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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 1/2/3 ADAPTIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF REGN14256+IMDEVIMAB FOR THE TREATMENT OF COVID-19 PATIENTS WITHOUT RISK FACTORS FOR PROGRESSION TO SEVERE DISEASE

Compound:	REGN14256+Imdevimab
Clinical Phase:	1/2/3
Protocol Number:	R14256-COV-2149
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Medical/Study Director:	[redacted]

[redacted]

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 1

The primary purpose of this amendment is to update the study design based on health authority feedback as follows.

Description of Change	Brief Rationale	Section(s)
Changes Based on Health Authority Feedback		
The study design was changed from a phase 3 study to an adaptive phase 1/2/3 protocol. • The first-in-human (FIH) **phase 1** portion of the study will enroll approximately 100 patients to evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy. There will be 2 sentinel safety analyses by an independent data monitoring committee (IDMC), during each of which study enrollment will be paused. • **Phase 2** portion of the study will assess the virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy (previously phase 3 part A). • **Phase 3** portion of the study will assess the clinical efficacy of REGN14256+imdevimab (previously phase 3 part B).	Change implemented per health authority feedback, with the aim of providing an enrollment pause for sentinel safety analysis during the FIH portion of the study	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 6.1 Study Description and Duration Section 6.1.3 Sentinel Cohort (Part A) [removed] Figure 1 Study Flow Diagram: Phase 1 [new] Figure 2 Study Flow Diagram: Phase 2 Figure 3 Study Flow Diagram: Phase 3 Table 1 Schedule of Events: Phase 1 [new] Table 2 Schedule of Events: Phase 2 Table 3 Schedule of Events: Phase 3 Section 11.1 Statistical Hypothesis
In addition to the oversight described in the original protocol, the IDMC will perform the following functions: • **Sentinel safety analysis 1.** In phase 1, after the first 40 patients reach study day 7 (6 days after dosing), the study will pause and the IDMC will review all unblinded safety data available at the time. After the IDMC evaluates these safety data, and if a positive recommendation to continue the study is provided, enrollment of the remaining phase 1 patients will begin. • **Sentinel safety analysis 2.** After phase 1 is fully enrolled and the last patient reaches study day 7, the study will pause and the IDMC will review all unblinded safety data available at the time. After the IDMC evaluates these safety data, and if a positive recommendation to continue the study is provided, enrollment in phase 2 will begin. Virologic and clinical efficacy data will remain blinded during the sentinel safety analyses by the IDMC, to facilitate subsequent phase 1/2 and phase 1/2/3 analyses of virologic and clinical efficacy. • **Planned interim safety analyses.** In phase 2, the IDMC will perform interim safety analyses,	To prospectively define sentinel safety analyses and planned interim safety analyses by the IDMC	Section 3.2.1.2 Safety and Tolerability and the Phase 1 Sentinel Safety Group Section 6.3.1 Independent Data Monitoring Committee

Description of Change	Brief Rationale	Section(s)
occurring (at minimum) after approximately half of the patients are enrolled and followed to study day 7. Based on these analyses, the IDMC may make recommendations on study conduct, including early study closure for safety. If phase 2 enrollment is slow, the IDMC will perform the interim safety analysis when approximately 200 patients have been enrolled in phase 2 and followed to day 7. Enrollment pauses are not planned during phase 2, unless otherwise indicated by review of ongoing phase 1 or phase 2 safety data. Additional information will be provided in the IDMC charter.		
The occurrence of one of the following events **at any time during the study** will trigger a review by the Sponsor, and communication with the IDMC, to assess if the study should be temporarily paused (ie, pausing of screening, randomization, and dosing of study drug): • Three treatment-related serious adverse events (SAEs) or adverse events of special interest (AESIs), **or** • One treatment-related SAE with a fatal outcome	To ensure adequate monitoring of safety-related events in the FIH portion of the study	Section 6.4 Study Stopping Rules
Grade ≥3 hypersensitivity reactions, rather than grade ≥2, will be reported as AESI through day 29. Note that definitions of injection-site reactions (ISRs) and hypersensitivity reactions through day 4 and day 29, respectively, were included in the original protocol in error and have been removed. While **all** ISRs and hypersensitivity reactions that occur anytime during or after subcutaneous injections will be recorded, only grade ≥3 ISRs through day 4 and grade ≥3 hypersensitivity reactions through day 29 will be reported as AESIs. NCI-CTCAE guidelines have been retained for severity evaluation of ISRs and hypersensitivity reactions.	For consistency with other studies using SC route of administration within the casirivimab+imdevimab clinical development program; and to provide clarity for AESI reporting	Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor Section 10.2.4 Injection-Site Reactions and Hypersensitivity Reactions [removed]
Additional information and clarifications have been provided: • Rationale for inclusion of REGN14256 and imdevimab monotherapy arms in phase 1/2 • Rationale for performing the phase 2 primary analysis (virologic efficacy) in patients who are seronegative at baseline • Clarification that outcomes in the phase 3 adolescent cohort will be analyzed descriptively and not be included in the primary clinical efficacy analysis • Clarification for the estimated sample size in phase 3 • Clarification that all efficacy hypotheses are tested with respect to placebo	To ensure accuracy and clarity in the statistical design	Section 3.2.1.1 Study Population Section 3.2.1.2 Safety and Tolerability and the Phase 1 Sentinel Safety Group Section 3.2.1.3 Assessment of Efficacy Section 3.2.1.4 Phase 3 Enrollment of Adolescents [new] Section 11.2 Justification of Sample Size Section 11.4.3 Efficacy Analyses
Other Changes		
In phase 1, the proportion of patients with treatment-emergent SAEs will be assessed throughout the study as a secondary endpoint rather than primary.	The primary endpoint for phase 1 (all treatment-emergent adverse events [TEAEs] through day 29) is	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints

Description of Change	Brief Rationale	Section(s)
	inclusive of SAEs through this early time period.	
Optional future biomedical research sub-study was removed.	Due to operational feasibility	Table 1 Schedule of Events: Phase 1 [new] Table 2 Schedule of Events: Phase 2 Table 3 Schedule of Events: Phase 3 Section 9.2.11 Future Biomedical Research (Optional) [removed]
Minor clarifications for consistency and other minor updates (typographical, editorial, formatting, administrative) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CDC	US Centers for Disease Control and Prevention
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
EQ-5D-5L	European Quality of Life Five Dimension-5 Level
EQ-5D-Y	European Quality of Life Five Dimension-Youth
ER	Emergency room
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	US Food and Drug Administration
FIH	First-in-human
GCP	Good clinical practice
IRB	Institutional Review Board
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
ISR	Injection-site reaction
IWRS	Interactive web response system
IV	Intravenous
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAV	Medically-attended visit
mFAS	Modified full analysis set
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
NP	Nasopharyngeal
NT-proBNP	N-terminal pro B-type natriuretic peptide
OP	Oropharyngeal
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PRO	Patient-reported outcome
PT	Preferred term
RBD	Receptor binding domain

Regeneron	Regeneron Pharmaceuticals, Inc.
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SE-C19	Symptom Evolution of COVID-19
SE-LC19	Symptom Evolution of Long COVID-19
SF-36	Short Form-36
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TWA	Time-weighted average
VBM	Variants Being Monitored
VOC	Variant of Concern
VOHC	Variant of High Consequence
VOI	Variant of Interest
VUI	Variant Under Investigation
VUS	Variants under surveillance
WHO	World Health Organization
WOCBP	Women of childbearing potential
WPAI+CIQ	Work Productivity and Activity Impairment and Classroom Impairment Questions

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 1/2/3 Adaptive Study to Evaluate the Safety, Tolerability, and Efficacy of REGN14256+Imdevimab for the Treatment of COVID-19 Patients Without Risk Factors for Progression to Severe Disease
Site Locations	The study will be conducted in approximately 80 sites in the United States and other countries.
Principal Investigator	To be determined

Objectives

Primary

Phase 1 (Safety and Tolerability)

- Evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent adverse events (TEAEs), injection-site reactions (ISRs), and hypersensitivity reactions

Phase 1/2 (Virologic Efficacy)

- Evaluate the virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy compared to placebo, as measured by time-weighted average (TWA) change from baseline in viral load through day 7

Phase 1/2/3 (Clinical Efficacy)

- Evaluate the clinical efficacy of REGN14256+imdevimab compared to placebo, as measured by COVID-19 symptoms resolution

Secondary

Phase 1 (Safety and Tolerability)

- Evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent serious adverse events (SAEs)

Phase 2 and Phase 3 (Safety and Tolerability)

- Evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by TEAEs, ISRs, hypersensitivity reactions, and SAEs

Phase 1, Phase 2, and Phase 3 (Virologic Efficacy, Drug Concentration, and Immunogenicity)

- Evaluate additional indicators of virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy
- Characterize the concentration-time profile of REGN14256 administered in combination with imdevimab or alone as a monotherapy
- Assess the immunogenicity of REGN14256 administered in combination with imdevimab or alone as a monotherapy

Study Design

The primary objective of the **phase 1** first-in-human (FIH) portion of the study is to assess the safety and tolerability of REGN14256 alone and in combination with imdevimab. Phase 1 will include 2 sentinel safety analyses (when the first 40 patients have reached study day 7 [6 days after dosing], then when all phase 1 patients have reached study day 7) during each of which study enrollment will pause for an unblinded IDMC review of all available safety data. Phase 2 enrollment will begin after the second sentinel safety analysis, if the IDMC provides a recommendation for the study to proceed.

In **phase 2**, the virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy will be evaluated, and will include virologic data obtained in phase 1 which will remain blinded during that phase.

In **phase 3**, the primary objective will be to assess the clinical efficacy, based on COVID-19 symptoms resolution, of REGN14256+imdevimab compared to placebo. Clinical efficacy analysis will include data obtained in all 3 study phases, as the symptoms data obtained in phase 1 and phase 2 will remain blinded during those phases. In addition to the adult patients, an adolescent cohort of 40 patients between ≥12 and <18 years of age will be enrolled during phase 3, where permitted by local requirements.

Study Periods	Each phase of the study consists of 3 periods: a screening/baseline period, a treatment period, and a follow-up period. **Screening/Baseline Period (Day -1 to Day 1 Before Dosing)** Patients will be assessed for eligibility during the screening/baseline period, which may occur up to 1 day prior to the baseline visit on study day 1. To be enrolled in the study, patients must have laboratory-confirmed SARS-CoV-2 infection and experience COVID-19 symptoms. Patients cannot have received any COVID-19 vaccination, nor present any underlying medical condition or other factors associated with high risk for progression to severe COVID-19. Other eligibility criteria apply and are described in the main text. During this period, eligible patients will be randomized and dosed on day 1. Prior to study drug administration on day 1, patients will have nasopharyngeal (NP) swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for laboratory safety, drug concentration, immunogenicity, and biomarkers analyses. After study drug dosing, adult patients will have a post-dose blood collection for drug concentration at least 1 hour after study drug administration. In phase 1, and in phase 3 adolescent patients, patients will remain at the study site for at least 5 hours after study drug administration for additional safety monitoring and post-dose blood collection for drug concentration assessment. **Treatment Period (Day 1 After Dosing Through Day 29)** The treatment period through day 29 includes the ***key clinical efficacy and safety analyses***. All patients will complete the Symptom Evolution of COVID-19 (SE-C19) electronic questionnaire through day 29 for the key clinical efficacy assessment of COVID-19 symptoms. Also, within the treatment period, the ***key virologic efficacy analysis*** will be performed through day 7. NP swab samples will be collected according to the Schedule of Events: in phase 1 and phase 2, every other day (days 1 [pre-dose], 3, 5, and 7) for the first week then at day 29; in phase 3, on days 1 (pre-dose), 7, and 29. In addition, information regarding any concomitant medication use and any COVID-19-related medically-attended visits (MAVs; eg, hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) will be recorded during this period and throughout the study. Patients will be asked to notify the investigator or study site personnel as soon as possible about such occurrences. Investigators and designated study site personnel must ensure that information about COVID-19-related symptoms and MAVs is collected as required. Patients will have blood samples at indicated visits according to the Schedule of Events for drug concentration, immunogenicity, and exploratory analyses. Safety will also be monitored throughout the study: In all study phases, all TEAEs and SAEs will be collected through the end of study, and select events (grade ≥3 ISRs through day 4 and grade ≥3 hypersensitivity reactions through day 29) will be reported to the Sponsor in an expedited manner as AESIs. **Follow-Up Period (Day 30 Through Day 169)** Following the treatment period, patients will enter a follow-up period of approximately 6 months through the end of study (EOS) on study day 169. In addition to safety monitoring and drug concentration data analysis, data and samples collected during this period will be used for research purposes related to long COVID. This will include electronic questionnaires such as the Symptom Evolution of Long COVID-19 (SE-LC19), NP swabs on days 120 and 169 to assess potential persistence of SARS-CoV-2 in the nasopharynx, blood draws on day 120, and queries regarding any COVID-19-related MAVs. On visit days when sample collection is not required (eg, when only electronic questionnaires are collected), the information indicated in the Schedule of Events may be collected by phone without an in-person visit. The EOS visit will take place approximately 6 months after study drug administration.
Study Duration	The duration of the study is approximately 170 days for each phase.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size	Up to approximately 1,359 patients are planned to be enrolled. • **Phase 1** will enroll approximately 100 adult patients (≥18 years of age).

- **Phase 2** will enroll approximately 610 adult patients.
- **Phase 3**will enroll approximately 609 adult patients and an additional adolescent cohort of 40 patients (≥12 and <18 years of age).

Target Population

This study will enroll non-hospitalized, low-risk, symptomatic patients with a baseline positive diagnostic test for SARS-CoV-2, and who have not previously received experimental, authorized or licensed COVID-19 vaccines.

A patient must meet the following criteria to be eligible for inclusion in the study. Other criteria also apply and are described in the main text:

- Is male or female between ≥18 and <65 years of age (or country's legal age of adulthood) at randomization, ***or***

  For the adolescent cohort in phase 3 only: Is male or female between ≥12 and <18 years of age at randomization

  Note: Adolescent cohort will only be enrolled where permitted by local requirements.
- **For the adolescent cohort in phase 3 only:** Weighs ≥40 kg at randomization
- 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 nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization. A historical record of a positive result is acceptable as long as the sample was collected ≤72 hours prior to randomization
- Has symptoms consistent with COVID-19 (as determined by the investigator) with onset ≤7 days before randomization, and doesn't have a medical condition or other factors associated with high risk for progression to severe COVID-19 as outlined in the exclusion criteria

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

- Has a medical condition or other factors associated with high risk for progression to severe COVID-19:
  a. Cancer
  b. Cardiovascular disease (such as heart failure, coronary artery disease, cardiomyopathies, congenital heart disease or hypertension)
  c. Chronic lung disease including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension
  d. Chronic kidney disease at any stage
  e. Chronic liver disease (such as alcohol-related, nonalcoholic fatty liver disease, cirrhosis)
  f. Dementia or other chronic neurological condition
  g. Diabetes mellitus (type 1 or type 2)
  h. Immunodeficiency disease or taking immunosuppressive treatment
  i. Medical-related technological dependence [for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)]
  j. Neurodevelopmental disorder (for example, cerebral palsy) or other condition that confers medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
  k. Overweight (defined as BMI >25 kg/m^2) or obesity (defined as BMI ≥30 kg/m^2)
  l. Poorly controlled HIV infection or AIDS
  m. Pregnancy
  n. Sickle cell disease or thalassemia
  o. Stroke or cerebrovascular disease
- Prior, current (at randomization) or planned use (within time period given per CDC guidance [90 days]) of any authorized or approved vaccine for COVID-19
- Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
- Has a known prior SARS-CoV-2 infection or positive SARS-CoV-2 serologic test

- Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
- Prior, current, or any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

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

Treatments

Phase 1 and Phase 2

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

- Co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose
- REGN14256, 600 mg SC single dose
- Imdevimab, 600 mg SC single dose
- Co-administered casirivimab and imdevimab combination therapy, 1200 mg (600 mg each of casirivimab and imdevimab) SC single dose
- Placebo SC single dose

All patients will receive 4 SC injections of blinded study drug on day 1, each containing 2.5 mL (300 mg) of active study drug or placebo.

