Clinical Study Protocol

A PHASE 2A, OPEN-LABEL STUDY ASSESSING PHARMACOKINETICS, SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF SINGLE-DOSE SUBCUTANEOUS ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES (CASIRIVIMAB AND IMDEVIMAB) IN HIGH-RISK PEDIATRIC SUBJECTS UNDER 12 YEARS OF AGE

Compound:	Casirivimab+Imdevimab
Clinical Phase:	2a
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Medical /Study Director:	[redacted]

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AMENDMENT HISTORY

Amendment 2

The primary purpose of this amendment is to shorten the length of the follow-up period from 225 days to 169 days (32 weeks to 24 weeks), and to add that the end of study visit (EOS) visit is required to be performed in person.

Description of Change	Brief Rationale	Section(s)
The length of the follow-up period for assessment of drug concentrations, safety, and immunogenicity has been shortened and the EOS date has been amended from day 225 to day 169 accordingly. Study visits scheduled for day 197 and day 225 have been removed from the Schedule of Events.	The reason for shortening the follow-up period from day 225 to day 169 was to align the duration of follow-up across pediatric studies as it relates to the current state of the COVID-19 pandemic and the development program of casirivimab and imdevimab. The longer follow-up period of day 225 was initially intended to evaluate for antibody mediated enhancement of disease by casirivimab and imdevimab, however antibody mediated enhancement of disease has not been observed in the program. Additionally, antibody mediated enhancement of disease is no longer relevant while the Omicron variant is dominant because neutralization activity against Omicron by casirivimab and imdevimab was below the level of quantitation. A follow-up period of 169 days is aligned with health authority agreements.	Clinical Study Protocol Synopsis Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Table 3 Schedule of Events Figure 1 Study Flow Diagram
EOS visit at day 169 will be performed in person.	Prior to this amendment (#2), the EOS visit day 225 was an in person visit, which is aligned with the key endpoint of safety in this early phase safety study in a new population (pediatric). The new end of study visit, day 169, will also be an in-person visit, to maintain the overall study design.	Figure 1 Study Flow Diagram Section 9.1.1 Footnotes for the Schedule of Events Table, #3
Unused and residual biological samples collected during the study may be kept for use in assay development or validation, and/or for diagnostic test development or validation.	Change implemented to provide flexibility for potential future use of unused and residual samples.	Section 9.1.1 Footnotes for the Schedule of Events Table, #1 Section 9.2.8.3

Amendment 1

The primary purpose of this amendment is to implement changes per health authority feedback, including the route of administration in subjects with lower body weight (subcutaneous rather than intramuscular), additional sample collections for drug concentration assessment at later time points, and addition of multisystem inflammatory syndrome in children (MIS-C) as an adverse event of special interest (AESI).

Description of Change	Brief Rationale	Section(s)
Health Authority Requests		
All subjects will receive study drug by subcutaneous administration, including those who weigh <10 kg at the time of study enrollment. In the original protocol, subjects <10 kg were planned to receive intramuscular administration.	Change implemented per health authority feedback, with the aim of utilizing a route of administration in the lowest weight pediatric subjects that has already been used in ongoing studies. Intramuscular administration has not yet been utilized in casirivimab+imdevimab clinical trials.	Study Title Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.2.3.1 Overall Pharmacokinetics Objective of Study Section 3.2.3.3 Rationale for Intramuscular Dosing in Subjects Weighing Under 10 Kilograms [deleted] Section 4.2 Secondary Endpoints Section 8.1 Investigational Treatments Table 2 Weight-Tiered Dosing of Casirivimab+Imdevimab Section 8.3.1.1 Systemic Injection Reactions (Hypersensitivity) Section 11.2 Justification of Samples Size Section 11.4.4.1 Analysis of Drug Concentration Data Section 20 Investigator's Agreement
In addition to the previously-indicated time points, sample collection for drug concentration assessment will be performed on day 57 (schedule 1) and day 113 (schedule 2).	Change implemented per health authority feedback, to ensure comprehensive collection of pharmacokinetics data	Table 3 Schedule of Events
Multisystem inflammatory syndrome in children (MIS-C) has been added as an adverse event of special interest (AESI): • MIS-C will be defined according the Centers for Disease Control (CDC, 2021c). • Occurrences of MIS-C will require expedited reporting. • MIS-C will not be evaluated as a secondary endpoint.	For consistency with other Sponsor studies of casirivimab+imdevimab conducted in pediatric populations to ensure that a known complication of COVID-19 in pediatric populations is expeditiously reported and captured.	Section 2.2 Secondary Objectives Section 3.2.2.1 Risk Factors for Severe COVID-19 in the Pediatric Population Section 4.2 Secondary Endpoints Section 6.1 Study Description and Duration Section 6.6.2 Safety Monitoring Team Section 10.1.3 Events that Require Expedited Reporting to Sponsor
The total sample size has been increased from 24 to 28 subjects <12 years of age.	Change implemented per health authority feedback	Section 7.1 Number of Subjects Planned
Enrollment will include minimum targets for the following weight categories: • ≥10 kg to <40 kg: at least 12 subjects • ≥3 kg to <10 kg: at least 12 subjects	Change implemented per health authority feedback, to ensure adequate representation of body weight in study analyses.	Section 7.1 Number of Subjects Planned Section 11.2 Justification of Samples Size
Other Changes		
The following exclusion criterion has been added: • Treatment with another investigational (not authorized or approved) agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit	For consistency with other Sponsor studies of casirivimab+imdevimab	Section 7.2.2 Exclusion Criteria, #14 [new]

Description of Change	Brief Rationale	Section(s)
The following prior medications will be recorded if they were given to a subject within 6 months prior to their screening visit: • Other investigational (not authorized or approved) drugs • Investigational SARS-CoV-2 vaccines • Authorized or approved SARS-CoV-2 vaccines • Investigational, authorized, or approved passive antibody for prophylaxis of SARS-CoV-2 infection, including convalescent plasma, convalescent sera, hyperimmune globulin, or other monoclonal antibodies (eg, bamlanivimab and etesevimab, sotrovimab)	To ensure relevant prior medications are captured, particularly in light of the anticipated availability of COVID-19 vaccination for individuals <12 years of age	Section 9.2.1.3 Medication History [new]
Visit windows of ±1 day have been added to day 2 and day 4 as follows: **Day 2** • For all subjects, the visit may occur on day 3 • For subjects assigned to **schedule 1**, if the day 2 visit **cannot** occur on day 2 or day 3, subjects may have the day 2 blood draw for analysis of drug concentration on day 1, at least 4 hours after study drug administration. If this blood sample is collected, the day 2 visit can be omitted. The day 2 visits should be scheduled for day 2 or day 3 whenever possible. **Day 4** • For all subjects the visit may occur on day 3 or day 5	To provide scheduling flexibility	Table 3 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #14
An Independent Data Monitoring Committee (IDMC) will be chartered to actively review safety data throughout the study.	For consistency with other Sponsor studies of casirivimab+imdevimab conducted in pediatric populations; change not implemented due to any safety concerns related to casirivimab+imdevimab	Section 6.6.1 Independent Data Monitoring Committee [new] Section 6.6.2 Safety Monitoring Team
Analysis of neutralizing antibodies has been added to the analysis of immunogenicity	For consistency with other Sponsor studies of casirivimab+imdevimab conducted in pediatric populations	Section 4.2 Secondary Endpoints Section 5.4 Immunogenicity Variables Section 9.1.1 Footnotes for the Schedule of Events Table, #14 Section 9.2.7 Immunogenicity Measurements and Samples Section 11.3.3 Immunogenicity Analysis Sets Section 11.4.5.1 Analysis of ADA Data Section 11.4.5.2 Analysis of NAb Data
Clarified that interim reviews of PK and safety data may be performed before subjects complete the end of study.	For consistency with the planned study analyses	Section 6.7 Planned Interim Analysis Section 11.5 Interim Analysis
Secondary endpoints related to adverse events have been rephrased to remove reference to “proportion of subjects”.	To provide flexibility with respect to statistical analyses	Section 4.2 Secondary Endpoints
Corrected typographical error in footnote 10; the indicated blood samples may be collected at any point during the screening period;	To ensure accuracy in the schedule of events.	Section 9.1.1 Footnotes for the Schedule of Events Table, #10

Description of Change	Brief Rationale	Section(s)
previous text indicated that screening collection could only occur on day -1.		
"Casirivimab and imdevimab" has been changed to "casirivimab+imdevimab"	For nomenclature consistency with other Sponsor studies of casirivimab+imdevimab	Throughout the document
Minor clarifications for consistency and other minor updates (typographical, editorial, formatting) 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
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
Casirivimab+imdevimab	REGN10933 and REGN10987; also referred to by the proprietary name conditionally accepted by the FDA (REGEN-COV™) and by the EMA (RONPAPREVE®)
CDC	United States Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CVID	Common variable immunodeficiency
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
IWRS	Interactive Web Response System
IV	Intravenous

