments
Hematocrit	≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) for Male or ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) for Female and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male or > 0.32 v/v or >LLN (if LLN≤0.32 v/v) for Female* ≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male; ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN≤0.32v/v) for Female ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) for Male or ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) for Female and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female* ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male ; ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female	Two Criteria are independent *The default criteria. By gender (male and female) are optional.
RBC	≥6 Tera/L or ≥ULN (if ULN≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN≥6 Tera/L)	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
Platelets	<100 Giga/L or <LLN (if LLN≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN≥700 Giga/L) and baseline < 700 Giga/L or <ULN (if ULN≥700 Giga/L)	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 or ≤LLN (if LLN≤4.6) and baseline > 4.6 or >LLN (if LLN≤4.6) ≥8 or ≥ULN (if ULN≥8) and baseline < 8 or <ULN (if ULN≥8)	Two independent criteria

Parameter	**PCSV**	**Comments**
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING
Weight	≥ 5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

10.3. Symptom Evolution of COVID-19 (SE-C19) VERSION 2.2

On a scale of 0 to 3, with 0 being 'no symptom' and 3 being 'severe', how would you rate your COVID-19 symptoms at the worst moment during the last 24 hours?

	No Symptom	Mild	Moderate	Severe
1. Fever	0	1	2	3
2. Cough	0	1	2	3
3. Sputum/phlegm	0	1	2	3
4. Shortness of breath/difficulty breathing	0	1	2	3
5. Chills	0	1	2	3
6. Fatigue	0	1	2	3
7. Headache	0	1	2	3
8. Sore throat	0	1	2	3
9. Runny nose	0	1	2	3
10. Sneezing	0	1	2	3
11. loss of taste/smell	0	1	2	3
12. Loss of appetite	0	1	2	3
13. Confusion	0	1	2	3
14. Diarrhea	0	1	2	3
15. Nausea	0	1	2	3
16. Vomiting	0	1	2	3
17. Dizziness	0	1	2	3
18. Pressure/tightness in chest	0	1	2	3
19. Chest pain	0	1	2	3
20. Body aches such as muscle pain or joint pain	0	1	2	3
21. Stomach ache	0	1	2	3
22. Rash	0	1	2	3
23. Red/watery eyes	0	1	2	3
24. Other_____	0	1	2	3

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