Phase 3 (≥18 Years)

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

- Co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose
- Co-administered casirivimab and imdevimab combination therapy, 1200 mg (600 mg each of casirivimab and imdevimab) SC single dose
- Placebo SC single dose

All patients will receive 4 SC injections of blinded study drug on day 1, each containing 2.5 mL (300 mg) of active study drug or placebo.

Phase 3 (≥12 and <18 Years)

Eligible patients will receive open-label REGN14256+imdevimab (1200 mg; 600 mg each of REGN14256 and imdevimab) SC single dose on day 1. All patients will receive 4 SC injections of study drug on day 1, each containing 2.5 mL (300 mg) of active study drug.

Endpoints

Primary

Phase 1 (Safety and Tolerability)

- Treatment-emergent adverse events (TEAEs) and severity of TEAEs through day 29
- Proportion of patients with injection-site reactions (ISRs) and severity of ISRs throughout the study
- Proportion of patients with hypersensitivity reactions and severity of hypersensitivity reactions over time

Phase 1/2 (Virologic Efficacy)

- Time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples

Phase 1/2/3 (Clinical Efficacy)

- Time to COVID-19 symptoms resolution

Secondary	**Phase 1 (Safety and Tolerability)** • Proportion of patients with treatment-emergent SAEs throughout the study **Phase 2 and Phase 3 (Safety and Tolerability)** • TEAEs and severity of TEAEs through day 29 • Proportion of patients with ISRs and severity of ISRs throughout the study • Proportion of patients with hypersensitivity reactions and severity of hypersensitivity reactions over time • Proportion of patients with treatment-emergent SAEs throughout the study **Phase 1, Phase 2, and Phase 3 (Virologic Efficacy, Drug Concentration, and Immunogenicity)** • TWA change from baseline in viral load at each timepoint, as measured by RT-qPCR in NP samples **(phase 1 and phase 2 only)** • Change from baseline in viral load at each timepoint through day 7, as measured by RT-qPCR in NP samples • Proportion of patients with viral loads below the limit of detection at each visit • Concentrations of REGN14256 and imdevimab in serum over time • Incidence and titer of anti-drug antibodies (ADA) to REGN14256 and imdevimab over time

Procedures and Assessments	Procedures and assessments will include the following:
	• NP swabs for SARS-CoV-2 RT-qPCR
	• SE-C19 electronic questionnaire
	• Blood collection for serology
	• TEAEs through day 169
	• Treatment-emergent SAEs through day 169
	• Treatment-emergent adverse events of special interest (AESIs):
	  o Grade ≥3 ISRs through day 4
	  o Grade ≥3 hypersensitivity reactions through day 29
	• Blood collection for safety labs
	• Vital signs and concomitant medications
	• Vital status; pregnancy testing, pregnancy status, and pregnancy outcome (WOCBP only)
	• COVID-19-related MAVs details
	• Blood collection for biomarker, drug concentration, and immunogenicity analyses
	• Electronic questionnaires (SE-LC19, PGIS, PGIC, return to usual health, return to usual activities, SF-36, WPAI+CIQ, and EQ-5D-5L/Y)
	• Wearable device (phase 1 patients, and adult patients in phase 3 only)

Statistical Plan	
Statistical Hypotheses	**Phase 1** No formal hypothesis testing is planned for phase 1. The safety and tolerability objectives will be evaluated by estimating the proportion of patients with TEAEs and SAEs through day 29 and AESIs, which will include ISRs (grade ≥3) through day 4 and hypersensitivity reactions (grade ≥3) through day 29. **Phase 1/2**

There are two null hypotheses to be tested in phase 1/2 (ie, based on data from phase 1 and phase 2):

- **H_{a1}**: There is no treatment difference between REGN14256 in combination with imdevimab compared to placebo in terms of time weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 for the seronegative patients.
- **H_{a2}**: There is no treatment difference between REGN14256 alone compared to placebo in terms of time weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 for the seronegative patients.

Phase 1/2/3

The primary null hypothesis to be tested in phase 1/2/3 (ie, based on data from phase 1, phase 2, and phase 3) is:

- **H_{b1}**: There is no difference in time to COVID-19 symptoms resolution for REGN14256 in combination with imdevimab compared to placebo for the seronegative patients.

A hierarchical testing procedure will be applied to control for multiplicity and to maintain the study-wise type I error rate at two-sided 0.05 level.

Justification of Sample Size

Phase 1

Phase 1 will enroll approximately 100 patients (approximately 20 patients per arm) randomized to 5 treatment groups.

Phase 1/2

The primary virologic efficacy analysis will be based on data from patients enrolled in phase 1 and phase 2. After the IDMC provides the recommendation to proceed with enrollment in phase 2, at least 610 additional patients will be randomized in the phase 2 portion of the study, for a total sample size in phase 1 and 2 of at least 710 randomized patients.

The sample size is based on the primary virologic endpoint of time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 using a two-sample t-test at a two-sided significance of α=0.05, in patients who are seronegative and who have a positive RT-qPCR value at baseline. Assuming a standard deviation of 1.2 log10 copies/mL, a sample size per arm of n=85 seronegative patients with positive value on RT-qPCR at baseline provides at least 90% power to detect a difference of 0.6 log_{10} copies/mL in TWA daily change from baseline viral load between any treatment group and placebo.

If approximately 60% of patients are seronegative and have a positive value on RT-qPCR at baseline, it is estimated that ~142 patients would be required to be randomized into each treatment arm in order to yield ~85 seronegative patients per group.

During enrollment, if the proportion of seronegative patients is observed to be different from that initially assumed, the study will continue to enroll until the required number of seronegative patients are met for the assessment of the primary virology endpoint.

Phase 1/2/3

The total sample size for the study is based on having sufficient power to analyze the primary endpoint of time to COVID-19 symptoms resolution. The primary clinical efficacy analysis will be based on data from patients enrolled in phase 1, phase 2, and phase 3.

Based on data from the seronegative mFAS patients from the COV-2067 study (defined as the subset of seronegative patients with a positive central-lab determined SARS-CoV-2 RT-qPCR result from NP swab samples at randomization), the difference in median time to symptoms resolution was 4 days (8.0 days for casirivimab+imdevimab 2400 mg IV vs 12.0 days for placebo). Therefore, the sponsor conservatively assumes a difference in median time to symptoms resolution of 3.5 days for the comparison between co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose and placebo.

Therefore, assuming a median time to COVID-19 symptoms resolution of 12 days for placebo, 354 total events are needed to detect a difference in medians of 3.5 days with 90% power using a log-rank test (2 sided) with an overall type 1 error of 0.05, which corresponds to a median time to COVID-19

symptoms resolution of 8.5 days in the REGN14256 and imdevimab combination therapy group (HR=1.41).

Assuming 29 days of follow up per patient, an accrual duration of 90 days, a total of 412 seronegative patients (206 per group) are required to achieve 354 total events in a pairwise comparison between REGN14256+imdevimab combination therapy and placebo. Given that phase 3 has 3 treatment arms with a 1:1:1 randomization ratio, 618 seronegative patients (206 per group) are required to be randomized. Furthermore, assuming approximately 60% of patients are seronegative and have a positive value on RT-qPCR at baseline, approximately 345 mFAS patients per arm in the relevant treatment groups will need to be randomized to have approximately 1035 patients for testing the clinical efficacy endpoint of time to COVID-19 symptoms resolution.

Because 142 patients per group in the relevant treatment arms in phase1/2 will be contributing to the analysis of time to COVID-19 symptoms resolution, therefore, in phase 3, approximately 609 additional patients (203 per group) are required to be randomized into the 3 arms in a 1:1:1 ratio in order to yield 345 patients per group for the statistical hypothesis testing.

During enrollment, the number of events among seronegative patients will be monitored in a blinded manner to ensure that the comparison of time to symptoms resolution is adequately powered. The sample size for the phase 3 portion of the study will be adjusted accordingly if the design, objective and/or assumptions are changed.

Statistical Methods

All efficacy hypotheses are tested with respect to placebo.

Phase 1/2: Primary Virologic Efficacy Analysis

The primary virologic efficacy variable is time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples. The primary analysis will be conducted in the Seronegative mFAS population. The estimands for the primary hypotheses is the difference in means between the SARS-CoV-2 combination mAb treatment (REGN14256+imdevimab) vs. placebo and the difference in means between REGN14256 vs. placebo.

The analyses will be based on the observed data with no imputation for missing data except the following cases: uncertain viral load values with less than the lower limit of quantification of the PCR assay but with positive qualitative results are imputed with half of lower limit of quantification of the PCR assay; uncertain values with negative RNA are imputed with 0 $\log_{10}$ copies/mL if the reason for the uncertain values is not a failed test. The primary efficacy variable will be calculated using trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. More details are provided in the main text.

Phase 1/2/3: Primary Clinical Efficacy Analysis

COVID-19 symptoms included in the analysis are as follows: body aches such as muscle pain or joint pain, chest pain, chills, cough, diarrhea, dizziness, fatigue, feverish, headache, loss of appetite, loss of taste/smell, nausea, pressure/tight chest, red or watery eyes, runny nose, shortness of breath/difficulty breathing, sore throat, sputum/phlegm, and stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the patient scored ‘no symptom’ (score of 0) on all of the above symptoms except cough, fatigue, and headache, which can be ‘mild/moderate symptom’ (score of 1) or ‘no symptom’ (score of 0). Time to COVID-19 symptoms resolution will be analyzed using the log-rank test. The analyses will be performed in the seronegative mFAS. More details are provided in the main text.

Control of Multiplicity

A hierarchical testing procedure will be used to control the overall type I error rate at 0.05 for the testing of the primary virology endpoints (REGN14256 alone and in combination with imdevimab in comparison to the placebo arm) and the clinical endpoint (time to symptoms resolution in patients in the REGN14256+imdevimab arm in comparison to the placebo arm). The hierarchical testing order will be detailed in the SAP.

Interim Analyses

No formal interim analysis is planned.

At the time of primary virologic efficacy assessment, the Sponsor may conduct an administrative interim analysis for time to COVID-19 symptoms resolution in order to inform regulatory interactions and/or internal decision making.

An alpha penalty of 0.001 will apply for the testing of the clinical endpoint of time to symptoms resolution if an administrative look occurs.

To protect the integrity of study results, unblinding for the primary virology analyses will occur after all patients enrolled in phase 2 have reached day 29. Individuals unblinded to the patient-level data for the first step or any subsequent analysis will no longer be involved in the day-to-day conduct of the ongoing study. Patient-level results will not be released to any site-facing personnel or anyone who is directly involved in the conduct of the study.

1. INTRODUCTION

1.1. SARS-CoV-2 and COVID-19

Severe acute respiratory syndrome coronavirus (SARS-CoV-2), a novel betacoronavirus, was initially identified in patients experiencing atypical pneumonia in Wuhan City, China, and later determined to be the pathogen responsible for coronavirus disease 2019 (COVID-19) (WHO, 2020) (Wu, 2020) (Zhu, 2020).

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein. The resulting capsid is surrounded by an outer envelope 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. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). By mediating binding to the host receptor angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 S protein facilitates membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020). The S protein is composed of two functional subunits: the S1 subunit, which contains the receptor binding domain (RBD) that binds ACE2, and the S2 subunit, which mediates virus-cell membrane fusion (Walls, 2020).

1.2. Casirivimab+Imdevimab: A Combination of Two Non-Competing Monoclonal Antibodies that Target the SARS-CoV-2 S Protein RBD

To address the emerging COVID-19 pandemic in early 2020, Regeneron Pharmaceuticals, Inc. (Regeneron) developed casirivimab and imdevimab, two non-competing recombinant monoclonal antibodies (mAbs) that bind simultaneously to the RBD and block its interaction with ACE2. As a co-administered combination therapy, casirivimab+imdevimab has demonstrated efficacy as an antiviral agent for the treatment and prevention of COVID-19, across a variety of populations, and is generally well-tolerated with a favorable safety and tolerability profile. In the outpatient treatment setting, casirivimab+imdevimab enhances viral clearance and reduce rates of COVID-19-related hospitalization or all-cause death (Weinreich, 2021). Casirivimab+imdevimab also reduces all-cause death in hospitalized patients (Horby, 2021). When given in a prophylaxis setting to household contacts of SARS-CoV-2-infected individuals, casirivimab+imdevimab reduces asymptomatic and symptomatic infections, produces faster viral clearance, and in those who develop symptoms, leads to shorter symptoms duration (O'Brien, 2021).

Based on the demonstrated efficacy and safety profile, casirivimab+imdevimab has been approved, authorized, or conditionally authorized by a number of global health authorities for the treatment and/or prevention of COVID-19 (FDA, 2020a) (MHRA, 2021) (EMA, 2021).

1.3. Emergence of SARS-CoV-2 Variants

As an RNA virus, SARS-CoV-2 has a high mutation rate. New viral variants have evolved since the beginning of the pandemic with mutations that confer certain advantages to the virus, such as a higher infectivity rate or escape from the host immune response. In an effort to coordinate pandemic responses to emerging variants, the World Health Organization (WHO), United States (US) Centers for Disease Control and Prevention (CDC), and United Kingdom (UK) Public Health England have categorized SARS-CoV-2 variants based on important biological and epidemiological characteristics, including known or potential impact on disease severity,

transmissibility, or ability to resist treatments. Variants may be categorized differently by the WHO, US CDC, and/or Public Health England based on the evolving levels of public health threat in regions of interest. The US CDC variant categories represent an increasing degree of evidence that the variant represents a public health threat: variant being monitored (VBM), variant of interest (VOI), variant of concern (VOC), and variant of high consequence (VOHC), while the WHO recognizes variants under monitoring (VUM), VOI, and VOC (CDC, 2021c) (WHO, 2021a) . The United Kingdom (Public Health England) additionally categorizes variants under the labels variant under investigation (VUI) and monitoring, according to regional prevalence (PublicHealthEngland, 2021). Based on these differences in terminology, these variants are collectively referred to as variants under surveillance (VUS) by the Sponsor.