LDH	Lactate dehydrogenase
MIS-C	Multisystem inflammatory syndrome in children
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
RBD	Receptor binding domain
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
S protein	Spike protein
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
XLA	X-linked agammaglobulinemia

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2a, Open-Label Study Assessing the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of a Single Dose of Subcutaneous Anti-Spike SARS-CoV-2 Monoclonal Antibodies Casirivimab and Imdevimab in High-Risk Pediatric Subjects Under 12 Years of Age
Site Locations	The study will be conducted in approximately 8 sites in the United States.
Principal Investigator	To be determined
Objectives	
Primary	• To characterize the concentrations of casirivimab+imdevimab in serum over time after a single subcutaneous (SC) administration
Secondary	• To assess the safety and tolerability of SC single administration of casirivimab+imdevimab • To assess the occurrence of grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions, in subjects treated with SC doses of casirivimab+imdevimab • To assess the immunogenicity of casirivimab+imdevimab
Study Design	This is an open label, phase 2a study to assess the pharmacokinetics (PK), safety, tolerability, and immunogenicity of casirivimab+imdevimab in subjects <12 years old who are not infected with SARS-CoV-2 but are at high risk to develop severe COVID-19 if they become infected. Subjects will be assessed for eligibility during the screening period, which may occur up to 7 days prior to the day 1 (baseline) visit. To be eligible, subjects must not have symptoms consistent with COVID-19, and must be confirmed negative for SARS-CoV-2 infection prior to study drug administration according to the window specified in the exclusion criteria. This study will enroll subjects at baseline into two analysis groups, with each group defined according to body weight. All subjects will receive a single dose of casirivimab+imdevimab, adjusted for body weight. Each subject will be observed for one hour after completion of dosing, and the subject (or their parent or guardian) will be contacted by phone within 24 hours of dosing to assess for any potential adverse events (AEs). Following dose administration, subjects will be followed for approximately 24 weeks (169 days) to monitor for TEAEs. At each scheduled site visit, the Investigator or designee will assess and document the subject's general health and AEs since the last contact. If a scheduled visit cannot be performed in person (for example, due to COVID-19 restrictions), or if no assessments or collections require the subject to be contacted in person, the visit may be conducted virtually (ie, by telemedicine or phone). Grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions that occur after study drug administration will be captured as AESIs, to allow for expedited reporting. Multisystem inflammatory syndrome in children (MIS-C) will also be captured as an AESI. During the first five weeks after study drug administration, subjects will have samples collected for clinical laboratory tests (hematology, blood chemistry), drug concentration, and immunogenicity. On day 1, subjects in group A and group B will each be assigned using an Interactive Web Response System (IWRS) to one of two staggered PK-ADA sampling schedules (schedule 1 and schedule 2). Subjects and their caregivers will be provided with contact information for the clinical study site and will be given written and verbal instructions to call site personnel with any changes in their health status. They will be asked to promptly notify site personnel by phone of any symptoms or signs potentially related to COVID-19. Additionally, subjects and their caregivers will be contacted regularly during the study for symptoms or signs of COVID-19. In the event of suspected COVID-19, subjects will continue in the study and undergo additional unscheduled visits, as described in the main text.

Study Duration	The duration of the study is approximately 25 weeks, including up to 1 week of screening.
End of Study Definition	The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study subject can no longer be contacted by the Investigator).
Population	
Sample Size	Approximately 28 subjects are planned to be enrolled. This includes at least 12 subjects with body weight ≥10 kg and <40 kg, and at least 12 subjects with body weight ≥3 kg to <10 kg.
Target Population	The study will enroll subjects <12 years old who are not infected with SARS-CoV-2 but are at high risk to develop severe COVID-19 if they become infected. Subjects 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 <12 years of age and ≥3 kg to <40 kg at the time parental/guardian consent is signed • Has at least one risk factor for developing severe COVID-19 if they were to become infected, such as: a. Obesity (BMI [kg/m^2] ≥95th percentile for age and sex based on CDC growth charts) b. Cardiovascular disease c. Chronic lung disease d. Type 1 or type 2 diabetes mellitus e. Chronic kidney disease, including those on dialysis f. Chronic liver disease g. Immunocompromised or immunodeficient, based on Investigator's assessment (examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV infection, sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications) h. Medical complexities (examples include any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease) i. **Any other condition** deemed by the Investigator to be a risk factor for severe COVID-19 Subjects who meet any of the following criteria will be excluded from the study. Other criteria also apply and are described in the main text: • Has positive diagnostic test for SARS-CoV-2 infection from a sample collected during screening ≤7 days prior to study drug administration *Note: The sample for the test should be collected ≤7 days within study drug administration, and the result should be reviewed and confirmed negative prior to dosing. Historical records will not be accepted.* • Has active respiratory or non-respiratory symptoms consistent with COVID-19 in the opinion of the investigator • Has subject-reported clinical history of COVID-19, as determined by Investigator, within the last 90 days • Has subject-reported history of prior EUA/approved positive diagnostic test for SARS-CoV-2 infection within the last 90 days • Is currently hospitalized or was hospitalized for >24 hours for any reason within 14 days of the screening visit
Treatments	Subjects will receive a single dose of co-administered casirivimab+imdevimab combination therapy subcutaneous single dose, administered as subcutaneous (SC) injections based on body weight: • **≥20 kg to <40 kg**: 792 mg (396 mg per mAb) • **≥10 kg to <20 kg**: 408 mg (204 mg per mAb) • **≥5 kg to <10 kg**: 144 mg (72 mg per mAb) • **≥3 kg to <5 kg**: 96 mg (48 mg per mAb)

Endpoints	
Primary	• Concentrations of casirivimab and imdevimab in serum over time
Secondary	• Treatment-emergent adverse events (TEAEs), and severity of TEAEs, through end of study • Grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions through day 4 • Immunogenicity as measured by anti-drug antibodies (ADA) to casirivimab and imdevimab over time
Procedures and Assessments	Procedures and assessments will include the following: • Blood collection for PK-ADA • Blood collection for SARS-CoV-2 serology status • Mid-turbinate swab sample collection for SARS-CoV-2 RT-qPCR • COVID-19-related medically-attended visits, signs and symptoms of COVID-19 • Adverse events, including AESIs (grade ≥3 injection-site reactions, grade ≥3 hypersensitivity reactions, and multisystem inflammatory syndrome in children [MIS-C] as defined by the CDC) • Safety labs, vital signs, targeted physical examination, concomitant medications and procedures, and pregnancy test (all WOCBP, regardless of pregnancy status)
Statistical Plan	
Statistical Hypothesis	No formal hypothesis testing is planned in this study.
Justification of Sample Size	Analyses of PK, safety, tolerability, immunogenicity, and serology data will be descriptive. The sample size was chosen based on PK considerations and is consistent with early phase studies to assess PK. At least 12 subjects are needed to enroll in each weight group (Group A: ≥10 kg to <40 kg, and Group B: ≥3 kg to <10 kg) to assess drug concentration. The study plans to enroll approximately 28 subjects in total. The sample size and dosing may be adjusted if planned SC dosing of casirivimab+imdevimab does not achieve concentrations in serum similar to, or higher than, that observed in adults (≥18 years of age) after casirivimab+imdevimab 1200 mg (600 mg per mAb) SC administration. PK will be evaluated on an ongoing basis to determine if dose adjustments are needed and whether more subjects are needed for analysis.
Analysis of Drug Concentration Data	Analysis will be performed according to two groups: • Group A: body weight ≥10 kg to <40 kg • Group B: body weight ≥3 kg to <10 kg The concentrations of total casirivimab and total imdevimab over time will be summarized by descriptive statistics for each weight group. Stratification of the analysis may be performed if subjects receive a treatment that has the potential to impact the pharmacokinetics of casirivimab+imdevimab (eg, IVIG)
Interim Analyses	No formal interim analysis is planned. Interim reviews of the PK and safety data may be performed before subjects complete the end of study.

1. INTRODUCTION

1.1. COVID-19 and the Role of Spike (S) Protein in SARS-CoV-2 Viral Pathogenesis

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in December 2019 and was declared a global pandemic in March 2020 (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 S protein facilitates membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020). The S protein is itself composed of 2 functional subunits: the S1 subunit, which contains the receptor binding domain (RBD) responsible for binding to ACE2 on host cells, and the S2 subunit, which mediates fusion of the viral and cellular membranes (Walls, 2020). COVID-19 cases continue to rise globally, but there are no approved or recommended therapeutic options for pre- or post-exposure prophylaxis against SARS-CoV-2 infection (NIH, 2021).