While authorized vaccines are generally highly effective, there are data to suggest that some VUS may reduce vaccine effectiveness, highlighting that emerging viral variants pose a very real threat to natural and vaccine immunity and therapeutic efficacy (Brown, 2021) (Noori, 2021) (Wang, 2021) (Ministry of Health Israel, 2021). Additionally, these emerging circulating variants have already reduced the effectiveness of other mAbs and resulted in decisions to no longer distribute these other mAb therapeutics (Planas, 2021).

Variants may arise through natural selection during circulation (eg, selection for enhanced transmissibility), but may also be driven by direct selective pressures such as expanding herd immunity, vaccine-induced immunity, and antiviral therapies with mutations that can promote treatment escape. In vitro studies have shown that individual mAb therapies directed at the RBD, as well as mAb combination therapies whose mAbs share competing RBD epitopes, are often susceptible to such escape mutants. These mutations appear to arise predominantly within the RBD, and in some cases, a single amino acid residue becomes the target of multiple unique amino acid substitutions (Baum, 2021) (Copin, 2021). These data suggest that strategic mAb therapy design, such as the simultaneous use of two highly potent, non-competing antibodies, may be required to effectively safeguard against the selection of treatment-emergent resistance variants and highlights the inherent risk of monotherapy against SARS-CoV-2.

A key element in the development of casirivimab+imdevimab was the strategic decision to include a pair of non-competing antibodies that can simultaneously bind distinct epitopes of the SARS-CoV-2 S protein to reduce the likelihood of drug resistant variants and provide coverage against circulating variants (Baum, 2020). Casirivimab+imdevimab has retained in vitro neutralization potency against all known VOI/VOCs, and an initial analysis of viral samples taken from clinical studies suggests that casirivimab+imdevimab does not lead to escape variants (Copin, 2021). However, some variants have emerged (eg, B.1.351 [Beta] and P.1 [Gamma] variants) that impact the potency of the casirivimab component of the casirivimab+imdevimab combination, creating a potential risk that casirivimab+imdevimab may behave functionally as a monotherapy against certain variants. Moreover, new variants may emerge in the future that carry a different resistance profile to vaccines and/or casirivimab+imdevimab. To mitigate this risk, active surveillance of circulating viruses and continued development of updated antibody combinations where multiple components maintain coverage against emerging variants should be an important focus for the future of antiviral mAb therapeutics. To ensure an effective combination of two antibodies that bind to non-competing epitopes of the S protein RBD, and where each component retains activity against circulating VOI/VOCs, the Sponsor is developing REGN14256 as a potential substitute for casirivimab at equivalent dose to form the basis of an updated combination therapy (REGN14256+imdevimab). REGN14256 is a human IgG1 mAb that has similar properties to

casirivimab with regard to its structure, potency, and manufacturing, except that it binds a distinct epitope from casirivimab, and retains neutralization potency against all known VOI/VOCs, including those that impact the activity of casirivimab.

1.4. A Randomized, Placebo-Controlled Study of REGN14256+Imdevimab in Non-Hospitalized, Low-Risk Patients with COVID-19

This phase 1/2/3 adaptive study will evaluate the safety, tolerability, virologic efficacy, and clinical efficacy of REGN14256+imdevimab compared to placebo in non-hospitalized patients with COVID-19 who are at low risk of progressing to severe disease. Casirivimab+imdevimab will be included as a calibrator arm. To assess the contribution of individual components, the virologic efficacy of REGN14256 monotherapy and imdevimab monotherapy will also be evaluated during phase 2.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on REGN14256+imdevimab and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objectives

2.1.1. Phase 1 (Safety and Tolerability)

The primary objective is to evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent adverse events (TEAEs), injection-site reactions (ISRs), and hypersensitivity reactions.

2.1.2. Phase 1/2 (Virologic Efficacy)

The primary objective is to evaluate the virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy compared to placebo, as measured by time-weighted average (TWA) change from baseline in viral load through day 7.

2.1.3. Phase 1/2/3 (Clinical Efficacy)

The primary objective is to evaluate the clinical efficacy of REGN14256+imdevimab compared to placebo, as measured by COVID-19 symptoms resolution.

2.2. Secondary Objectives

2.2.1. Phase 1 (Safety and Tolerability)

The secondary objective is to evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent serious adverse events (SAEs).

2.2.2. Phase 2 and Phase 3 (Safety and Tolerability)

The secondary objective is to evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by TEAEs, ISRs, hypersensitivity reactions, and SAEs.

2.2.3. Phase 1, Phase 2, and Phase 3 (Virologic Efficacy, Drug Concentration, and Immunogenicity)

The secondary objectives are to:

- Evaluate additional indicators of virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy
- Characterize the concentration-time profile of REGN14256 administered in combination with imdevimab or alone as a monotherapy
- Assess the immunogenicity of REGN14256 administered in combination with imdevimab or alone as a monotherapy

2.3. Exploratory Objectives

The exploratory objectives are to:

- Evaluate SARS-CoV-2 variants at baseline and post-treatment
- Evaluate the virologic efficacy of REGN14256 alone (as applicable) and in combination with imdevimab, compared to placebo, in reducing viral load of SARS-CoV-2 variants under surveillance (VUS)
- Evaluate the clinical efficacy of REGN14256 in combination with imdevimab, compared to placebo (phase 1 and phase 2, as applicable)
- Evaluate additional indicators of clinical efficacy of REGN14256 in combination with imdevimab, compared to placebo (phase 3 only)
- Evaluate the impact of REGN14256+imdevimab treatment, given during acute SARS-CoV-2 infection, on long COVID symptoms, compared to placebo
- Explore the effects of REGN14256 alone (as applicable) and in combination with imdevimab on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays
- Explore biomarkers predictive of safety, efficacy, and/or disease progression and COVID-19 clinical outcomes of REGN14256 alone (as applicable) or in combination with imdevimab
- Explore the underlying mechanisms of action and biology of REGN14256 alone (as applicable) and in combination with imdevimab, SARS-CoV-2, and COVID-19
- Explore relationships between REGN14256 alone (as applicable) and in combination with imdevimab exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- Characterize the concentrations of casirivimab and imdevimab in serum over time

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

In non-hospitalized adult patients with symptomatic SARS-CoV-2 infection, treatment with REGN14256+imdevimab will reduce viral load and shorten COVID-19 symptoms duration.

Information concerning statistical hypotheses is provided in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

This phase 1/2/3, randomized, double-blind, placebo-controlled adaptive study will assess the virologic and clinical efficacy, safety, tolerability, pharmacokinetics (PK), and immunogenicity of REGN14256+imdevimab in non-hospitalized, unvaccinated patients with symptomatic SARS-CoV-2 infection who are at low risk for progressing to severe COVID-19.

The study will utilize an adaptive design, which will allow for phase 3 adaptations as needed based on data obtained in phase 1 and phase 2 (Section 11.5).

3.2.1.1. Study Population

Casirivimab+imdevimab is currently authorized and available for individuals who are at higher-risk for progression to severe COVID-19 (FDA, 2020a). Accordingly, a study population of symptomatic, non-hospitalized patients **without** such risk factors was selected to prevent higher-risk patients from being randomized to the placebo control arm. Of note for an adequate assessment of virologic efficacy, study COV-2067 (an adaptive phase 1/2/3 efficacy and safety study in adult outpatients with mild to moderate COVID-19) showed that participants who had ≥1 risk factor for severe COVID-19 had a similar baseline viral load compared to those who did not have risk factors and a similar degree of improvement in the time to resolution of COVID-19 symptoms.

The primary analysis population will consist of patients who are seronegative (ie, without endogenous antibodies against SARS-CoV-2) at baseline. The intent is to ensure that the assessment of virologic efficacy of REGN14256+imdevimab or REGN14256 monotherapy is reasonably similar to casirivimab+imdevimab. The assessment of the true pharmacological activity of the mAbs with respect to viral load reduction will be confounded if analyzed in patients with prior immunity due to either previous symptomatic or asymptomatic SARS-CoV-2 infection or to COVID-19 vaccination. Previous studies with casirivimab+imdevimab have shown that it is difficult to demonstrate treatment-related reductions in viral load in individuals that are seropositive at baseline, even though these patients may derive clinical benefit on outcomes. Previous studies have also shown that the virologic and clinical efficacy of casirivimab+imdevimab is greater in those who are seronegative at baseline compared with those who are seropositive (Weinreich, 2021) (O'Brien, 2021) (Horby, 2021). Focusing phase 2 analyses on the baseline seronegative population of patients allows greater precision with smaller sample sizes compared to analyzing all patients regardless of baseline serostatus.

3.2.1.2. Safety and Tolerability and the Phase 1 Sentinel Safety Group

The first-in-human (FIH) phase 1 portion of the study will enroll approximately 100 patients (approximately 20 patients per arm) who will be randomized to 5 treatment groups that are also planned to be evaluated in phase 2. The aim of phase 1 will be to assess safety and tolerability, and there will be 2 sentinel safety analyses by an independent data monitoring committee (IDMC; Section 6.3.1):

- After the first 40 patients reach study day 7 (6 days after dosing), the study will pause and the IDMC will review all unblinded safety data available at the time. After the IDMC evaluates these safety data, and if a positive recommendation to continue the study is provided, enrollment of the remaining phase 1 patients will begin.
- After phase 1 is fully enrolled and the last patient reaches study day 7, the study will pause and the IDMC will review all unblinded safety data available at the time. After the IDMC evaluates these safety data, and if a positive recommendation to continue the study is provided, enrollment in phase 2 will begin.

Virologic and clinical efficacy data will remain blinded during the sentinel safety analyses by the IDMC, to facilitate subsequent phase 1/2 and phase 1/2/3 analyses of virologic and clinical efficacy (Section 11).

In all study phases, **all** TEAEs and SAEs will be collected through the end of study, and select events (grade ≥3 ISRs through day 4 and grade ≥3 hypersensitivity reactions through day 29) will be reported to the Sponsor in an expedited manner, ie, as AESIs (Section 10.1).

3.2.1.3. Assessment of Efficacy

Phase 2 will be powered to allow for a robust assessment of the virologic efficacy of REGN14256+imdevimab as a primary endpoint. To assess the contribution of individual components, during phase 2, the virologic efficacy of REGN14256 monotherapy and imdevimab monotherapy will also be evaluated. As new variants may emerge that carry a different resistance profile to current vaccines and/or therapies, understanding the key clinical characteristics of the individual mAb components will be an important criterion in defining future potential combinations. As such, the evaluation of individual monotherapy components will provide valuable data to inform the development of current and future therapies involving different combinations of individual antibodies. Of note, the Sponsor does not intend to pursue commercialization of monotherapy for the prevention or treatment of COVID-19.

Finally, casirivimab+imdevimab combination therapy will be included as a calibrator arm given its established virologic and clinical efficacy, and the ongoing changes in the prevalence of circulating variant strains and disease morbidity.

Combination therapy arms (REGN14256+imdevimab and casirivimab+imdevimab) and placebo will be continued into phase 3 and powered to allow for a robust determination of the impact of treatment on clinical outcomes, namely COVID-19 symptoms resolution. Assessment of viral load reduction, comparing active treatment arms with placebo, will also be performed during phase 3. Additionally, outcomes in the adolescent cohort will be analyzed descriptively and not included in the primary clinical efficacy analysis.

Rationale for Virologic Efficacy Assessment

Virologic efficacy has been evaluated in all clinical efficacy studies and used as a proximal indicator of pharmacological activity, showing that the burden of disease following SARS-CoV-2 infection is correlated with high viral load and consistently associated with clinical efficacy. For example, in the phase 3 portion of study COV-2067, placebo participants with a COVID-19-related hospitalization or all-cause death through study day 29 had a higher mean baseline viral load compared to placebo participants who did not experience an event (7.54 $\log_{10}$ copies/mL versus 6.62 $\log_{10}$ copies/mL) and cleared virus slower (day 7 viral load 5.36 $\log_{10}$ copies/mL versus 3.60 $\log_{10}$ copies/mL). Similarly, in study COV-2066 assessing the efficacy of casirivimab+imdevimab for the treatment of COVID-19 in hospitalized patients, a higher proportion of participants in the placebo group with high viral load at baseline progressed to death or mechanical ventilation (19.7% for subgroup with $>10^4$ copies/mL versus 0% for subgroup with $<10^4$ copies/mL).

Overall, across all studies and in all populations analyzed, results from the change from baseline and TWA daily change from baseline show that casirivimab+imdevimab significantly and comparably reduced SARS-CoV-2 viral load compared to placebo over approximately 1 week across all populations. This was demonstrated in studies of non-hospitalized patients with asymptomatic SARS-CoV-2 infection that were presumed to have been recently infected and were at the earliest stages of their disease course (ie, in study COV-2069 cohort B [including those with known exposure to an infected household contact and positive for SARS-CoV-2 at baseline] and study COV-20145 [a dose-ranging study in outpatients with COVID-19]).

Rationale for Clinical Efficacy Assessment

Regeneron's COVID-19 antibody development program includes several controlled phase 3 studies which have all shown consistent and substantial clinical benefit from treatment with casirivimab and imdevimab combination across the entire SARS-CoV-2/COVID-19 disease spectrum, spanning uninfected individuals to those with asymptomatic SARS-CoV-2 infection, and to outpatients and hospitalized patients with COVID-19. These studies have demonstrated efficacy on clinically-meaningful endpoints, including reduction in mortality (in patients hospitalized for COVID-19), in risk of COVID-19-related hospitalization and/or all-cause death through study day 29 (in outpatients with COVID-19), symptoms resolution, and risk of progression to symptomatic disease (in infected, asymptomatic individuals).

This study will assess the time to COVID-19 symptoms resolution in patients who receive REGN14256+imdevimab, compared to placebo, as a primary endpoint (data collected using electronic questionnaires as described in Section 3.2.1.4, and analyzed at the end of the study based on data from patients enrolled in all 3 study phases, with the exception of the adolescent cohort). Findings from study COV-2067 showed that treatment with casirivimab+imdevimab was associated with a statistically significant and clinically meaningful 4-day reduction in time to symptoms resolution, where the median time to symptoms resolution was 10 days for both 1200 mg and 2400 mg, versus 14 days for the placebo group ($p<0.0001$). Similar results for reduction in the duration of symptoms have been observed in patients with or without risk factors for severe COVID-19, where the median time to symptoms resolution was 9 days for 2400 mg versus 12 days for the placebo group ($p=0.0048$). It is therefore assumed that similar effects will be observed here in patients without risk factors for severe COVID-19.

3.2.1.4. Phase 3 Enrollment of Adolescents

Phase 3 of the study will also include an open-label adolescent cohort to assess the safety, tolerability, and PK of REGN14256+imdevimab in patients between ≥12 and <18 years of age. Outcomes in these adolescent patients will be analyzed descriptively and not included in the primary clinical efficacy analysis.

3.2.1.5. Assessment of COVID-19 Symptoms During Acute COVID-19 (Through Day 29)

The types of COVID-19 related symptoms, as well as their duration and severity will be collected by patients through the use of electronic diaries/questionnaires, including the Symptom Evolution of COVID-19 (SE-C19) questionnaire. The SE-C19 instrument was developed by the Sponsor with the aim to better understand the symptomatic course of COVID-19 infection over time and is based on current available evidence on symptoms of COVID-19 (Arentz, 2020) (Chen, 2020a) (Chen, 2020b) (Huang, 2020) (Lapostolle, 2020) (Mizrahi, 2020) (Song, 2020) (Wang, 2020). The good measurement principles outlined in the FDA Patient-Reported Outcome (PRO) Guidance (FDA, 2009) and the four methodological Patient-Focused Drug Development guidance's were also considered in their design (FDA, 2020b). To aid interpretation, other questionnaires including the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS) scales will also be completed by patients. Refer to Section 9.2.4 for background and procedural information regarding these instruments.