1.2. Casirivimab+Imdevimab: Human Monoclonal Antibodies, Targeting SARS-CoV-2 S Protein, for the Treatment and Prevention of COVID-19

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

In phase 3 clinical trials, the combination of casirivimab+imdevimab was shown to be effective and well-tolerated in the treatment of outpatient and hospitalized adults with COVID-19, and in the prevention of SARS-CoV-2 infection in adults and adolescents (Horby, 2021) (O'Brien, 2021a) (O'Brien, 2021b) (Weinreich, 2021b) (see Section 3.3 for additional information). Casirivimab and imdevimab (1200 mg; 600 mg of each mAb) is currently authorized under Emergency Use Authorization (EUA) for the treatment of outpatients 12 years and older who are at high risk for developing severe COVID-19 (FDA, 2020).

1.3. An Open-Label Study to Assess the Pharmacokinetics and Safety Profile of Casirivimab+Imdevimab in High-Risk Pediatric Subjects

This protocol describes a phase 2a, open-label study to assess the pharmacokinetics (PK), as well as safety, tolerability, and immunogenicity, of casirivimab+imdevimab in children under 12 years old who are uninfected but at high risk to develop severe COVID-19 if they become infected (CDC, 2021a).

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to characterize the concentrations of casirivimab and imdevimab in serum over time after a single subcutaneous (SC) administration

2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of SC single administration of casirivimab+imdevimab
- To assess the occurrence of grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions in subjects treated with SC doses of casirivimab+imdevimab
- To assess the immunogenicity of casirivimab and imdevimab

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess the occurrence of COVID-19 during the study
- To assess the occurrence of COVID-19-related medically-attended visits during the study
- To assess the occurrence of SARS-CoV-2 seroconversion during the study
- To identify biomarkers associated with the safety and exposure of casirivimab+imdevimab and/or SARS-CoV-2 infection
- To assess viral genetic variation in SARS-CoV-2 in any subject with a positive SARS-CoV-2 RT-qPCR test

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

No formal statistical hypothesis will be tested. The pharmacokinetics hypothesis for this study is defined in Section 3.2.3.1.

3.2. Rationale

3.2.1. Rationale for Study Design

This study will assess the PK, safety, tolerability, and immunogenicity of casirivimab+imdevimab in subjects <12 years old who are not infected with SARS-CoV-2 but are at high risk to develop severe COVID-19 if they were to become infected.

Collection of Pharmacokinetics Data to Inform Efficacy Extrapolation. To date, the efficacy of casirivimab+imdevimab has not been evaluated in study participants under 12 years of age, either in the prophylaxis or treatment settings. The Sponsor proposes to utilize efficacy data collected in clinical trials of adult populations, in conjunction with a PK data in subjects under 12 years of age, to extrapolate efficacy in the younger population. The Sponsor considers an extrapolation approach for pediatric efficacy to be justified by the similarities between adult and pediatric populations with respect to SARS-CoV-2 viral distribution, viral burden, and course of viral infection over time, and the corollary expectation that anti-viral response would be the same in these populations.

The frequency of blood draws at early timepoints (Table 3) is required in order to achieve adequate sampling for PK analysis in the study population (<12 years of age and weighing <40 kg; Section 7.2.1) for which such data have not been previously collected. Staggered sampling schedules will be utilized to increase coverage of timepoints for PK analysis while simultaneously minimizing the frequency of blood draws in this younger population. Drug concentration data will be evaluated on a regular basis to inform whether sample size adjustments are required.

Open-Label Design with No Placebo. Prior to this study, casirivimab+imdevimab have been administered in clinical trials to subjects 12 years and older, with an acceptable safety profile. The study utilizes an open label design with no placebo control group, a design is considered appropriate in light of the safety profile of casirivimab+imdevimab observed in subjects 12 years and older, as well as its demonstrated clinical efficacy as a prophylactic agent (Section 3.3.1), which may benefit the study target population in particular (Section 3.2.2).

Length of Follow-up Period. Subjects will undergo a follow-up period of approximately 24 weeks (six months) for assessment of drug concentrations, safety, and immunogenicity. In COV-2069, a single 1200 mg SC dose resulted in an observed half-life of approximately 32.4 days (casirivimab) and 27.0 days (imdevimab). The duration of the follow-up period in the current study is thus intended to allow observation of drug concentration and safety in subjects for more than five half-lives (six months) following study drug administration. The length of the follow-up period may be modified based on drug concentration data observed in this study, as well as ongoing nonclinical data as they become available.

Collection of Serology for SARS-CoV-2 Serostatus. Subjects will be assessed for antibodies against SARS-CoV-2, which may include but not be limited to antibodies against spike (S) and/or nucleocapsid (N) protein, at the screening/baseline visit and (depending on the subject's weight at the time of study drug administration) during scheduled and/or unscheduled visits following study drug administration. These assessments will allow detection of prior SARS-CoV-2 infection and/or seroconversion subsequent to a SARS-CoV-2 infection that occurs during the study.

3.2.2. Rationale for Target Population

3.2.2.1. Risk Factors for Severe COVID-19 in the Pediatric Population

In this study, the target population consists of individuals <12 years of age with at least one risk factor for developing severe COVID-19. The suggested risk factors includes known risk factors and allows for any condition deemed by the Investigator to pose a risk for severe COVID-19 (Section 7.2.1), and is intended to allow flexibility for study inclusion in light of the evolving understanding of risk factors in the pediatric population.

Pediatric patients generally have asymptomatic or mild disease; however, certain pediatric populations are at high risk for developing severe COVID-19 (CDC, 2021a) (Bellino, 2020) (Graff, 2021). A study reviewing children with SARS-CoV-2 infection found that nearly half (45%) had at least 1 comorbid condition. The most common types of comorbid conditions identified were pulmonary (16.7%), gastrointestinal (10.8%), and neurologic disease (10.6%) (Graff, 2021). Other genetic conditions (eg, sickle cell disease) also put children at increased risk for severe disease (CDC, 2021a).

A complication of COVID-19 in the pediatric population is the occurrence of multisystem inflammatory syndrome in children (MIS-C). A large observational study in the United States found that MIS-C cases, which occurred at an incidence of 2.1 cases per 100,000 individuals <21 years of age, coincided with peak COVID-19 cases with a lag of 2 to 5 weeks. These data suggest that MIS-C occurs approximately 2 to 5 weeks after the initial COVID-19 infection. The incidence of MIS-C. In the study, a majority of children experiencing MIS-C had asymptomatic or mild COVID-19 infection initially. Most patients developed hypotension or shock, with about 60% being admitted for intensive care. Myocarditis, cardiac dysfunction, or coronary artery dilatations were reported in approximately 30% of patients. Currently, it is unknown if any preexisting condition presents a higher risk for MIS-C, and the pathophysiology of MIS-C is still being investigated (Belay, 2021). To ensure expeditious reporting of any MIS-C that may occur during this study, MIS-C will be captured as an AESI.

In light of these and other risk factors for developing severe COVID-19, the pediatric population in this study may benefit from receipt of casirivimab+imdevimab as prophylaxis against SARS-CoV-2 infection.

3.2.2.2. Prophylaxis as a Complementary Approach to Vaccination in High-Risk Pediatric Populations

Prophylaxis with casirivimab+imdevimab, which provides immediate protection against SARS-CoV-2 infection (Section 3.3.1), may complement vaccination strategies, which require two weeks or more (and sometimes several doses) to generate protection. Casirivimab+imdevimab may be particularly useful to prevent infection in those at high risk of infection who may not mount a fully

protective immune response after receipt of a vaccine, or are otherwise unable to be vaccinated (for example, due to allergies to vaccine components) and therefore remain susceptible to infection (Boyarsky, 2021a) (Boyarsky, 2021b) (Cavanaugh, 2021) (Teran, 2021) . For example, pediatric patients with B-cell dysfunction/deficiency (eg, X-linked agammaglobulinemia [XLA], common variable immunodeficiency [CVID], X-linked hyper-IgM, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and selective IgG class deficiency) and pediatric patients receiving B-cell depleting therapies for conditions such as Crohn's disease, Ulcerative Colitis, and certain pediatric autoimmune diseases are unlikely to respond to COVID-19 vaccines. Pediatric patients with B-cell dysfunction/deficiency may routinely receive IVIG, but it is unclear whether IVIG will contain protective antibodies to prevent SARS-CoV-2 infection.

In summary, pediatric populations who have not yet received a vaccine against SARS-CoV-2, are unable to receive a vaccine, and/or who are not expected to develop protective immunity after vaccination, may benefit from prevention with casirivimab+imdevimab.

3.2.3. Rationale for Dose Selection

3.2.3.1. Overall Pharmacokinetics Objective of Study

In this study, subjects will be evaluated separately in two groups, with each group defined according to body weight (Section 11.4.4.1). For each group, dosing will be adjusted by weight as described in Section 8.1. The target for dosing in the study population (<12 years of age and weighing <40 kg) is for ≥95% of subjects to achieve a similar or higher exposure of each antibody to that observed in adults (≥18 years of age) after a single SC dose of casirivimab+imdevimab 1200 mg (600 mg per mAb).

Hypothesis: In high-risk subjects <12 years old, a single body weight-adjusted dose of SC casirivimab+imdevimab will achieve serum concentrations similar to, or higher than, that observed in adults (≥18 years of age) after casirivimab+imdevimab 1200 mg (600 mg per mAb) SC administration, and will be well-tolerated.

3.2.3.2. Population Pharmacokinetics Modeling to Predict Exposure in Study Population

To predict exposure in the target population of the study, two 2-compartment population PK models with linear elimination and first-order absorption following SC dosing were developed for casirivimab+imdevimab. These models were based on observed data from COV-2069 (single SC dose for prevention in household contacts of SARS-CoV-2-infected individuals), COV-20145 (single SC or IV dose for treatment in outpatients with low-risk or asymptomatic infection), and COV-2067 (single IV dose for treatment in outpatients, including those with risk factors) following IV and SC dosing in adults. Allometric scaling (with an exponent of 1 for volume and 0.75 for clearance) was applied on PK parameters to account for the effect of body weight in pediatric populations. In addition, age impact (gestational age + age) was applied on clearance to account for the effect of body size and age (on top of body weight) in pediatric populations (Robbie, 2012). Simulations of concentration vs. time were performed to predict exposure metrics for subjects in each weight category receiving casirivimab+imdevimab. The proposed doses are predicted to result in similar or higher exposure (C_{max}, C_{28}, AUC_{0-28}) to adults in ≥95% of pediatric subjects within each weight tier (Table 1).

For subjects <12 years of age and weighing <40 kg, the 95th percentiles of predicted C_{max} and AUC_{0-28} across the pediatric weight-tiered groups were 40% to 92% higher than the predicted 95th percentiles in adults after a single SC dose of 1200 mg (600 mg per mAb). However, the 95th percentiles of C_{max} and AUC_{0-28} in pediatric weight-tiered groups were lower than the observed mean values following a single 2400 mg IV dose in adults, a dose with an acceptable safety and tolerability profile.

PK will be evaluated on an ongoing basis to determine if dose adjustments are needed.

Table 1: Predicted Exposure (Population PK Model) of Total Casirivimab (REGN10933) and Total Imdevimab (REGN10987) in Serum of Pediatric Subjects (<12 Years)

Exposure Metrics	Population	Dose	Casirivimab[1]	Imdevimab[1]
C_{28} (mg/L)	Adult	600 mg SC	29.5 (19.4, 43.8)	25.1 (16.9, 36.5)
	≥40 kg	600 mg SC	33.3 (20.8, 57.3)	28.3 (18.1, 48.4)
	≥20 to <40 kg	400 mg SC	56.9 (37.0, 85.9)	48.6 (32.2, 72.3)
	≥10 to <20 kg	200 mg SC	57.1 (36.3, 91.8)	49.3 (31.8, 79.3)
	≥5 to <10 kg	75 mg SC	51.0 (32.2, 75.3)	45.1 (28.9, 64.8)
	≥2.5 to <5 kg	50 mg SC	59.9 (41.0, 90.1)	52.5 (36.9, 77.5)
	<2.5 kg	25 mg SC	49.0 (35.9, 71.4)	42.9 (32.3, 61.2)
C_{max} (mg/L)	Adult	600 mg SC	51.1 (33.4, 72.6)	48.2 (32.2, 67.8)
	≥40 kg	600 mg SC	55.8 (32.4, 97.6)	52.6 (31.2, 91.1)
	≥20 to <40 kg	400 mg SC	92.1 (58.2, 139.4)	86.5 (55.6, 129.4)
	≥10 to <20 kg	200 mg SC	85.0 (54.6, 131.5)	79.7 (52.1, 121.5)
	≥5 to <10 kg	75 mg SC	69.3 (42.9, 104.0)	64.6 (40.8, 95.1)
	≥2.5 to <5 kg	50 mg SC	83.8 (54.4, 127.7)	77.2 (51.5, 115.6)
	<2.5 kg	25 mg SC	71.2 (49.7, 107.0)	65.0 (46.9, 96.3)
AUC_{0-28} (mg*day/L)	Adult	600 mg SC	1093 (752, 1533)	993 (708, 1361)
	≥40 kg	600 mg SC	1214 (738, 2087)	1104 (693, 1868)
	≥20 to <40 kg	400 mg SC	2060 (1331, 3052)	1865 (1238, 2714)
	≥10 to <20 kg	200 mg SC	1956 (1274, 3048)	1775 (1180, 2746)
	≥5 to <10 kg	75 mg SC	1648 (1031, 2452)	1508 (961, 2197)
	≥2.5 to <5 kg	50 mg SC	1976 (1298, 2980)	1796 (1216, 2661)
	<2.5 kg	25 mg SC	1657 (1182, 2474)	1497 (1107, 2200

[1] All values are represented as median (5th percentile, 95th percentile).

3.3. Risk-Benefit

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

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

3.3.1. Summary of Efficacy and Safety Profile in Clinical Trials

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

Intravenous Administration of Casirivimab+Imdevimab in Clinical Trials. In COV-2067 (R10933-10987-COV-2067), the phase 3 outpatient treatment trial, a single intravenous dose of casirivimab+imdevimab was shown (relative to placebo) to reduce COVID-19-related hospitalizations or all-cause death by 71.3% (2400 mg dose) and 70.4% (1200 mg dose), reduce symptom duration by 4 days (2400 mg and 1200 mg), and reduce viral load over the first 7 days. Serious adverse events occurred more frequently in the placebo group (4.0%) than in either treatment group (2400 mg, 1.1%; 1200 mg, 1.3%), and grade ≥2 infusion-related reactions were infrequent (<0.3% in all groups) (Weinreich, 2021b). Similar virologic efficacy and a similar safety profile were observed in the phase 1/2 portion of this trial, which evaluated casirivimab+imdevimab at 8000 mg and 2400 mg IV doses (Weinreich, 2021a).

In the controlled open-label platform study RECOVERY in hospitalized patients, a single dose of casirivimab+imdevimab 8000 mg given in addition to standard of care (compared to standard of care alone) reduced the incidence of death through day 28 by 20% in those who were seronegative at baseline (ie, those who had not yet mounted an immune response to SARS-CoV-2). Among seronegative patients, the median duration of hospitalization was 4 days shorter in the casirivimab+imdevimab group, and the proportion of patients discharged alive by day 28 was greater by 19%. The reported frequency of fever (4% versus 3%), sudden hypotension (4% versus 2%), and thrombotic events (2% versus 1%) was slightly higher in the casirivimab+imdevimab group than the placebo group, while the frequency of sudden worsening in respiratory status (21% versus 22%) and clinical hemolysis (1% versus 2%) was slightly lower. There were 5 reports of SAEs believed to be treatment-related (Horby, 2021). These findings are consistent with preliminary data from a much smaller phase 1/2 study in hospitalized patients, which also demonstrated rapid reduction of viral load and trends for reducing the risk of death or mechanical ventilation, particularly in those who were seronegative at baseline (Regeneron, 2020).

Subcutaneous Administration of Casirivimab+Imdevimab in Clinical Trials. In COV-2069 (R10933-10987-COV-2069), the phase 3 prevention trial in those at high risk of infection by a household contact, a single subcutaneous dose of casirivimab+imdevimab (1200 mg) reduced (relative to placebo) symptomatic SARS-CoV-2 infection by 81.4%, and reduced overall SARS-CoV-2 infection by 66.4%. Serious adverse events occurred at similar frequencies in the treatment group (1%) and placebo group (1%). Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (2%), but no injection-site reactions in the study were grade 3 or above. The majority of injection site reactions occurred within one day and resolved within two days (O'Brien, 2021b).

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

In COV-2069, efficacy results were similar in adolescents (age 12 to <18) as observed in adults: 0% of subjects in the 1200 mg SC treatment group experienced symptomatic infection, compared with 9.3% of subjects in the placebo group. Safety data in adolescent subjects were also similar to that observed in adults. Injection site reactions were more common in the treatment group (5.9%) compared to the placebo group (1.6%), but none were grade 3 or above in any group.