For the primary clinical efficacy analysis, the time in days to COVID-19 symptoms resolution will be assessed using SE-C19 through day 29 in all participants. Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the patient scores 0 (no symptom) on all 19 symptoms except cough, fatigue, and headache, for which the patient can have a score of 1 (mild symptom), 2 (moderate symptom), 3 (severe symptom) or 0 (no symptom). To ensure that any observed recovery is likely to be a true treatment effect and not natural progression of disease, patients with a raw score of ≤3 at baseline will be censored at day 0. Without this aspect of the definition, patients could potentially start the study already meeting the responder definition due to natural resolution of the disease.

3.2.1.6. Assessment of Long COVID (Day 30 to Day 169)

To understand better the biology of long COVID and the potential impact of prior treatment with REGN14256+imdevimab (during the acute phase of SARS-CoV-2 infection) on the development of long COVID symptoms, patients will be evaluated using measures including patient-reported outcomes questionnaires including the Symptom Evolution of Long COVID-19 (SE-LC19) questionnaire (Section 9.2.4), wearable device data collection (Section 9.2.10), and blood sample collections for biomarker analyses (Section 9.2.8.3.1). These analyses will be exploratory in nature.

3.2.2. Rationale for Dose Selection

This phase 1/2/3 adaptive study will evaluate 1200 mg SC of REGN14256+imdevimab (1:1 ratio, 600 mg/mAb), 1200 mg SC of casirivimab+imdevimab (600 mg per mAb), 600 mg SC dose of REGN14256, and 600 mg SC dose of imdevimab.

The high-level dosing strategy in this study is to mirror the clinical dose (1200 mg SC) of casirivimab+imdevimab authorized in the US for treatment and post-exposure prophylaxis of COVID-19 (FDA, 2020a). The 1:1 ratio for REGN14256 + imdevimab 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 comparable in vitro binding and neutralization properties. REGN14256 has similar in vitro potency to casirivimab, an improved resistance profile against known variants, given the pre-clinical PK data, and because both molecules target an exogenous protein, similar PK profiles for REGN14256 and casirivimab are anticipated.

A 600 mg SC dose of each mAb (REGN14256 or imdevimab), either for the monotherapy arms or combination arms planned for this study was chosen based on extensive PK characterization of casirivimab and imdevimab combination therapy generated in the casirivimab+imdevimab clinical development program (ie, study COV-2067 and study COV-2069). Both antibodies (casirivimab and imdevimab) at a 1200 mg SC dose are present in significant excess [relative to the IC_{90} against the ancestral strain of SARS-CoV-2 virus and circulating variants (eg, E484K variant)], through day 29. The IV and SC doses (600 mg per mAb) for the combination of casirivimab and imdevimab have been shown to improve clinical outcomes in patients with COVID-19, when compared to placebo (Weinreich, 2021) (O'Brien, 2021) (FDA, 2020a). Given the measured IC_{90} for REGN14256 is similar or lower than that for imdevimab, especially against variants of concern such as L452R/T478K (Delta variant), and the similar expected PK profile for REGN14256 to that of casirivimab, the choice of 600 mg per mAb as the dose for the combination of REGN14256 and imdevimab to be given SC is also expected to provide robust efficacy against relevant VUS.

For the monotherapy arms, the SC dose of each single mAb (600 mg) is matched to that in the combination, to facilitate a comparison for each single antibody and provide evidence of biological effect for the single mAbs, which are also predicted to be present in significant excess relative to relevant IC_{90}'s for VUS.

As the lower end of the proposed body weight range for adolescent subjects ≥12 years of age (40 kg) falls within the range of expected body weights for adult subjects, similar exposures are expected between these 2 populations for a single 1200 mg (600 mg of each mAb) SC dose of REGN14256+imdevimab.

The lack of a dose effect between the 1200 mg IV and 1200 mg SC of 1:1 combination of casirivimab+ imdevimab in key clinical and virologic outcomes (COV-20145) and their similar safety profiles, irrespective of the route of administration, led to selection of SC injections as the only route to be employed this study. Intravenous (IV) administration requires access to a medical facility with trained medical professionals to set-up an IV infusion and determine appropriate dosing/infusion rate and time. In contrast, SC administration allows therapeutics to be self-administered by patients or healthcare providers using a variety of different drug delivery systems. Because SC administration facilitates patient self-administration in home or outpatient clinical environments, SC administration provides a reduction in medical facility fixed costs. SC administration also provides flexibility in the anatomical infusion site, and SC infusion systems can be designed with smaller needle sizes, which may decrease pain during infusion. In studies comparing SC to IV administration, patients reported a higher preference for subcutaneous administration (88.9%) versus IV (9.6%) (Jin, 2015).

The dosing regimen of REGN14256 (600 mg SC) is expected to be well tolerated and is supported by the results from a toxicology study in healthy cynomolgus monkeys with a NOAEL of 150

mg/kg IV and SC of REGN14256, the highest doses tested in the study. On a weight basis, this dose is approximately 20 times higher than the proposed clinical dose of 600 mg (or 7.5 mg/kg based on an 80 kg person).

For additional information, refer to the Investigator's Brochure.

3.3. Risk-Benefit

REGN14256 has not yet been administered to humans, alone or in combination with imdevimab. therefore, there is no evidence that it can provide clinical benefit and there are no identified risks with its clinical use in individuals with or without SARS-CoV-2 infection. However, imdevimab has been used in combination with casirivimab in other clinical studies, with an identified risk of hypersensitivity reactions (including anaphylaxis and ISRs).

Preliminary results from nonclinical toxicology studies in nonhuman primates showed that REGN14256 was well tolerated without adverse findings. For individuals infected with SARS-CoV-2, and for those at risk for infection due to exposure, neutralization of SARS-CoV-2 with REGN14256+imdevimab may provide clinical benefit by reduction of clinical disease severity and by post-exposure prevention.

Currently there is no identified risk associated with REGN14256+imdevimab. The potential risks for REGN14256+imdevimab, as with all other mAbs, are systemic hypersensitivity reactions, clinical consequences of immunogenicity, and embryo-fetal toxicity.

- As REGN14256 and imdevimab are fully human IgG1 mAbs, the risk of hypersensitivity (including ISRs) is expected to be low. Individuals with known allergy or hypersensitivity to study drug component(s) are excluded from clinical studies. In addition, this study protocol describes the process of monitoring and management guidelines (Section 8.5).
- Protein therapeutics carry the potential risk of an immunogenic response in the form of anti-drug antibody (ADA) development following administration, with possible consequences on safety and efficacy. Therefore, blood samples for immunogenicity assessment will be collected during this study.
- Reproductive and developmental toxicity studies have not been conducted at this stage; therefore, the effects of REGN14256+imdevimab on reproductive organs in males and females are unknown. Pregnant women are excluded from enrolling in this study. If a female patient was pregnant or were to become pregnant during this study, the pregnancy will be followed until outcome and any safety issue observed get reported (Section 10.1.3). There has been limited experience concerning pregnancy exposure from other clinical studies with imdevimab administered with casirivimab, in which pregnant women were not excluded. The limited safety data available from clinical studies to date, have not found any evidence of embryo-fetal toxicity.

For additional information, refer to the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary Endpoints

4.1.1. Phase 1 (Safety and Tolerability)

The primary safety endpoints of phase 1 are:

- TEAEs and severity of TEAEs through day 29
- Proportion of patients with ISRs and severity of ISRs throughout the study
- Proportion of patients with hypersensitivity reactions and severity of hypersensitivity reactions over time

4.1.2. Phase 1/2 (Virologic Efficacy)

The primary endpoint is time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

4.1.3. Phase 1/2/3 (Clinical Efficacy)

The primary endpoint is time to COVID-19 symptoms resolution.

4.2. Secondary Endpoints

4.2.1. Phase 1 (Safety and Tolerability)

The secondary endpoint is proportion of patients with treatment-emergent SAEs throughout the study.

4.2.2. Phase 2 and Phase 3 (Safety and Tolerability)

The secondary endpoints are:

- TEAEs and severity of TEAEs through day 29
- Proportion of patients with ISRs and severity of ISRs throughout the study
- Proportion of patients with hypersensitivity reactions and severity of hypersensitivity reactions over time
- Proportion of patients with treatment-emergent SAEs throughout the study

4.2.3. Phase 1, Phase 2, and Phase 3 (Virologic Efficacy; Drug Concentration and Immunogenicity)

The secondary endpoints are:

- Time-weighted average change from baseline in viral load at each timepoint, as measured by RT-qPCR in NP samples (**phase 1 and phase 2 only**)
- Change from baseline in viral load at each timepoint through day 7, as measured by RT-qPCR in NP samples

- Proportion of patients with viral loads below the limit of detection at each visit
- Concentrations of REGN14256 and imdevimab in serum over time
- Incidence and titer of anti-drug antibodies (ADA) to REGN14256 and imdevimab over time

4.3. Exploratory Endpoints

The exploratory endpoints are:

Virologic

- SARS-CoV-2 sequence and variant classification in positive RT-qPCR samples
- Viral load reduction in variants under surveillance (VUS)
- Proportion of patients with positive SARS-CoV-2 test results after randomization through day 169
- Change from baseline in viral load through day 29, and at day 120 and day 169, as measured by RT-qPCR in NP swab samples
- Time-weighted average as measured by daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples **(phase 3 only)**

Clinical

- Proportion of patients with COVID-19-related hospitalization or all-cause mortality through day 29 and day 169
- Proportion of patients with COVID-19-related hospitalization, emergency room (ER) visit, or all-cause mortality through day 29 and day 169
- Proportion of patients with a COVID-19-related medically attended visit (MAV) through day 29 and day 169

  Note: COVID-19-related MAV is defined in Section 9.2.9.
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29 and day 169
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29 and day 169
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29 and day 169
- Total number of COVID-19-related MAVs through day 29 and 169
- All-cause mortality by day 29 and day 169
- Proportion of patients with ≥1 symptom from SE-LC19 Category A, B, C by day 169
- Proportion of patients with ≥2 symptoms from SE-LC19 Category A, B, C by day 169

Note: SE-LC19 symptom categories are provided in Table 5. Additional analyses related to psychometric validation of the SE-LC19 as well as potential biomarkers predicting long COVID will be outlined in separate statistical analysis plan(s).

Drug Concentration

- Concentrations of casirivimab and imdevimab in serum over time

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

Efficacy variables will differ according to study phase and will be defined in the SAP. Depending on the phase, efficacy variables may include viral load (log_{10} copies/mL), time to COVID-19 symptoms resolution, number of patients with a COVID-19-related MAV, 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 as described in Section 10.1.1.

5.4. Pharmacokinetic Variables

The PK variables are the concentration of REGN14256, casirivimab, and imdevimab in serum and time/visit. Samples will be collected according to the relevant Schedule of Events (Section 9.1).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time/visit. Samples will be collected according to the relevant Schedule of Events (Section 9.1).

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory variables may include, but are not limited to, parameters reported in hematology (including differential), blood chemistry, serology, SARS-CoV-2 sequencing, and PRO measures.

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

6. STUDY DESIGN

This is a phase 1/2/3, randomized, double-blind, placebo-controlled adaptive study to assess the safety, tolerability, virologic and clinical efficacy of REGN14256+imdevimab, compared to placebo, in non-hospitalized adults (≥18 years of age) with COVID-19. Additionally, this study

will evaluate the safety and tolerability of REGN14256+imdevimab in non-hospitalized adolescents (≥12 and <18 years of age) with COVID-19.

The primary objective of the **phase 1** FIH portion of the study is to assess the safety and tolerability of REGN14256 alone and in combination with imdevimab. Phase 1 will include 2 sentinel safety analyses (when the first 40 patients have reached study day 7 [6 days after dosing], then when all phase 1 patients have reached study day 7) during each of which study enrollment will pause for an unblinded IDMC review of all available safety data (Section 3.2.1.2). Phase 2 enrollment will begin after the second sentinel safety analysis, if the IDMC provides a recommendation for the study to proceed.

In **phase 2,** the virologic efficacy of REGN142565+imdevimab and REGN14256 monotherapy will be evaluated, and will include virologic data obtained in phase 1 which will remain blinded during that phase (Section 11.4.3). In **phase 3**, the primary objective will be to assess the clinical efficacy, based on COVID-19 symptoms resolution, of REGN14256+imdevimab compared to placebo. Clinical efficacy analysis will include data obtained in all 3 study phases, as the symptoms data obtained in phase 1 and phase 2 will remain blinded during those phases. In addition to the adult patients, an adolescent cohort of 40 patients between ≥12 and <18 years of age will be enrolled during phase 3 (Section 6.1.3), where permitted by local requirements.

6.1. Study Description and Duration

Each phase of the study consists of 3 periods: a screening/baseline period, a treatment period, and a follow-up period.

Refer to the study flow diagrams (Figure 1 for phase 1, Figure 2 for phase 2, and Figure 3 for phase 3). The Schedule of Events is provided in Section 9.1 (Table 1 for phase 1, Table 2 for phase 2, and Table 3 for phase 3), and additional information on study procedures is provided in Section 9.2.

6.1.1. Study Periods

Screening/Baseline Period (Day -1 to Day 1 Before Dosing)

Patients will be assessed for eligibility during the screening/baseline period, which may occur up to 1 day prior to the baseline visit on study day 1. To be enrolled in the study, patients must have laboratory-confirmed SARS-CoV-2 infection and experience COVID-19 symptoms. Patients cannot have received any COVID-19 vaccination, nor present any underlying medical condition or other factors associated with high risk for progression to severe COVID-19. Other eligibility criteria apply (Section 7.2.1 and Section 7.2.2).

During this period, eligible patients will be randomized (Section 8.1) and dosed on day 1. Prior to study drug administration on day 1, patients will have nasopharyngeal (NP) swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for laboratory safety, drug concentration, immunogenicity, and biomarkers analyses. After study drug dosing, adult patients will have a post-dose blood collection for drug concentration at least 1 hour after study drug administration. Phase 1 patients, and phase 3 adolescent patients (Section 6.1.3), will remain at the study site for at least 5 hours after study drug administration, for additional safety monitoring and post-dose blood collection for drug concentration assessment.

Treatment Period (Day 1 After Dosing Through Day 29)

The treatment period through day 29 includes the ***key clinical efficacy and safety analyses***. All patients will complete the Symptom Evolution of COVID-19 (SE-C19) electronic questionnaire through day 29 for the key clinical efficacy assessment of COVID-19 symptoms. Also, within the treatment period, the ***key virologic efficacy analysis*** will be performed through day 7. NP swab samples will be collected according to the Schedule of Events: in phase 1 and phase 2, every other day (days 1 [pre-dose], 3, 5, and 7) for the first week then at day 29; in phase 3, on days 1 (pre-dose), 7, and 29.