In HV-2093 (R10933-10987-HV-2093), an adult volunteer study evaluating multiple doses of subcutaneous administration of casirivimab+imdevimab (monthly dosing over 6 months), injection site reactions were more common in the casirivimab+imdevimab group (34.6%) compared with the placebo group (15.8%), but none were grade 3 or above in any group.

3.3.2. Summary of Risks

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

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

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

Reproductive and developmental toxicology studies have not been conducted, and the effects of casirivimab, imdevimab, or casirivimab+imdevimab combination therapy on the fetus and reproductive organs in males and females are unknown. There is also currently limited clinical experience in the use of casirivimab, imdevimab, or casirivimab+imdevimab combination therapy in female patients who are pregnant or breastfeeding.

Human IgG1 antibodies are known to cross the placental barrier and are present in breast milk. Casirivimab+imdevimab combination therapy therefore has the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of casirivimab+imdevimab, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of casirivimab or imdevimab was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of casirivimab+imdevimab combination therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

The combination of or casirivimab+imdevimab therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. Pregnancy that occurs during this study will be reported and followed, including any complications and pregnancy outcome, as described in Section 10.1.3.

Other Theoretical Risks. Theoretical risks of casirivimab+imdevimab include interference with the patient's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19. In this study, risk mitigation includes prohibition of SARS-CoV-2 vaccination for 90 days after study drug administration (Section 8.7.1), consistent with current CDC guidance (CDC, 2021b).

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances Fc gamma receptor (FcγR)-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). Casirivimab and imdevimab each retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014), there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All subjects will have follow-up assessments during the drug elimination period (for over five half-lives; Section 3.2.1), and subjects will be monitored for any signal of ADE.

3.3.3. Potential Benefit of Casirivimab+Imdevimab in the Study Population

As detailed in Section 3.2.2.2, the target population to be enrolled in this study represents an at-risk population, who have an elevated risk of SARS-CoV-2 infection and either cannot be vaccinated or may not mount a protective immune response after vaccination. There is therefore a potential benefit to providing casirivimab+imdevimab to this population as prophylaxis against SARS-CoV-2 infection and development of COVID-19 that could potentially develop into severe disease.

3.3.4. Summary

Based on the available clinical and nonclinical data for casirivimab+imdevimab demonstrating anti-viral efficacy with an acceptable safety profile, as well as the unmet need for preventative therapy in the at-risk pediatric population to be enrolled in this study, it is the opinion of the Sponsor that the overall risk-benefit balance for casirivimab+imdevimab is acceptable to allow evaluation of this mAb combination in the study population.

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is the concentrations of casirivimab and imdevimab in serum over time.

4.2. Secondary Endpoints

The secondary endpoints are:

- Treatment-emergent adverse events (TEAEs), and severity of TEAEs, through end of study
- Grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions through day 4

- Immunogenicity as measured by anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to casirivimab and imdevimab over time

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

The variables for baseline characteristics include standard demography (eg, age, race, weight, height), medical history, and medication history.

5.2. Safety Variables

Safety variables include recording, measurements, or laboratory test results for individual subjects of the following: TEAEs, vital signs (including pulse rate, blood pressure, respiration rate, and body temperature), targeted physical examination findings, results of laboratory tests (including hematology, blood chemistry, pregnancy test), and diagnostic assay for SARS-CoV-2 infection (at baseline for all subjects; and at the time when signs of COVID-19 are identified in subjects).

5.3. Pharmacokinetic Variables

The PK variables are concentrations of casirivimab and imdevimab in serum and time. The sampling time points are specified in Table 3.

5.4. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and NAb status at nominal sampling time/visit. Serum samples for ADA will be collected at the visits specified in Table 3. Samples positive in the ADA assays will be further characterized for ADA titers and when feasible, NAb status.

5.5. Other Variables

Other variables include anti-SARS-CoV-2 serology test results and time, and COVID-19-related medically-attended visits. The sampling time points are specified in Table 3.

6. STUDY DESIGN

6.1. Study Description and Duration

This is an open label, phase 2a study to assesses the PK, safety, tolerability, and immunogenicity of casirivimab+imdevimab in subjects <12 years old who are not infected with SARS-CoV-2 but are at high risk to develop severe COVID-19 if they become infected. Risk factors are defined as inclusion criteria in Section 7.2.1). A diagram depicting the study design is provided in Figure 1. The Schedule of Events is provided in Section 9.

Subjects will be assessed for eligibility during the screening period, which may occur up to 7 days prior to the day 1 (baseline) visit. To be eligible, subjects must not have symptoms consistent with

COVID-19, and must be confirmed negative for SARS-CoV-2 infection prior to study drug administration according to the window specified in the exclusion criteria.

This study will enroll subjects into two analysis groups at baseline, with each group defined according to body weight (Section 11.4.4.1). All subjects will receive a single dose of casirivimab+imdevimab, adjusted for body weight as described in Section 8.1. Each subject will be observed for one hour after completion of dosing, and the subject (or their parent or guardian) will be contacted by phone within 24 hours of dosing to assess for any potential adverse events (AEs).

Following dose administration, subjects will be followed for approximately 24 weeks (169 days) to monitor for TEAEs. At each scheduled site visit, the investigator or designee will assess and document the subject's general health and adverse events since the last contact. If a scheduled visit cannot be performed in person (for example, due to COVID-19 restrictions), or if no assessments or collections require the subject to be contacted in person, the visit may be conducted virtually (ie, by telemedicine or phone). Grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions that occur after study drug administration will be captured as AESIs, to allow for expedited reporting. Multisystem inflammatory syndrome in children (MIS-C) will also be captured as an AESI.

During the first five weeks after study drug administration, subjects will have samples collected for clinical laboratory tests (hematology, blood chemistry), drug concentration, and immunogenicity. On day 1, subjects in group A and group B will each be assigned using an Interactive Web Response System (IWRS) to one of two staggered PK-ADA sampling schedules (schedule 1 and schedule 2).

6.2. Monitoring for Potential COVID-19

Subjects and their caregivers will be provided with contact information for the clinical study site and will be given written and verbal instructions to call site personnel with any changes in their health status. They will be asked to promptly notify site personnel by phone of any symptoms or signs potentially related to COVID-19. Additionally, subjects and their caregivers will be contacted regularly during the study for symptoms or signs of COVID-19.

In the event of suspected COVID-19, subjects will continue in the study and undergo additional unscheduled visits, as described in Section 6.3.

6.3. Management of Subjects With Suspected COVID-19

Unscheduled Visit to Confirm SARS-CoV-2 Infection and COVID-19 Symptoms. Subjects who have signs or symptoms consistent with COVID-19 will have an unscheduled visit to collect a mid-turbinate nasal swab sample for SARS-CoV-2 RT-qPCR testing and viral genome sequencing, evaluate signs and symptoms of COVID-19 (by the Investigator or designee), collect blood for drug concentration and immunogenicity, and (depending on the subject's weight category) collect blood for serology and exploratory research (Table 3).

Medical Management of SARS-CoV-2-Positive Subjects. Subjects with laboratory confirmed SARS-CoV-2 infection and/or the parent or guardian should be informed as soon as possible. Local or CDC guidance should be followed to reduce the risk of transmission. Subjects with acute illness

should be medically managed according to local standard of care and per the discretion of the treating physician.

Continuation of the Schedule of Events for SARS-CoV-2-Positive Subjects. Subjects with confirmed SARS-CoV-2 infection will continue to follow the Schedule of Events as planned. If a scheduled visit cannot be performed in person (for example, due to COVID-19 restrictions), or if no assessments or collections require the subject to be contacted in person, the visit may be conducted virtually (ie, by telemedicine or phone).

Additional Weekly Unscheduled Visits for Viral Testing of SARS-CoV-2-Positive Subjects. Subjects with confirmed SARS-CoV-2 infection will have weekly unscheduled visits to collect a mid-turbinate nasal swab sample for SARS-CoV-2 testing. These visits will include all assessments indicated in the 'SARS-CoV-2 Confirmation' visit in the Schedule of Events (Table 3). Note that these weekly visits will be held in addition to the visits that are planned as part of the study. If a weekly visit occurs within the same window as a planned visit, all assessments indicated in the 'SARS-CoV-2 Confirmation' visit must be performed during the planned visit. Assessments or samples that are indicated for both visits in the Schedule of Events will only be collected once. The weekly unscheduled visits will continue until two consecutive negative SARS-CoV-2 test results are obtained from samples collected ≥24 hours apart.