In addition, information regarding any concomitant medication use and any COVID-19-related medically-attended visits (MAVs; eg, hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) will be recorded during this period and throughout the study. Patients will be asked to notify the investigator or study site personnel as soon as possible about such occurrences. Investigators and designated study site personnel must ensure that information about COVID-19-related symptoms and MAVs is collected as required. Patients will have blood samples at indicated visits according to the Schedule of Events for drug concentration, immunogenicity, and exploratory analyses. Safety will also be monitored throughout the study: In all study phases, all TEAEs and SAEs will be collected through the end of study, and select events (grade ≥3 ISRs through day 4 and grade ≥3 hypersensitivity reactions through day 29) will be reported to the Sponsor in an expedited manner as AESIs. Refer to Section 10.1 for AE recording and reporting requirements.

Follow-Up Period (Day 30 Through Day 169)

Following the treatment period, patients will enter a follow-up period of approximately 6 months through the end of study (EOS) on study day 169. In addition to safety monitoring and drug concentration data analysis, data and samples collected during this period will be used for research purposes related to long COVID. This will include electronic questionnaires such as the Symptom Evolution of Long COVID-19 (SE-LC19), NP swabs on days 120 and 169 to assess potential persistence of SARS-CoV-2 in the nasopharynx, blood draws on day 120, and queries regarding any COVID-19-related MAVs.

On visit days when sample collection is not required (eg, when only electronic questionnaires are collected), the information indicated in the Schedule of Events may be collected by phone without an in-person visit. The EOS visit will take place approximately 6 months after study drug administration.

6.1.2. Electronic Questionnaires to Assess Patient-Reported Symptoms and Outcomes

To assess COVID-19 symptoms and other patient-reported outcomes, electronic questionnaires will be completed by patients throughout the study according to the Schedule of Events (Table 1 for phase 1, Table 2 for phase 2, and Table 3 for phase 3). Refer to Section 9.2.4 for background and procedural information regarding these instruments.

SE-C19. For assessment of COVID-19 symptoms during acute disease, the Symptom Evolution of COVID-19 (SE-C19) patient-reported questionnaire will be completed at baseline (study day 1), then on a daily basis from study day 2 through 29 (inclusive).

SE-LC19. Patients will complete the Symptom Evolution of Long COVID-19 (SE-LC19) developed by the Sponsor to evaluate the eventual occurrence of long COVID. This electronic

survey will be completed on a daily basis from study day 30 through 45 (inclusive), then at study days 60, 90, 120, and 169. Note that SE-LC19 will be completed on a daily basis during the week leading up to study day 120 (study day 114 through 120, inclusive) **and** during the week leading up to study day 169 (study day 163 through 169, inclusive).

PGIS, return to usual health, and return to usual activities questionnaires. To aid interpretation of SE-C19 and SE-LC19, Patient Global Impression of Severity (PGIS) and surveys for return to usual health or activities will be completed at baseline (study day 1), on a daily basis from study day 2 through 45 (inclusive), then at study days 60, 90, 120, and 169. Note that Patient Global Impression of Change (PGIC), return to usual healthy survey, and return to usual activities survey will also be completed on a daily basis during the week leading up to study day 120 (study day 114 through 120, inclusive) **and** during the week leading up to study day 169 (study day 163 through 169, inclusive).

PGIC, SF-36, WPAI+CIQ, and EQ-5D-5L/EQ-5D-Y. Patient Global Impression of Change (PGIC), Short Form-36 (SF-36), Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ), and European Quality of Life Five Dimension-5 Level (EQ-5D-5L)/European Quality of Life Five Dimension-Youth (EQ-5D-Y) will be completed according to the Schedule of Events. Note that all adult patients in part A and part B will complete EQ-5D-5L, while adolescent patients in part B will complete the youth version, EQ-5D-Y, instead.

6.1.3. Adolescent Cohort (Phase 3)

During the phase 3 portion of the study, a cohort of 40 adolescent patients (≥12 and <18 years of age) will be enrolled. These patients will receive open label REGN14256+indevimab with the primary goal of collecting safety and PK data. In addition, clinical outcomes data (eg, time to symptoms resolution) will also be collected. This group of adolescent cohort patients will have to meet all the same eligibility criteria as the adult patients enrolled in the study (Section 7.2).

Patients enrolled in the adolescent cohort will follow the same Schedule of Events as adult patients enrolled in phase 3, unless otherwise noted. Outcomes in these adolescent patients will be analyzed descriptively and not included in the primary clinical efficacy analysis.

Figure 1: Study Flow Diagram: Phase 1

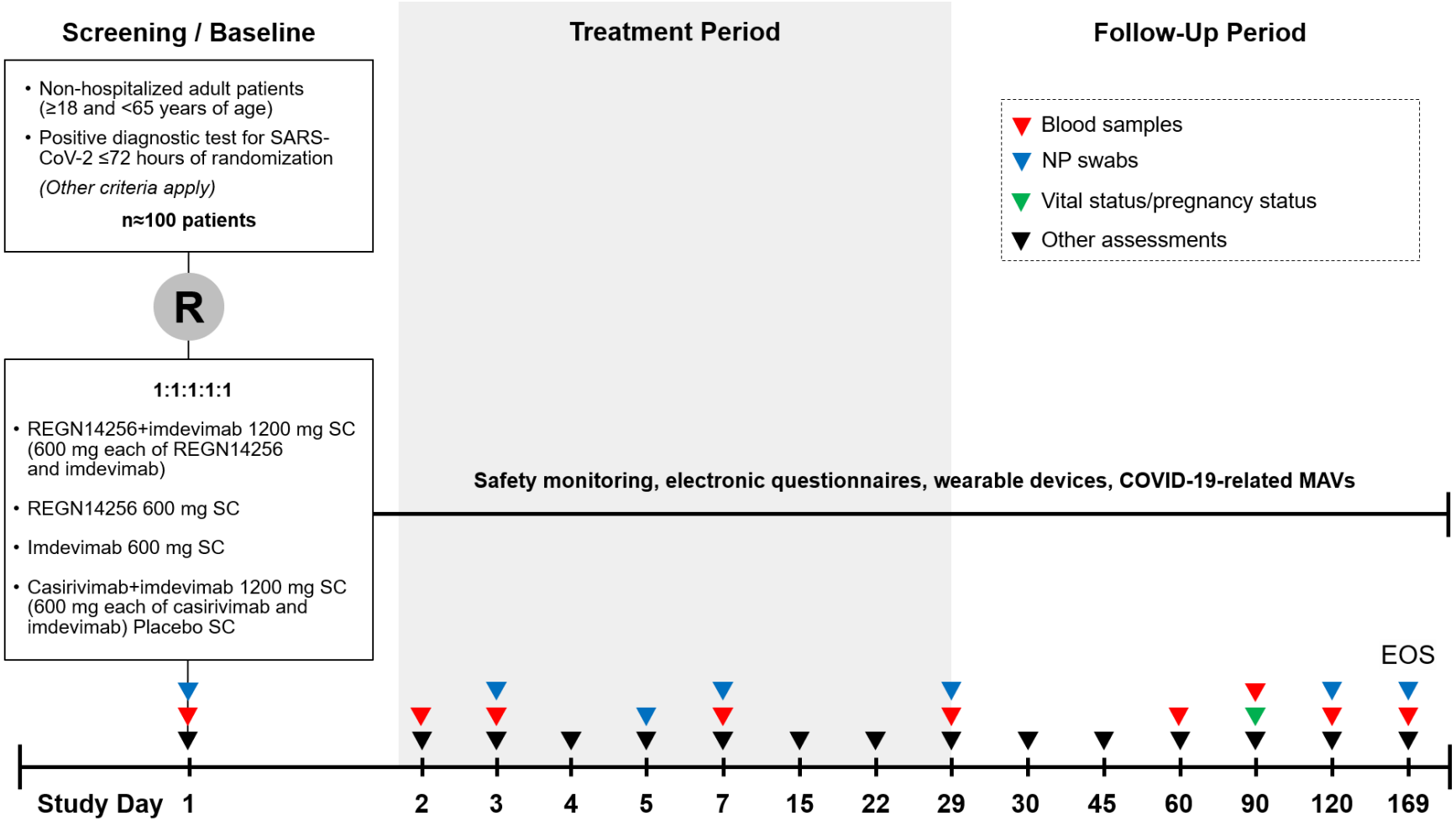


Figure 2: Study Flow Diagram: Phase 2

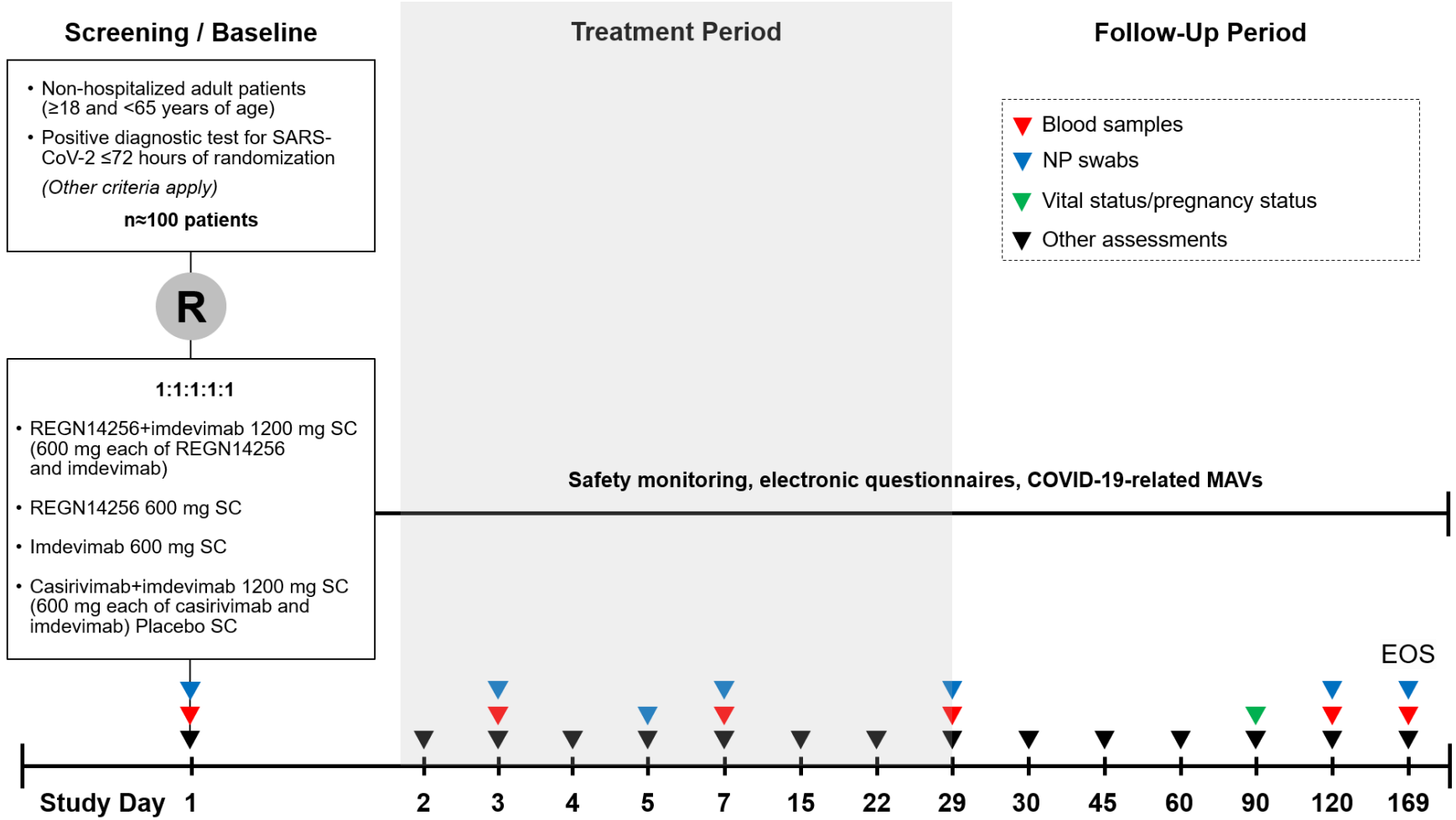
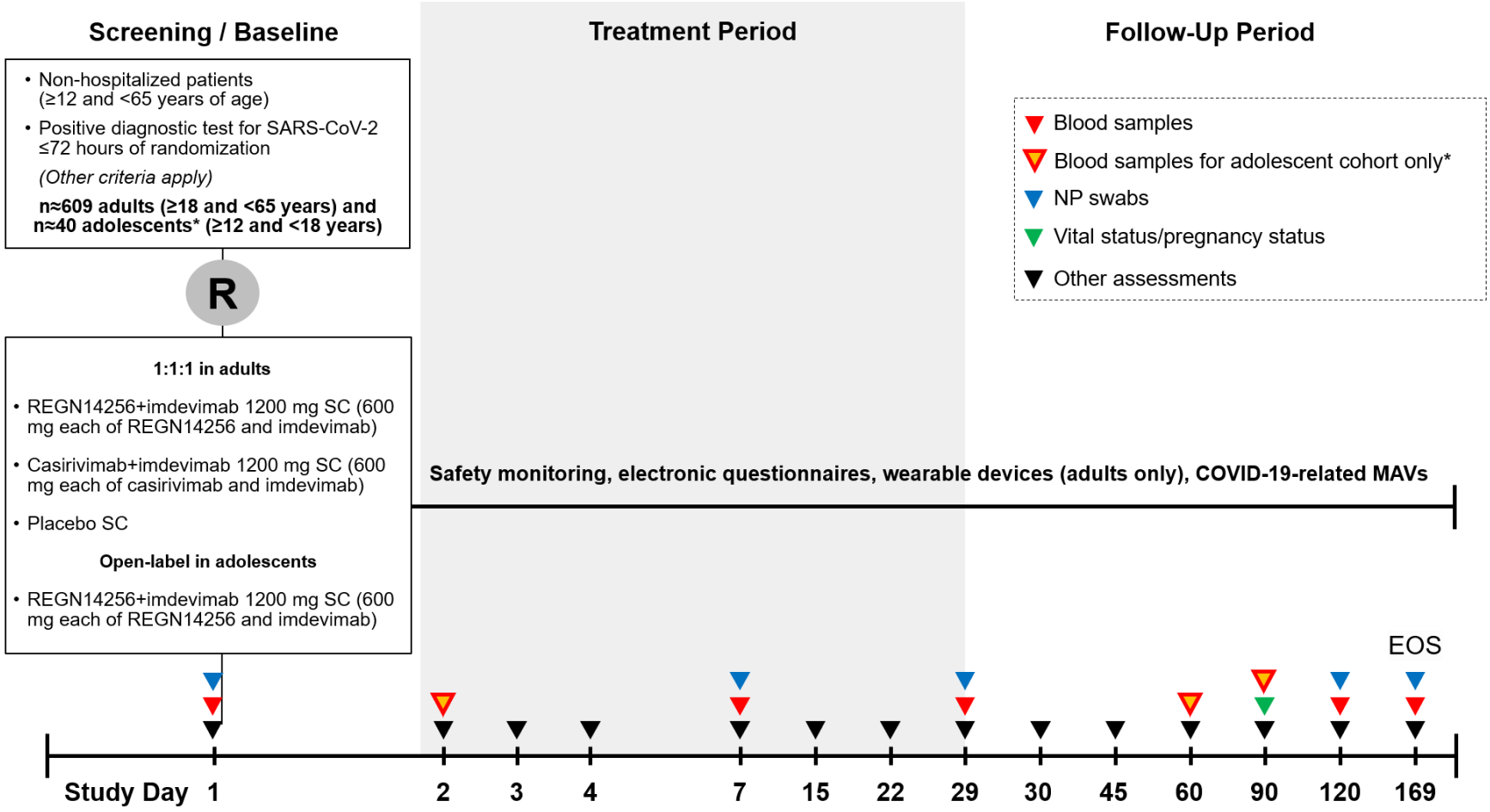


Figure 3: Study Flow Diagram: Phase 3



6.1.4. End of Study Definition

The end of study is defined as the date when the last 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. Planned Interim Analysis

No formal interim analysis is planned. Refer to Section 11.5.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor patient safety data during phases 1, 2 and 3, and clinical efficacy data during phase 3. The IDMC can make recommendations about early study closure or changes to the study conduct. This will prompt a review by the Sponsor who will decide to implement, modify, or reject the recommendation, and relevant health authorities will be notified. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

In phase 1, the IDMC will review the initial safety data in 2 sentinel safety analyses, during each of which study enrollment will be paused as described in Section 3.2.1.2.