Additional Assessment of Adverse Events in SARS-CoV-2-Positive Subjects. Subjects with confirmed SARS-CoV-2 infection will be assessed by the Investigator or designee for adverse events (Section 10.1) and details of COVID-19-related medically-attended visits (Section 9.2.4.6). This assessment will occur at minimum on a weekly basis during the unscheduled visits described above. Subjects may be assessed for adverse events on a more frequent basis, if deemed clinically appropriate by the Investigator or designee. If more frequent assessments are performed, these will be reported as additional unscheduled visits.

Requirements for SARS-CoV-2 Testing During Unscheduled Visits. Any SARS-CoV-2 test conducted during an unscheduled visit will be recorded as a concomitant procedure and associated with the adverse event "COVID-19". The preferred method of SARS-CoV-2 testing is by central laboratory RT-qPCR using a mid-turbinate nasal swab sample. Central laboratory samples that have been confirmed positive for SARS-CoV-2 may be used for exploratory viral sequencing analysis (Section 9.2.8.4).

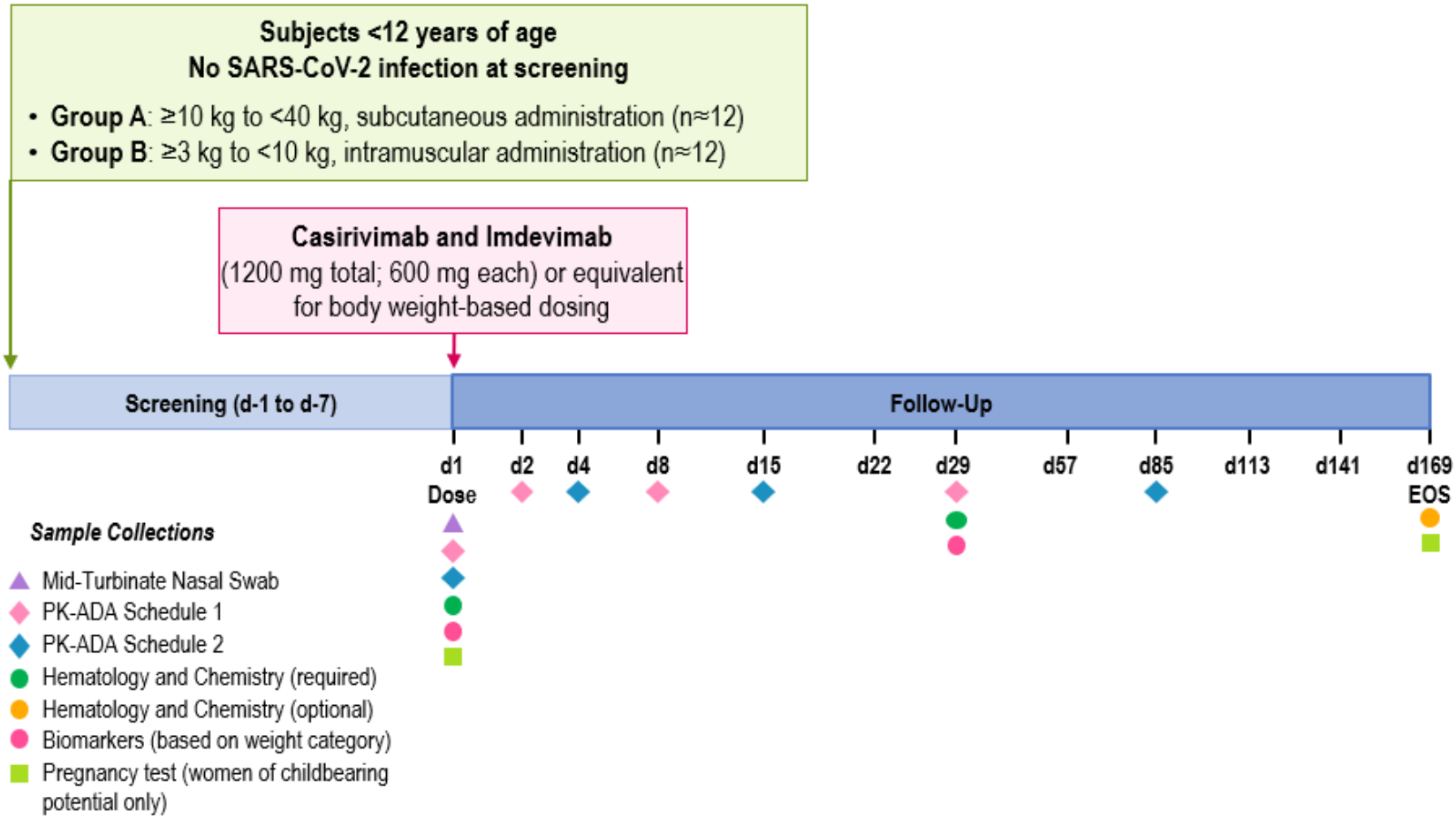
Note: If a subject is unable or unwilling to visit the study site for SARS-CoV-2 testing as part of an unscheduled visit, central laboratory testing of a mid-turbinate swab sample may not be feasible. If this occurs, a local diagnostic assay (eg, molecular assay such as RT-PCR for SARS-CoV-2), using an appropriate sample such as nasopharyngeal, nasal, oropharyngeal, or saliva, is allowable.

The local diagnostic assay for SARS-CoV-2 must be considered acceptable for clinical use by local standards. If the test has not been approved or has not received authorization, such as EUA issued by the US FDA or authorization by the equivalent local health authority, the Sponsor must be consulted. The use of RT-PCR is highly recommended.

In the event that the subject obtains SARS-CoV-2 testing at a facility not affiliated with the site, study site personnel will attempt to obtain and record all information from SARS-CoV-2 tests conducted in local laboratories that are associated with other medical facilities. This information

will include test results, name of the assay(s) utilized, and whether the laboratory or laboratories conducting the assay(s) are CLIA certified (or equivalent).

Figure 1: Study Flow Diagram



The EOS visit will be performed in person. In the case that the day 169 visit was conducted prior to Amendment #2, the subject should return to the clinical trial unit for 1 additional visit for the EOS visit as soon as possible after Amendment #2 is approved by local regulatory and ethics as required.

6.4. Study Stopping Rules

The Sponsor will monitor safety data on an ongoing basis to assess the risk/benefit profile of casirivimab+imdevimab. The Sponsor team may be comprised of the medical/study directors, a Global Patient Safety representative, representatives from Biostatistics and Data Management, as well as representatives from Clinical Operations and Regulatory Affairs. The data to be reviewed will include, but are not limited to the following:

- TEAEs that result in an early study drug discontinuation
- Grade ≥3 TEAEs
- Treatment-emergent SAEs
- Treatment-emergent AESIs
- Selected laboratory tests, as deemed appropriate

If there are significant safety concerns, a recommendation may be made to temporarily pause, alter, or terminate the study. Appropriate action, if needed, will be taken based upon this review and in consultation with additional Sponsor team members, as needed. 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.

6.5. End of Study Definition

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

6.6. Study Committees

6.6.1. Independent Data Monitoring Committee

An IDMC (Independent Data Monitoring Committee) will actively review data throughout the study to monitor patient safety and efficacy data. The IDMC can make recommendations about early study closure or changes to the study conduct. The operation of the IDMC is governed by a charter describing further details, such as procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor. The IDMC will conduct periodic data reviews as detailed in the IDMC charter. These data reviews will include all available safety data, including deaths, from all enrolled study participants up to the cutoff date for the analysis.

6.6.2. Safety Monitoring Team

A safety monitoring team at Regeneron may meet periodically to review blinded safety data as needed. The team may be comprised of the medical directors, a Global Patient Safety representative, a Clinical Pharmacology representative and representatives from Biostatistics and Data Management, as well as representatives from Clinical Operations and Regulatory Affairs. The data to be reviewed include, but are not limited to:

- Treatment-emergent adverse events that result in an early study withdrawal
- Serious adverse events (SAEs)
- Selected laboratory tests, as deemed appropriate by the safety monitoring team
- Grade ≥3 injection-site reactions or grade ≥3 hypersensitivity reactions
- Multisystem inflammatory syndrome in children (MIS-C)
- Drug concentration

Appropriate action, if needed, will be taken based upon this review and in consultation with the medical monitor.

6.7. Planned Interim Analysis

No formal interim analysis is planned for the study. Interim reviews of PK and safety data may be performed before subjects complete the end of study.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

The study will enroll approximately 28 subjects <12 years. This includes at least 12 subjects with body weight ≥10 kg and <40 kg, and at least 12 subjects with body weight ≥3 kg to <10 kg. Sample size and dosing may be adjusted based on PK analyses conducted (Section 3.2.3).