In phase 2 and phase 3, the IDMC will perform interim safety analyses, occurring (at minimum) after approximately half of the patients are enrolled and followed to day 7. Based on these analyses, the IDMC may make recommendations on study conduct, including early study closure for safety (Section 6.4). If phase 2 and/or phase 3 enrollment is slow, the IDMC will perform the interim safety analysis when approximately 200 patients have been enrolled in a given phase and followed to day 7. Enrollment pauses are not planned during phase 2 or phase 3 unless otherwise indicated by review of ongoing safety data.

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. The IDMC charter will be updated or amended as necessary, particularly at the time of initiation of the phase 3 portion study when planned interim efficacy analyses and criteria to stop the trial for futility will be defined.

6.4. Study Stopping Rules

An IDMC will actively monitor interim data to review the ongoing safety of patients and may recommend halting or pausing the study, or implementing changes in study conduct as deemed necessary.

Appropriate action, if needed, will be taken based upon this review and in consultation with Regeneron Safety Oversight Committee (RSOC), which will include senior clinical, regulatory, and pharmacovigilance leaders at Regeneron. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

In addition, the occurrence of one the following events at any time during the study will trigger a review by the Sponsor, and communication with the IDMC, to assess if the study should be temporarily paused (ie, pausing of screening, randomization, and dosing of study drug):

- Three treatment-related SAEs or AESIs (defined in Section 10.1.3), **or**
- One treatment-related SAE with a fatal outcome

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

This study will enroll up to approximately 1,359 patients in total.

- **Phase 1** will enroll approximately 100 adult patients (≥18 years of age).
- **Phase 2** will enroll approximately 610 adult patients.
- **Phase 3** will enroll approximately 609 adult patients and an additional adolescent cohort of 40 patients (≥12 and <18 years of age).

7.2. Study Population

This study will enroll non-hospitalized, low-risk, symptomatic patients with a baseline positive diagnostic test for SARS-CoV-2, and who have not previously received experimental, authorized or licensed COVID-19 vaccines.

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 between ≥18 and <65 years of age (or country's legal age of adulthood) at randomization.

   or

   For the adolescent cohort in phase 3 only: Is male or female between ≥12 and <18 years of age at randomization

   Note: Adolescent cohort will only be enrolled where permitted by local requirements..

2. **For the adolescent cohort in phase 3 only:** Weighs ≥40 kg at randomization
3. Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization. A historical record of a positive result is acceptable as long as the sample was collected ≤72 hours prior to randomization
4. Has symptoms consistent with COVID-19 (as determined by the investigator) with onset ≤7 days before randomization, and doesn't have a medical condition or other factors

associated with high risk for progression to severe COVID-19 as outlined in the exclusion criteria

5. Maintains O_2 saturation ≥93% on room air
6. Is willing and able to:
   a. Provide informed consent signed by study patient or legally authorized representative *Note: Age-appropriate assent will be collected from the study patient according to local regulatory (competent authority/ethics) guidelines.*
   b. Comply with clinic visits, study-related procedures, including completion of the electronic diary and providing samples for viral load testing
   c. Understand and complete study-related questionnaires
7. Is judged by the investigator to be in good health based on medical history, physical examination, vital sign measurements, and ECG's performed at screening and/or prior to administration of study

7.2.2. Exclusion Criteria

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

1. Has a medical condition or other factors associated with high risk for progression to severe COVID-19:
   a. Cancer
   b. Cardiovascular disease (such as heart failure, coronary artery disease, cardiomyopathies, congenital heart disease or hypertension)
   c. Chronic lung disease including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension
   d. Chronic kidney disease at any stage
   e. Chronic liver disease (such as alcohol-related, nonalcoholic fatty liver disease, cirrhosis)
   f. Dementia or other chronic neurological condition
   g. Diabetes mellitus (type 1 or type 2)
   h. Immunodeficiency disease or taking immunosuppressive treatment
   i. Medical-related technological dependence [for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)]
   j. Neurodevelopmental disorder (for example, cerebral palsy) or other condition that confers medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
   k. Overweight (defined as BMI >25 kg/m^2) or obesity (defined as BMI ≥30 kg/m^2)
   l. Poorly controlled HIV infection or AIDS
   m. Pregnancy
   n. Sickle cell disease or thalassemia
   o. Stroke or cerebrovascular disease
2. Prior, current (at randomization) or planned use (within time period given per CDC guidance [90 days]) of any authorized or approved vaccine for COVID-19

3. Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
4. Has a known prior SARS-CoV-2 infection or positive SARS-CoV-2 serologic test
5. Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
6. 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 within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
7. Prior, current, or any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

   Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening
8. Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test
9. Has known allergy or hypersensitivity to components of the study drugs
10. Has been discharged, or is planned to be discharged, to a quarantine center
11. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
12. Is a member of the clinical site study team or is an immediate family member of the site study team
13. Is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
14. **For phase 1 only:** Women of childbearing potential (WOCBP)[1] who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment and for at least 6 months after study drug administration

    Highly effective contraceptive measures include:

    a. Abstinence[2,3]
    b. 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
    c. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
    d. Bilateral tubal ligation

    [1]WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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 the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

[2]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.

[3]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 the early termination visit, as described in Section 9.1.2.

7.4. Replacement of Patient

Patients prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. Refer to Section 9.2.2 for instructions on study drug administration.

8.1.1. Phase 1 and Phase 2

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

- Co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose

- REGN14256, 600 mg SC single dose
- Imdevimab, 600 mg SC single dose
- Co-administered casirivimab and imdevimab combination therapy, 1200 mg (600 mg each of casirivimab and imdevimab) SC single dose
- Placebo SC single dose

All patients will receive 4 SC injections of blinded study drug on day 1, each containing 2.5 mL (300 mg) of active study drug or placebo.

8.1.2. Phase 3

8.1.2.1. Patients Aged ≥18 Years

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

- Co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose
- Co-administered casirivimab and imdevimab combination therapy, 1200 mg (600 mg each of casirivimab and imdevimab) SC single dose
- Placebo SC single dose

All patients will receive 4 SC injections of blinded study drug on day 1, each containing 2.5 mL (300 mg) of active study drug or placebo.

8.1.2.2. Patients Aged ≥12 and <18 Years

Eligible patients will receive open-label REGN14256+imdevimab 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose on day 1. All patients will receive 4 SC injections of study drug on day 1, each containing 2.5 mL (300 mg) of active study drug.

8.2. Background Treatment

No background treatment will be allowed. Patients may self-administer non-prescribed medications (eg, antipyretics) and continue other concomitant medications unless they are prohibited in Section 8.10.1.

8.3. Rescue Treatment

There will be no specific protocol-defined rescue therapy. Patients with signs or symptoms suggestive of progression to severe COVID-19 may be treated according to local standard of care as per the discretion of the investigator or treating physician. Any rescue medication use should be captured in the concomitant medication eCRF. If possible, the treating physician should notify the Regeneron Medical monitor prior to implementing any rescue therapy.

8.4. Dose Modification and Study Treatment Discontinuation/Termination Rules

8.4.1. Dose Modification

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

8.4.2. Study Drug Discontinuation/Termination

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

As study drug is administered in 4 consecutive SC injections, administration 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 (severe confusion, loss of consciousness, severe paresthesia, paralysis, etc) or any other symptom or sign that, in the opinion of the investigator, warrants termination of study drug administration. If the study drug injections are interrupted for safety or any other reason (eg, mechanical failure of a syringe), the total volume of study drug that has been administered successfully will be recorded.

8.5. Management of Acute Injection Reactions

8.5.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. Acute systemic reactions following SC injection of study drug should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4. Systemic reactions occurring through day 29 are considered adverse events of special interest (AESIs) and require expedited reporting to the Sponsor (Section 10.1.2).

8.5.2. Local Injection-Site Reactions

Local injection-site reactions must be reported as AEs and graded according to Section 10.2.4.

Injection-site reactions occurring through day 4 are considered AESIs and require expedited reporting to the Sponsor (Section 10.1.2).

8.6. Method of Treatment Assignment

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

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 SC 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 data as needed for safety review or other data review (see Section 6.2). The team performing the interim data reviews will be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

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

8.8. Emergency Unblinding

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

If unblinding is required:

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

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

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

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

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

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

- Dispensed to each patient
- 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 and Procedures

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

For more information on recording of concomitant medications and procedures, refer to Section 9.2.5.3.

8.10.1. Prohibited Medications and Procedures

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (Section 7.2.2) unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures.

Based on CDC guidance and per protocol, the use of any authorized or approved COVID-19 vaccine should be deferred for at least 90 days after dosing to reduce potential interference of the study drug with vaccine-induced immune responses. Refer to the latest CDC guidance (CDC, 2021a).

8.10.2. Permitted Medications and Procedures

Other than the prohibited medications and vaccines listed in Section 8.10.1, treatment with concomitant medications is permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor. Any medications used by the study subject should be captured in the concomitant medication eCRF.

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 for phase 1, Table 2 for phase 2, and Table 3 for phase 3 .

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: Schedule of Events: Phase 1

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]							
	Day -1 to 1																			
	Screen	Pre-dose	Dose	Post-Dose	2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Screening/Baseline																				
Inclusion/Exclusion	X																			
Informed Consent	X																			
PGx sub-study consent (optional)[5]	X																			
Antigen or molecular diagnostic test for SARS-CoV-2[6]	X																			
Serology for serostatus (central lab)[16]	X																			
Medical history (including COVID-19 symptoms)	X																			
Demographics	X																			
Weight and height	X																			
Randomization		X																		
Treatment																				
Study drug administration[7]			X																	
Virologic Outcomes																				
Nasopharyngeal swab for SARS-CoV-2 RT-qPCR (central lab)	X					X		X	X			X						X		X
Electronic Survey for Patient-Reported Symptoms																				
SE-C19[8]	X				Daily															
Electronic Surveys for Exploratory Patient-Reported Outcomes																				
SE-LC19[8]													Daily		X	X	X[8]	X[8]	X[8]	X[8]
PGIS[8]	X				Daily										X	X	X[8]	X[8]	X[8]	X[8]
PGIC[8]												X								X
Return to usual health[8]	X				Daily										X	X	X[8]	X[8]	X[8]	X[8]
Return to usual activities[8]	X				Daily										X	X	X[8]	X[8]	X[8]	X[8]
SF-36[8]													X	X	X	X		X		X
WPAI+CIQ[8]	X								X	X	X	X			X	X		X		X
EQ-5D-5L[8]	X								X	X	X	X			X	X		X		X
Safety																				
Vital Signs[2]	X	X		X																
Treatment-emergent AEs[10]				← Continuous monitoring →																
Treatment-emergent SAEs [10]				← Continuous monitoring →																

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]							
	Day -1 to 1																			
	Screen	Pre-dose	Dose	Post-Dose	2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Treatment-emergent grade ≥3 ISRs[10]				←Continuous monitoring→																
Treatment-emergent grade ≥3 hypersensitivity reactions[10]				← Continuous monitoring →																
Concomitant medications and procedures[11]	X			← Continuous monitoring →																
Pregnancy test (WOCBP)[12]	X																	X		X
Vital status																X				
Pregnancy status[12]																X				
Safety information (newborns of study participants)[12]																				X
Central Laboratory Safety Testing																				
Hematology (including differential)	X[13]								X											
Blood Chemistry	X[13]								X											
Pharmacokinetics and Immunogenicity Sampling																				
Serum for drug concentration (PK)[14]	X			X[15]	X	X			X			X			X	X		X		
Serum for immunogenicity (ADA)[16]	X											X						X		
Central Laboratory Biomarker Testing																				
Serum for exploratory research[17]	X											X						X		X
Plasma for exploratory research[17]	X											X						X		X
Exploratory Patients Outcomes Assessments																				
COVID-19-related MAV details[18]	X				← Continuous monitoring →															
Wearable device[19]	X	← Continuous monitoring →																		
Pharmacogenomics (Optional Sub-Study)																				
Blood for DNA[5]	X																			

Table 2: Schedule of Events: Phase 2

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]							
	Day -1 to 1																			
	Screen	Pre-dose	Dose	Post-Dose	2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Screening/Baseline																				
Inclusion/Exclusion	X																			
Informed Consent	X																			
PGx sub-study consent (optional)[5]	X																			
Antigen or molecular diagnostic test for SARS-CoV-2[6]	X																			
Serology for serostatus (central lab)[16]	X																			
Medical history (including COVID-19 symptoms)	X																			
Demographics	X																			
Weight and height	X																			
Randomization		X																		
Treatment																				
Study drug administration[7]			X																	
Virologic Efficacy																				
Nasopharyngeal swab for SARS-CoV-2 RT-qPCR (central lab)	X					X		X	X			X						X		X
Electronic Survey for Patient-Reported Symptoms																				
SE-C19[8]	X				Daily															
Electronic Surveys for Exploratory Patient-Reported Outcomes																				
SE-LC19[8]													Daily	X	X	X[8]	X[8]	X[8]	X[8]	
PGIS[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
PGIC[8]												X								X
Return to usual health[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
Return to usual activities[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
SF-36[8]													X	X	X	X		X		X
WPAI+CIQ[8]	X								X	X	X	X			X	X		X		X
EQ-5D-5L[8]	X								X	X	X	X			X	X		X		X
Safety																				
Vital Signs[9]	X	X		X																
Treatment-emergent AEs[10]				← Continuous monitoring →																