Refer to Section 11.2 for justification of sample size.

7.2. Study Population

7.2.1. Inclusion Criteria

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

1. Is <12 years of age and ≥3 kg to <40 kg at the time parental/guardian consent is signed
2. Has at least one risk factor for developing severe COVID-19 if they were to become infected, such as:
   a. Obesity (BMI [kg/m^2] ≥95th percentile for age and sex based on CDC growth charts)
   b. Cardiovascular disease
   c. Chronic lung disease
   d. Type 1 or type 2 diabetes mellitus
   e. Chronic kidney disease, including those on dialysis
   f. Chronic liver disease
   g. Immunocompromised or immunodeficient, based on Investigator's assessment (examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV infection, sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications)

h. Medical complexities (examples include any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease)
i. **Any other condition** deemed by the Investigator to be a risk factor for severe COVID-19

3. Is willing and able to comply with clinic visits and study-related procedures
4. Has provided informed consent signed by subject or legally acceptable representative

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

7.2.2. Exclusion Criteria

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

1. Has positive diagnostic test for SARS-CoV-2 infection from a sample collected during screening ≤7 days prior to study drug administration

   Note: The sample for the test should be collected ≤7 days within study drug administration, and the result should be reviewed and confirmed negative prior to dosing. Historical records will not be accepted.

2. Has active respiratory or non-respiratory symptoms consistent with COVID-19 in the opinion of the Investigator
3. Has subject-reported clinical history of COVID-19, as determined by Investigator, within the last 90 days
4. Has subject-reported history of prior EUA/approved positive diagnostic test for SARS-CoV-2 infection within the last 90 days
5. Is currently hospitalized or was hospitalized for >24 hours for any reason within 14 days of the screening visit
6. Prior use (within 90 days prior to study drug administration) or current use of any investigational, authorized, or approved passive antibody for prophylaxis of SARS-CoV-2 infection, including convalescent plasma, convalescent sera, hyperimmune globulin, or other monoclonal antibodies (eg, bamlanivimab and etesevimab, sotrovimab)
7. Has initiated vaccination for SARS-CoV-2 with an investigational or approved vaccine, but has not completed the vaccine schedule as recommended by the vaccine manufacturer.
8. Plans to receive an investigational or approved SARS-CoV-2 vaccine within 90 days after study drug administration, or per the recommended time frame from the current Centers for Disease Control vaccination guidelines (CDC, 2021b)
9. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
10. Has a history of significant multiple and/or severe allergies (eg, latex gloves), or has had an anaphylactic reaction to prescription or non-prescription drugs or food

    Note: This is to avoid possible confounding of the safety analysis and not due to any presumed increased risk of these individuals to a reaction to the investigational product.

11. Has a known allergy or hypersensitivity to components of the study drug
12. Has any physical examination findings, history of any illness, or any concomitant medications, that in the opinion of the investigator might confound the results of the study or pose an additional risk to the subject by their participation in the study
13. Has received any live vaccine within 4 weeks prior to study drug administration
14. Treatment with another investigational (not authorized or approved) agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit

7.3. Premature Withdrawal from the Study

A subject 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 subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject's continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.2.2.

7.4. Replacement of Subjects

Subjects prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational Treatments

The following drug product will be provided. Instructions on dose preparation are provided in the pharmacy manual.

Casirivimab+imdevimab, to be co-administered:

- Casirivimab: supplied as a 120 mg/mL solution for SC injection
- Imdevimab: supplied as a 120 mg/mL solution for SC injection

Subjects will receive a single dose of casirivimab+imdevimab, administered as 1 to 4 subcutaneous (SC) injections based on body weight. Table 2 provides (according to body weight) the total dose, volume, route of administration, and number of injections that will be administered. This table also describes additional requirements and allowances for dose administration.

For study drug administration which requires multiple SC injections, it is recommended to use different quadrants of the abdomen (avoiding navel and waist areas) and/or upper thighs. 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). A numbing cream may be used at the planned site(s) of injection.

Table 2: Weight-Tiered Dosing of Casirivimab+Imdevimab

Weight-Tiered Dose Group	Total Dose (mg)	Route of Administration	Total Number of Injections	Total Volume (mL) of Injection[6]
≥20 kg to <40 kg	792 (396 per mAb)	SC[3]	4	6.6 (3.3 per mAb)
≥10 kg to <20 kg	408 (204 per mAb)	SC[3]	2 or 4[4]	3.4 (1.7 per mAb)
≥5 kg to <10 kg[1]	144 (72 per mAb)	SC	1 or 2[5]	1.2 (0.6 per mAb)
≥3 kg to <5 kg[2]	96 (48 per mAb)	SC	1	0.8 (0.4 per mAb)

[1] Subjects between 5 and 10 kg should not receive an injection containing more than 1.25 mL.
[2] Subjects <5 kg should not receive an injection containing more than 1 mL.
[3] For SC injection, Investigators may use an infusion pump containing the combined volume with both mAbs. This may improve tolerability through administration of a single injection.
[4] Study drug may be administered as 2 injections (1.7 mL of casirivimab and 1.7 mL of imdevimab) or 4 injections (0.8 mL of casirivimab, 0.9 mL of casirivimab, 0.8 mL of imdevimab, and 0.9 mL of imdevimab).
[5] Study drug may be administered as 1 injection (1.2 mL total) or as 2 injections (0.6 mL of casirivimab and 0.6 mL of imdevimab).
[6] The total volume of study drug per syringe and the number of injections will be recorded in the eCRF.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

Dose modification for an individual subject is not allowed.

8.2.2. Study Drug Discontinuation

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

8.3. Management of Acute Reactions

8.3.1. Acute Injection Reactions

8.3.1.1. Systemic Injection Reactions (Hypersensitivity)

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All systemic 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.

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.

8.3.1.2. Local Injection Site Reactions

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

8.4. Method of Treatment Assignment

This is an open-label study; subjects will receive the study drug on day 1 as assigned.

8.5. Blinding

This is an open-label study without blinding.

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

8.6.2. 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.

8.6.3. 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 subject
- 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.

8.6.4. Treatment Compliance

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

8.7. Concomitant Medications and Procedures

Any treatment administered during the on-treatment period (Section 11.4.3.1) will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

All concomitant medications and procedures will be captured in the eCRF.

Any positive SARS-CoV-2 test conducted during an unscheduled visit will be recorded as a concomitant procedure and associated with the COVID-19 AE.

8.7.1. Prohibited Medications

The following are prohibited as concomitant medication (as defined in Section 8.7) when used as prophylaxis in SARS-CoV-2-negative individuals:

- Other investigational drugs
- Investigational SARS-CoV-2 vaccines
- Authorized or approved SARS-CoV-2 vaccines (only prohibited within 90 days after study drug administration, or per the recommended time frame from current Centers for Disease Control vaccination guidelines) (CDC, 2021b)
- Investigational, authorized, or approved passive antibody for prophylaxis of SARS-CoV-2 infection, including convalescent plasma, convalescent sera, hyperimmune globulin, or other monoclonal antibodies (eg, bamlanivimab and etesevimab, sotrovimab) (only prohibited within 90 days after study drug administration)

Use of a prohibited medication during the on-treatment period may result in permanent discontinuation of a subject from the study.

8.7.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 8.7.1, use of concomitant medications and procedures is permitted during the study. If there is any question regarding whether a concomitant medication or procedure may be used during the study, the study site should contact the medical monitor.

Subjects with symptomatic laboratory-confirmed SARS-CoV-2 infection during the study will be treated according to local standard of care as per the discretion of the Investigator or treating physician.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 3.