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]							
	Day -1 to 1																			
	Screen	Pre-dose	Dose	Post-Dose	2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Treatment-emergent SAEs [10]				← Continuous monitoring →																
Treatment-emergent grade ≥3 ISRs[10]				←Continuous monitoring→																
Treatment-emergent grade ≥3 hypersensitivity reactions[10]				← Continuous monitoring →																
Concomitant medications and procedures[11]	X			← Continuous monitoring →																
Pregnancy test (WOCBP)[12]	X																	X		X
Vital status																X				
Pregnancy status[12]																X				
Safety information (newborns of study participants)[12]																				X
Central Laboratory Safety Testing																				
Hematology (including differential)	X[13]								X											
Blood Chemistry	X[13]								X											
Pharmacokinetics and Immunogenicity Sampling																				
Serum for drug concentration (PK)[14]	X			X		X			X			X						X		
Serum for immunogenicity (ADA)[16]	X											X						X		
Central Laboratory Biomarker Testing																				
Serum for exploratory research[17]	X											X						X		X
Plasma for exploratory research[17]	X											X						X		X
Exploratory Patient Outcomes Assessments																				
COVID-19-related MAV details[18]	X				← Continuous monitoring →															
Pharmacogenomics (Optional Sub-Study)																				
Blood for DNA[5]	X																			

Table 3: Schedule of Events: Phase 3

Day	*Screening/Baseline*[1]				*Treatment Period*[3]							*Follow Up Period*[3]							
	Day-1 to 1																		
	Screen	Pre-dose	Dose	Post-Dose	2	3	4	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
Window (Day)									±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Screening/Baseline																			
Inclusion/exclusion	X																		
Informed consent (or assent, as applicable)	X																		
PGx sub-study consent (optional)[5]	X																		
Antigen or molecular diagnostic test for SARS-CoV-2[6]	X																		
Serology for serostatus (central lab)[16]	X																		
Medical history (including COVID-19 symptoms)	X																		
Demographics	X																		
Weight and height	X																		
Randomization		X																	
Treatment																			
Study drug administration[7]			X																
Virologic Efficacy																			
Nasopharyngeal swab for SARS-CoV-2 RT-qPCR (central lab)	X							X			X						X		X
Electronic Survey for Patient-Reported Symptoms																			
SE-C19[8]	X				Daily														
Electronic Surveys for Exploratory Patient-Reported Outcomes																			
SE-LC19[8]												Daily		X	X	X[8]	X[8]	X[8]	X[8]
PGIS[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]
PGIC[8]											X								X
Return to usual health[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]
Return to usual activities[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]
SF-36[8]												X	X	X	X		X		X
WPAI+CIQ[8]	X							X	X	X	X			X	X		X		X
EQ-5D-5L (for patients ≥18 years of age)[8]	X							X	X	X	X			X	X		X		X
EQ-5D-Y (for patients <18 years of age)[8]	X							X	X	X	X			X	X		X		X
Safety																			
Vital Signs[9]	X	X		X															

Day	*Screening/Baseline*[1]				*Treatment Period*[3]							*Follow Up Period*[3]							
	Day-1 to 1																		
	Screen	**Pre-dose**	**Dose**	**Post-Dose**	**2**	**3**	**4**	**7**	**15**	**22**	**29**	**30**	**45**	**60**	**90**	**114–119**	**120**[8]	**163–168**	**169**[8] **EOS**
Window (Day)									**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7 or ±7**[4]		**+7 or ±7**[4]
Treatment-emergent AEs[10]				← Continuous monitoring →															
Treatment-emergent grade SAEs[10]				← Continuous monitoring →															
Treatment-emergent grade ≥3 ISRs[10]				←Continuous monitoring→															
Treatment-emergent grade ≥3 hypersensitivity reactions[10]				← Continuous monitoring →															
Concomitant medications and procedures[11]	X			← Continuous monitoring →															
Pregnancy test (WOCBP)[12]	X																X		X
Vital status															X				
Pregnancy status[12]															X				
Safety information (newborns of study participants)[12]																			X
Central Laboratory Safety Testing																			
Hematology (including differential)	X[13]							X											
Blood Chemistry	X[13]							X											
Pharmacokinetics and Immunogenicity Sampling																			
Serum for drug concentration (PK) for adult patients (≥18 years of age)[14]	X							X			X						X		
Serum for drug concentration (PK) for adolescent patients (≥12 and <18 years)[14]	X			X[15]	X			X			X			X	X		X		
Serum for immunogenicity (ADA) for all patients[16]	X										X						X		
Central Laboratory Biomarker Testing																			
Serum for exploratory research[17]	X										X						X		X
Plasma for exploratory research[17]	X										X						X		X
Exploratory Patient Outcomes Assessments																			
COVID-19-related MAV details[18]	X				← Continuous monitoring →														
Wearable device (≥18 years of age only)[19]	X	← Continuous monitoring →																	
Pharmacogenomics (Optional Sub-Study)																			
Blood for DNA[5]	X																		

9.1.1. Footnotes for the Schedule of Events

1. Screening visit may occur on the same day as the baseline visit (day 1), or the day prior to the baseline visit (day -1).
2. In **phase 1**, on day 1, vital signs (as described in Section 9.2.5.1) will be measured at pre-dose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4.
3. On visit days when sample collection is not required (eg, when only patient-reported questionnaires are collected), the information indicated in the Schedule of Events may be collected by phone without an in-person visit.
4. For all day 120 and day 169 questionnaires, a visit window of +7 days will be applied. For all other day 120 and day 169 assessments and sample collections, a visit window of ±7 days will be applied.
5. Patients must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for DNA should be collected at the day -1 or day 1 visit but may be collected at any visit.
6. The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2, either at screening **or** by historical record of a 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 nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva) collected ≤72 hours prior to randomization. For local tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF.
7. Refer to Section 9.2.2 for study drug administration instructions.
8. On visit days when other assessments or sample collections are required, the site will verify that questionnaires have been completed prior to all other assessments or collections. The questionnaires should be completed in the order listed. On days when a certain questionnaire is not required, it will be skipped while the overall order of the other required questionnaires remains the same. Note that questionnaires will only be administered to patients in study sites if regionally available, and will only be administered to patients who are able to complete the questionnaires in the language available at their study site. Refer to Section 9.2.4 for additional information regarding these questionnaires.

   Long-COVID electronic surveys (ie, SE-LC19, PGIS, return to usual health, return to usual activities) must be completed as indicated in the Schedule of Events, then daily during the week leading up to day 120 visit, and daily during the week leading up to EOS visit on day 169.
9. On day 1, vital signs (as described in Section 9.2.5.1) will be collected once before study drug administration and once after study drug administration is completed.

   Phase 2: Patients will be monitored for at least 1 hour after study drug administration then released from the study site, if medically appropriate.

Phase 3 adult patients: After study drug administration, patients should be monitored according to local medical practice, as medically appropriate rather than a predefined period of time per the study protocol.

Phase 3 adolescent cohort: Patients will be monitored for at least 1 hour after study drug administration.

10. Refer to Section 10 for more information on safety reporting and recording requirements for.
11. Concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.5.3 for more information.
12. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. For WOCBP, negative pregnancy must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Note that a paper pregnancy report form must be completed for each patient who becomes pregnant and safety information in newborns of study participants will be collected.
13. The indicated blood samples may be collected at either day -1 or day 1 (screening or pre-dose) but must be collected prior to randomization.
14. Actual dosing time and drug concentration (PK) sample collection times will be recorded. At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing (either at day -1 or day 1).

    The post-dose blood collection on day 1, if indicated, should occur at least 1 hour after study drug administration.
15. In **phase 1** patients, and in **adolescent cohort** patients in phase 3, the post-dose blood collection on day 1 should occur at least 5 hours after study drug administration.
16. The window for pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times will be recorded.
17. Baseline serum SARS-CoV-2 serology assays will be performed centrally to determine serostatus retrospectively. Other serologic and plasma-based exploratory assays will be performed centrally post-treatment.
18. COVID-19-related MAVs (defined as hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) will be recorded in the eCRF. At minimum, details listed in Section 9.2.9 will be included.
19. Wearable devices will be worn continuously, starting at least 15 minutes before study drug administration (preferably starting at screening). Refer to Section 9.2.10 for more information on the wearable device.

9.1.2. Early Termination Visit

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

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

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for collection of NP swabs, blood, serum, or plasma, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and sample collections that will be performed in this study. Procedures and sample collections will occur according to the Schedule of Events (Section 9.1).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

9.2.1.1. Informed Consent

Informed consent (and assent, as applicable) must be obtained according to the requirements described in Section 13.2. Optional informed consent/assent may be obtained for participation in the pharmacogenomics sub-study (Section 9.2.11).

9.2.1.2. Diagnostic Test for SARS-CoV-2

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

9.2.1.3. Serology for Baseline Serostatus

Serum serology assays will be performed to retrospectively determine baseline anti-SARS-CoV-2 serostatus.

9.2.1.4. Medical History

Medical history will include, but not be limited to the following:

- COVID-19 with start date as the date of onset of first symptoms related to COVID-19
- Menopausal history
- Pregnancy or breastfeeding status, if applicable

9.2.1.5. Demographics

Refer to Section 5.1.

9.2.1.6. Weight and Height

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

9.2.2. Study Drug Administration

See Section 8.1 for treatments to be administered.

For study drug administration which requires multiple SC injections, it is recommended to use different quadrants of the abdomen (avoiding navel and waist areas), front and upper outer sides of the thighs or the back side of the upper outer area of the arm. During the dose administration, each injection must be given in a different anatomical location (eg, 1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc). Numbing cream at the sites of injection should not be used as this will interfere with the safety assessment, ie, evaluation of ISRs.

9.2.3. Nasopharyngeal Swab Collection

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

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

9.2.4. Patient-Reported Symptoms

This section describes planned patient-reported symptom analyses, some of which may not be reported in the CSR. Note that any symptoms collected by the instruments described below will not be considered AEs and will not be reconciled with any AEs.

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

9.2.4.1. Symptom Evolution of COVID-19 (SE-C19), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC)

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

Patients rate each identified symptom as mild, moderate, or severe at the worst moment within the last 24 hours. An ‘other’ category is also available, where a free text field allows the addition of any symptom that is not on the list. Each score is assigned a numeric value: 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). Table 4 provides the symptoms evaluated in the SE-C19.

Table 4: Symptoms Evaluated in the Symptom Evolution of COVID-19 (SE-C19) Instrument

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

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

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

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

To better understand the symptomatic course of long COVID, the Sponsor developed the Symptom Evolution of Long COVID-19 (SE-LC19). The SE-LC19 expands upon the SE-C19, which was developed with the aim of evaluating the acute phase of the disease course. The SE-LC19 consists of 40 symptoms, identified based on an evaluation of the currently-available literature on symptoms associated with long COVID (CDC, 2021b) (NHS, 2021) (WHO, 2021b).

Participants are presented with a list of symptoms and are asked to identify all those that they are experiencing. Participants rate each symptom as mild, moderate, or severe at the worst moment within the last 24 hours. Each score is assigned a numeric value: 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). Table 5 lists the symptoms evaluated in the SE-LC19.

Table 5: Symptoms Evaluated in the Symptom Evolution of Long COVID-19 (SE-LC19) Instrument

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

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

9.2.4.3. Global Impression Items

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

9.2.4.4. SF-36

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

9.2.4.5. Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ)

Acute respiratory illnesses can lead to a significant economic burden owing to absenteeism and loss of workplace productivity (Li, 2007). The Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ) questionnaire measures the effect of a specific health problem (eg, infection with SARS-CoV-2) on work productivity and activity impairment. The specific outcomes measured by the questionnaire are absenteeism (work time missed), presenteeism (impairment while working), overall work impairment (absenteeism plus presenteeism), and activity impairment (impairment in regular activities). Each score is represented as a percentage, with higher scores indicating less productivity or greater impairment.

9.2.4.6. EQ-5D-5L and EQ-5D-Y

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

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

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

9.2.5. Safety Procedures

9.2.5.1. Vital Signs

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

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.

9.2.5.2. Adverse Event Monitoring

Treatment-emergent AEs (as defined in Section 10.1.1) will be recorded.

9.2.5.3. Record Concomitant Medications and Concomitant Procedures

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

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

9.2.5.4. Pregnancy Test for Women of Childbearing Potential

Negative pregnancy test must be confirmed prior to study drug administration. Pregnancy testing may be satisfied by either serum pregnancy test (to be performed at a central laboratory) or by urine β-HCG test (to be performed at the local laboratory). Pregnancy tests are a requirement for WOCBP only and should be completed regardless of pregnancy status.

Women of childbearing potential (WOCBP) are defined in Section 7.2.2 Exclusion Criterion #14.

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

9.2.5.5. Vital Status

Vital status (whether the patient is dead or alive) will be recorded, as well as the date of death, when applicable.

9.2.5.6. Pregnancy Status

When applicable, date of pregnancy and status of the pregnancy will be recorded. Refer to Section 10.1.3 for reporting requirements.

9.2.5.7. Safety Information in Newborns of Study Participants

The incidence and outcome of any SARS-CoV-2 infection will be collected for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant

at any time in the study. Note that this information is in addition to outcome reporting of all pregnancies (Section 10.1.3).

9.2.5.8. Laboratory Testing

Hematology, chemistry, and serum β-HCG pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Note that the laboratory tests listed below will only be performed based on samples that are collected according to the corresponding Schedules of Events (Section 9.1).

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

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

Other Test(s)

β-HCG pregnancy testing (serum)

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 an AE are provided in Section 10.1.1.

9.2.6. Drug Concentration and Measurements

Samples for assessment of drug concentration will be collected at the timepoints indicated in the corresponding Schedules of Events (Section 9.1). For information concerning unused samples and exploratory research, refer to Section 9.2.8.

9.2.7. Immunogenicity Measurements and Samples

Samples for assessment of immunogenicity will be collected at the timepoints indicated in the corresponding Schedules of Events (Section 9.1). 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 pharmacodynamic/biomarker analyses, some of which may not be reported in the CSR.

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

9.2.8.1. Virology

Viral Sequencing

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

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

Viral variants suspected to confer decreased susceptibility to REGN14256 and/or imdevimab will be evaluated in nonclinical work separate from this protocol.

The results of viral sequencing will be reported separately from the CSR.

Viral Infectivity

To explore the effects of REGN14256 and imdevimab on infectivity of SARS-CoV-2, the Sponsor may use PFU, viral culture or viral subgenomic mRNA RT-qPCR or other assays to study SARS-CoV-2. In vitro SARS-CoV-2 infectivity of cultured cells may be explored using NP samples. Infectivity of cells grown in culture may be assessed by PFU assays and/or immunofluorescence or other viral replication assays. The Sponsor may also use sub-genomic viral mRNA transcript assays, such as RT-qPCR or subgenomic mRNA sequencing, or other measures of in vivo infectivity potential. Viral sub-genomic mRNA is transcribed only in infected cells and is not

packaged into virions, and therefore may be an indicator of actively-infected cells. These data may be associated with RT-qPCR measuring viral load.

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

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

To explore the impact of baseline humoral activity against SARS-CoV-2 on the response to REGN14256+imdevimab, serological immunoassays will be used to detect antibodies at baseline against the SARS-CoV-2 spike protein RBD. Additional analyses of antibodies to other SARS-CoV-2 antigens may also be performed. 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 SARS-CoV-2 post-treatment may be tested for exploratory purposes.

9.2.8.3. Serum and Plasma for Exploratory Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN14256+imdevimab, 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, and other related analyses.

9.2.8.3.1. Long COVID

Serum and plasma samples will be collected and banked for subsequent analyses. Such analyses may include, but are not limited to, multiplex proteomic profiling and serologic immunoassays to detect antibodies against SARS-CoV-2 among other assays.

Serum and plasma-based analyses will be used to address scientific questions related to long COVID, such as the identification of prognostic biomarkers, understanding whether long COVID represents a single versus multiple unique pathologies and biological mechanisms, and associating biomarker profiles with patient-reported outcomes data. Analyses performed from banked samples may also be integrated with biomarker and other data from samples collected during the acute phase of SARS-CoV-2 infection. This will enable relationships between acute and long-term phases of COVID-19 to be explored, including better understanding the biology of COVID-19 over time, and evaluating potential biomarkers during acute infection that may be predictive of REGN14256+imdevimab response during the long-term phase of disease.

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

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

Medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF.

Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit

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

9.2.10. Wearable Device Data Collection

Exploratory parameters of pulse, respiratory rate, SpO_2, physical activities and sleep will be measured using a wearable device. Patients will wear the device on the wrist, day and night according to the Schedule of Events. The devices will be worn **continuously** except during designated battery charging periods, bathing, and swimming.

The wearable devices will be provided to study sites and appropriate training regarding patient use of these devices will be provided to the investigator and site staff.

9.2.11. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction will be collected at the timepoints indicated in the corresponding Schedule of Events (Section 9.1.1) should be collected on day 1/baseline (predose), but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of COVID-19 and related diseases. These samples will be single-coded as defined by the International Council for Harmonization (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the Sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN14256 alone or in combination with imdevimab, or combination of casirivimab and imdevimab, other COVID-19 clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of COVID-19 as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or COVID-19 and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the

course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

Below TEAEs will be recorded:

- Treatment-emergent adverse events (TEAEs) through day 169
- Treatment-emergent serious adverse events (SAEs) through day 169
- Treatment-emergent adverse events of special interest (AESIs):
  - Grade ≥3 injection-site reactions (ISRs) through day 4
  - Grade ≥3 hypersensitivity reactions through day 29

The investigator must promptly report the above TEAEs occurring during the observation period (defined in 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 TEAEs occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all TEAEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on TEAEs until they have resolved or are considered clinically stable.

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

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, require corrective treatment, or constitute an AE in the investigator's clinical judgement. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the informed consent form [ICF]) procedures, treatments requiring

hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

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

Any SAE occurring subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should be reported. In addition, any SAE resulting in death that occurs prior to study day 169 should also be reported, regardless of patient withdrawal or early termination.

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

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

10.1.2. Reporting Procedure

The TEAEs defined in Section 10.1.1 must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. For SAEs and AESIs, detailed narratives 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 Adverse Events of Special Interest (AESI):** Adverse events of special interest for this study include the following:
  - Grade ≥3 ISRs through study day 4
  - Grade ≥3 hypersensitivity reactions through study day 29
- **Pregnancy.** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification,

any pregnancy occurring in a female study patient during the study. A paper pregnancy report form must be completed for each patient who becomes pregnant.

Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor, including testing results for SARS-CoV-2 infection in the newborn, if performed.

10.2. 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 AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** 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 AE 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 (Section 10.1.3).

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. Severity

The severity of adverse events (including test findings classified as AEs) will be graded using the current version of the NCI-CTCAE v5.0.

Treatment-emergent AEs, SAEs, or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 6. The grading systems for anaphylaxis, allergic reaction (hypersensitivity), and injection-site reaction are provided in Table 7

Table 6: NCI-CTCAE (v5.0) Severity Grading System for Adverse Events: General Guideline

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

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

Table 7: NCI-CTCAE (v5.0) Severity Grading System for Anaphylaxis, Allergic Reactions and Injection-Site Reactions

Grade	CTCAE Term		
	Anaphylaxis[1]	**Allergic Reaction** *(hypersensitivity)*[2]	**Injection-Site Reaction**[3]
1	N/A	Systemic intervention not indicated	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
2	N/A	Oral intervention indicated	Pain; lipodystrophy; edema; phlebitis
3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Ulceration or necrosis; severe tissue damage; operative intervention indicated

4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death	Death

[1] Disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.
[2] Disorder characterized by an adverse local or general response from exposure to an allergen.
[3] Disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

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.

Include the following when applicable] For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

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

- **Related**:
  - The AE 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 AE 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 AE 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 AE 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 AE 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, GPS; 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/ 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/IRBs as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of 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 SAP will be issued before the first database lock.

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

11.1. Statistical Hypothesis

Phase 1

No formal hypothesis testing is planned for phase 1. The safety and tolerability objectives will be evaluated by estimating the proportion of patients with TEAEs and SAEs through day 29 and AESIs, which will include ISRs (grade ≥3) through day 4 and hypersensitivity reactions (grade ≥3) through day 29.

Phase 1/2

There are two null hypotheses to be tested in phase 1/2 (ie, based on data from phase 1 and phase 2):

- $\mathbf{H_{a1}}$: There is no treatment difference between REGN14256 in combination with imdevimab compared to placebo in terms of time weighted average daily change from baseline in viral load ($\log_{10}$ copies/mL) from day 1 to day 7 for the seronegative patients.
- $\mathbf{H_{a2}}$: There is no treatment difference between REGN14256 alone compared to placebo in terms of time weighted average daily change from baseline in viral load ($\log_{10}$ copies/mL) from day 1 to day 7 for the seronegative patients.

Phase 1/2/3

The primary null hypothesis to be tested in phase 1/2/3 (ie, based on data from phase 1, phase 2, and phase 3) is:

- $\mathbf{H_{b1}}$: There is no difference in time to COVID-19 symptoms resolution for REGN14256 in combination with imdevimab compared to placebo for the seronegative patients.

A hierarchical testing procedure will be applied to control for multiplicity and to maintain the study-wise type I error rate at two-sided 0.05 level.

11.2. Justification of Sample Size

Phase 1

Phase 1 will enroll approximately 100 patients (approximately 20 patients per arm) randomized to 5 treatment groups.

Phase 1/2

The primary virologic efficacy analysis will be based on data from patients enrolled in phase 1 and phase 2. After the IDMC provides the recommendation to proceed with enrollment in phase 2

(Section 3.2.1.2), at least 610 additional patients will be randomized in the phase 2 portion of the study, for a total sample size in phase 1 and 2 of at least 710 randomized patients.

The sample size is based on the primary virologic endpoint of time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 using a two-sample t-test at a two-sided significance of α=0.05, in patients who are seronegative and who have a positive RT-qPCR value at baseline. Assuming a standard deviation of 1.2 log_{10} copies/mL, a sample size per arm of n=85 seronegative patients with positive value on RT-qPCR at baseline provides at least 90% power to detect a difference of 0.6 log_{10} copies/mL in TWA daily change from baseline viral load between any treatment group and placebo.

If approximately 60% of patients are seronegative and have a positive value on RT-qPCR at baseline, it is estimated that ~142 patients would be required to be randomized into each treatment arm in order to yield ~85 seronegative patients per group.

During enrollment, if the proportion of seronegative patients is observed to be different from that initially assumed, the study will continue to enroll until the required number of seronegative patients are met for the assessment of the primary virology endpoint.

Phase 1/2/3

The total sample size for the study is based on having sufficient power to analyze the primary endpoint of time to COVID-19 symptoms resolution. The primary clinical efficacy analysis will be based on data from patients enrolled in phase 1, phase 2, and phase 3.

Based on data from the seronegative mFAS patients from the COV-2067 study (defined as the subset of seronegative patients with a positive central-lab determined SARS-CoV-2 RT-qPCR result from NP swab samples at randomization), the difference in median time to symptoms resolution was 4 days (8.0 days for casirivimab+imdevimab 2400 mg IV vs 12.0 days for placebo). Therefore, the sponsor conservatively assumes a difference in median time to symptoms resolution of 3.5 days for the comparison between co-administered REGN14256 and imdevimab combination therapy, 1200 mg (600 mg each of REGN14256 and imdevimab) SC single dose and placebo.

Therefore, assuming a median time to COVID-19 symptoms resolution of 12 days for placebo, 354 total events are needed to detect a difference in medians of 3.5 days with 90% power using a log-rank test (2 sided) with an overall type 1 error of 0.05, which corresponds to a median time to COVID-19 symptoms resolution of 8.5 days in the REGN14256 and imdevimab combination therapy group (HR=1.41).

Assuming 29 days of follow up per patient, an accrual duration of 90 days, a total of 412 seronegative patients (206 per group) are required to achieve 354 total events in a pairwise comparison between REGN14256+imdevimab combination therapy and placebo. Given that phase 3 has 3 treatment arms with a 1:1:1 randomization ratio, 618 seronegative patients (206 per group) are required to be randomized. Furthermore, assuming approximately 60% of patients are seronegative and have a positive value on RT-qPCR at baseline, approximately 345 mFAS patients per arm in the relevant treatment groups will need to be randomized to have approximately 1035 patients for testing the clinical efficacy endpoint of time to COVID-19 symptoms resolution.

Because 142 patients per group in the relevant treatment arms in phase1/2 will be contributing to the analysis of time to COVID-19 symptoms resolution, therefore, in phase 3, approximately 609

additional patients (203 per group) are required to be randomized into the 3 arms in a 1:1:1 ratio in order to yield 345 patients per group for the statistical hypothesis testing.

During enrollment, the number of events among seronegative patients will be monitored in a blinded manner to ensure that the comparison of time to symptoms resolution is adequately powered. The sample size for the phase 3 portion of the study will be adjusted accordingly if the design, objective, and/or assumptions are changed.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The **modified full analysis set (mFAS)** includes all randomized patients with a positive central-lab determined SARS-CoV-2 RT-qPCR result from NP swab samples at randomization and is based on the treatment received (as treated).

The **seronegative mFAS** is the subset of patients in the mFAS population who are seronegative at baseline. The seronegative mFAS will be used for all efficacy and pharmacodynamic analyses. The seronegative mFAS is the primary analysis population; secondary analyses will be conducted in the overall mFAS population.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Demographic and baseline characteristics, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

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

11.3.4. Immunogenicity Analysis Sets

The ADA analysis sets (AAS) include all patients who received any study drug and had at least one non-missing ADA result after first dose of the study drug.

Samples positive in the ADA assays will be characterized further for ADA titers. 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.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who have 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

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

All efficacy hypotheses are tested with respect to placebo.

11.4.3.1. Phase 1/2: Primary Virologic Efficacy Analysis

Note: the primary virologic efficacy analysis will be based on data from patients enrolled in phase 1 and phase 2.

The primary virologic efficacy variable is time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples. The primary analysis will be conducted in the Seronegative mFAS population. The estimands for the primary hypotheses is the difference in means between the SARS-CoV-2 combination mAb treatment (REGN14256+imdevimab) vs. placebo and the difference in means between REGN14256 vs. placebo.

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

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

11.4.3.2. Phase 1/2/3: Primary Clinical Efficacy Analysis

Note: the primary clinical efficacy analysis will be based on data from patients enrolled in phase 1, phase 2, and phase 3.

COVID-19 symptoms included in the analysis are as follows: body aches such as muscle pain or joint pain, chest pain, chills, cough, diarrhea, dizziness, fatigue, feverish, headache, loss of appetite, loss of taste/smell, nausea, pressure/tight chest, red or watery eyes, runny nose, shortness of breath/difficulty breathing, sore throat, sputum/phlegm, and stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the patient scored 'no symptom' (score of 0) on all of the above symptoms except cough, fatigue, and headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0). Time to COVID-19 symptoms resolution will be analyzed using the log-rank test. The analyses will be performed in the seronegative mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and 95% CI for time to COVID-19 symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis.

11.4.4. Control of Multiplicity

A hierarchical testing procedure will be used to control the overall type I error rate at 0.05 for the testing of the primary virology endpoints (REGN14256 alone and in combination with imdevimab in comparison to the placebo arm) and the clinical endpoint (time to symptoms resolution in patients in the REGN14256+imdevimab arm in comparison to the placebo arm). The hierarchical testing order will be 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 on-treatment period.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 treatment-emergent SAEs by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 injection-site reactions (grade ≥3) through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reaction (grade ≥3) through day 29 by PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- Treatment-related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized by treatment group.

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.

11.4.5.3. Treatment Exposure

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

11.4.5.4. Treatment Compliance

Treatment compliance is not applicable for this study, since the study drug is administered once at the site.

11.4.6. Analysis of Drug Concentration Data

All Patients in Phase 2 and Adolescent Patients in Phase 3

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

The concentrations of REGN14256, imdevimab, and casirivimab in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Adult Patients in Phase 3

The concentrations of REGN14256 and imdevimab in serum over time will be summarized descriptively for the REGN14256 and imdevimab treatment groups.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA status, ADA category, and maximum titer observed in patients in the ADA analysis set.

The ADA status of each subject may be classified as one of the following

- Positive
- Pre-existing – If the baseline sample is positive and all post-baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative – If all samples are found to be negative in the ADA assay

The ADA category of each positive subject is classified as:

- Treatment-emergent – A negative result or missing result at baseline with at least one positive post-baseline result in the ADA assay.
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
- Treatment-boosted – A positive result at baseline in the ADA assay with at least one post-baseline titer result ≥9-fold the baseline titer value.

The maximum category of each subject is classified as:

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

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by patient, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.5. Interim Analysis

No formal interim analysis is planned.

At the time of primary virologic efficacy assessment, the Sponsor may conduct an administrative interim analysis for time to COVID-19 symptoms resolution in order to inform regulatory interactions and/or internal decision making.

An alpha penalty of 0.001 will apply for the testing of the clinical endpoint of time to symptoms resolution if an administrative look occurs.

To protect the integrity of study results, unblinding for the primary virology analyses will occur after all patients enrolled in phase 2 have reached day 29. Individuals unblinded to the patient-level data for the first step or any subsequent analysis will no longer be involved in the day-to-day conduct of the ongoing study. Patient-level results will not be released to any site-facing personnel or anyone who is directly involved in the conduct of the study.

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
- Wearable devices

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

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

The study monitors will perform ongoing source data review to verify that data recorded in the CRF 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 CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). 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 (CRFs) within the EDC system by trained site personnel. All required CRFs 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 CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF 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 CRF will be entered in the CRF 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 or 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, CRFs, 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 CRF/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 ICF can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

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

Adult Patients

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

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

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

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

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

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

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

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

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

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

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form
- Patients who can understand but who can neither write nor read will have the assent form read to them by the person obtaining assent, who will sign and date the assent form to confirm that assent was given

The original assent form must be retained by the investigator as part of the patient's study record, and a copy of the signed assent form must be given to the patient's parent(s) or legal guardian(s).

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs 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 '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. Close-out 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 Phase 1/2/3 Adaptive Study to Evaluate the Safety, Tolerability, and Efficacy of REGN14256+Imdevimab for the Treatment of COVID-19 Patients Without Risk Factors for Progression to Severe Disease* 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 Phase 1/2/3 Adaptive Study to Evaluate the Safety, Tolerability, and Efficacy of REGN14256+Imdevimab for the Treatment of COVID-19 Patients Without Risk Factors for Progression to Severe Disease

Protocol Number: R14256-COV-2149

Protocol Version: Amendment 1

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

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ESig Approval	[redacted]2021 14:49:11 GMT+0000

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