Table 3: Schedule of Events

Study Procedure		Screening/Baseline[1]				Follow Up[2]										EOS[3]	Unscheduled Visits		
		Screen	Pre-Dose	Dose	Post-Dose												SARS-CoV-2 Confirmation[4]	ET[5]	Other
Visit Number		**1**	**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**			
Day (Week)		-7 to 1 (-1 to 1)	1 (1)			2 (1)[16]	4 (1)	8 (2)	15 (3)	22 (4)	29 (5)	57 (9)	85 (13)	113 (17)	141 (21)	169 (25)			
Window (day)						±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3			
Screening/Baseline																			
Informed consent (parent/guardian)		X																	
Informed assent (subject)		X																	
Inclusion/exclusion		X																	
Medical history		X																	
Demographics		X																	
Weight		X[1]	X[1]																
Height		X																	
Screening test for SARS-CoV-2 infection (molecular diagnostic test)[6]		X																	
Mid-turbinate nasal swab for SARS-CoV-2 infection (RT-qPCR by central laboratory)[6]			X														X[4]		
Pregnancy test (WOCBP only)[7]		X														X			X
Treatment																			
Study drug administration[8]				X															
Safety																			
Vital signs[9]			X		X						X						X	X	X
Targeted physical examination			X								X						X	X	
Concomitant medications and procedures		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[4]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
COVID-19 signs and symptoms[4]		X				X	X	X	X	X	X	X	X	X	X	X	X		
COVID-19-related medically-attended visit details						X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory																			
Hematology[10]		X[11]									X					X[12]	X[12]		X
Blood chemistry[10]		X[11]									X					X[12]	X[12]		X
Drug Concentration and Immunogenicity (all body weight tiers)																			
Serum for PK-ADA (schedule 1)[13,14]			X[15]			X[16]		X			X[15]	X					X	X	X
Serum for PK-ADA (schedule 2)[13,14]			X[15]				X		X				X[15]	X			X	X	X
Biomarkers (determined by body weight tier)																			
≥20 kg	Serum for SARS-CoV-2 serology	X[11]									X						X	X	
	Serum for exploratory research	X[11]									X						X	X	
	Plasma for exploratory research	X[11]									X						X	X	
≥10 kg to <20 kg	Serum for SARS-CoV-2 serology	X[11]									X						X	X	
≥3 kg to <10 kg	Serum for SARS-CoV-2 serology	X[11]									X						X[17]	X	

9.1.1. Footnotes for the Schedule of Events Table

1. Screening visit may occur on the same day as the baseline visit. If screening and baseline visits occur on different days, assessments and collections marked for both screening and baseline visits will be performed on both days. If screening and baseline occur on the same day, assessments and collections marked for both visits may be performed once, on the same day. Samples and data may be used for exploratory research and/or diagnostic test development.
2. If a scheduled visit cannot be performed in person (for example, due to COVID-19 restrictions), or if no assessments or collections require the subject to be contacted in person, the visit may be conducted virtually (ie, by telemedicine or phone).
3. The EOS visit will be performed in person. In the case that the day 169 visit was conducted prior to Amendment #2, the subject should return to the clinical trial unit for 1 additional visit for the EOS visit as soon as possible after Amendment #2 is approved by local regulatory and ethics as required.
4. Subjects will be assessed for signs and symptoms related to COVID-19. Refer to Section 9.2.4.4 and Section 9.2.4.5 for additional information on recording of adverse events and signs/symptoms of COVID-19 associated with these adverse events.

   Subjects who have signs or symptoms consistent with COVID-19 will have an unscheduled 'SARS-CoV-2 Confirmation' visit. If SARS-CoV-2 infection is confirmed, subjects will continue to follow the Schedule of Events and must have additional unscheduled visits. Refer to Section 6.3 for visit requirements for these subjects.
5. Subjects who prematurely discontinue the study will have an early termination (ET) visit for sample collection and assessments as indicated.
6. Refer to eligibility criteria (Section 7.2.2) for the acceptable sample collection window for screening test of SARS-CoV-2 infection. A confirmed local negative result is required prior to study drug administration.

   A mid-turbinate nasal swab will also be collected at baseline. For subjects whose screening and baseline visit occur on the same day, both the local molecular diagnostic assay and central mid-turbinate nasal swab assay will be performed.

   Refer to Section 9.2.1.4 for additional information regarding these collections.
7. Urine pregnancy test will be performed for all women of childbearing potential (WOCBP), regardless of pregnancy status. If urine pregnancy test is positive, a serum pregnancy test will be performed for confirmation A pregnancy report form will be completed for each subject who becomes pregnant or is pregnant at the time the parent or guardian signs consent.
8. Study drug will be administered after all sample collections and assessments are completed for the study visit.
9. Vital signs will be recorded prior to study drug administration, and approximately 1 hour after study drug administration. Vital signs may additionally be recorded as needed per local standard of care and Investigator discretion.

10. In the event that limited availability of blood prevents the collection of all indicated blood samples for a given visit, PK-ADA sample collection (when applicable) will be prioritized over other blood samples.
11. The indicated blood samples may be collected at either the screening or pre-dose visit, but must be collected prior to study drug administration. Efforts should be made to collect all screening/pre-dose blood samples on the same day, when feasible.
12. Indicated hematology/blood chemistry sample collection is optional, and may be collected if considered clinically appropriate by the investigator or designee.
13. On day 1, subjects in group A and group B will each be assigned using IWRS to one of two staggered PK-ADA sampling schedules (schedule 1 and schedule 2).
14. Actual dosing time and sample collection times will be recorded for all drug concentration/immunogenicity ("PK-ADA") samples. The pre-dose PK-ADA sample collection must be performed on the same day as study drug administration. The window for pre-dose PK-ADA sample collection is as close to administration of study drug as is reasonable.
15. PK-ADA sample may be analyzed for ADA and NAb, if feasible, in samples collected pre-dose, on day 29 (schedule 1), and on day 85 (schedule 2).
16. Note that the day 2 visit may occur with a window of ±1 day. For all subjects, the day 2 visit may occur on day 3 (+1 window). For subjects assigned to **schedule 1**, if the day 2 visit **cannot occur** on day 2 or day 3, subjects may have the day 2 blood draw for analysis of drug concentration on day 1, at least 4 hours after study drug administration (-1 window). If this blood sample is collected, the day 2 visit can be omitted. The day 2 visits should be scheduled for day 2 or day 3 whenever possible.
17. Sample will only be collected if the 'SARS-CoV-2 Confirmation' visit occurs after study day 29.

9.1.2. Early Termination Visit

Subjects who prematurely discontinue the study will have an early termination (ET) visit as described in Table 3.

9.1.3. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for confirmation of suspected COVID-19, or for any other reason, as warranted.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

Procedures to be performed for the purpose of determining study eligibility or characterizing the baseline population include: informed consent and assent (as applicable), medical history, demographics, (including weight and height), and SARS-CoV-2 diagnostic testing.

9.2.1.1. Informed Consent and Assent

Informed consent (and assent, as applicable) will be obtained according to the requirements described in Section 13.2.

9.2.1.2. Body Weight

Body weight will be assessed using calibrated scales. Subjects should void (empty bladder) prior to weight assessment. During weight assessment, subjects should be wearing undergarments only and should not wear shoes. Body weight will be recorded to the nearest 0.1 kg.

9.2.1.3. Medication History

The following prior medications will be recorded if they were given to a subject within 6 months prior to their screening visit:

- Other investigational (not authorized or approved) drugs
- Investigational SARS-CoV-2 vaccines
- Authorized or approved SARS-CoV-2 vaccines
- Investigational, authorized, or approved passive antibody for prophylaxis of SARS-CoV-2 infection, including convalescent plasma, convalescent sera, hyperimmune globulin, or other monoclonal antibodies (eg, bamlanivimab and etesevimab, sotrovimab)

9.2.1.4. Diagnostic Testing for SARS-CoV-2 at Screening and Baseline

Screening. The Investigator or sub-Investigator will verify that the subject tests negative for SARS-CoV-2 by a local molecular diagnostic assay for SARS-CoV-2 virus (eg, RT-PCR) using an appropriate sample such as nasopharyngeal, nasal, oropharyngeal, or saliva. The local diagnostic assay for SARS-CoV-2 must be considered acceptable for clinical use by local standards. If the test has not been approved or has not received authorization, such as EUA issued by the US FDA or authorization by the equivalent local health authority, the Sponsor must be consulted. The use of RT-PCR is highly recommended. Antigen tests are not permitted for diagnostic testing.

The local diagnostic test result, specimen type (eg, nasal swab), assay type, and date of test will be recorded in the eCRF. The sample type collected will depend on local lab requirements. Historical test results will not be accepted.

Baseline. A mid-turbinate swab sample will be collected at baseline to test for SARS-CoV-2 by RT-qPCR using a central laboratory**.**

Screening/Baseline Performed on the Same Study Visit. For subjects whose screening and baseline visit occurs on the same day, both the local molecular diagnostic assay and central mid-turbinate assay will be performed.

9.2.2. SARS-CoV-2 Viral Testing in the Event of Suspected or Confirmed SARS-CoV-2 Infection

Samples will be collected during unscheduled visits in the event of suspected COVID-19 or confirmed SARS-CoV-2 infection that occurs after a subject receives study drug. Requirements for this testing are described in Section 6.3.

9.2.3. Study Drug Administration

Refer to Section 8.1.

9.2.4. Safety

9.2.4.1. Vital Signs

Vital signs will include body temperature, blood pressure, pulse rate, and respiratory rate. Vital signs will be measured after the subject has been resting quietly for at least approximately 5 minutes and may be obtained in seated or supine position. Refer to Section 9.1.1 for additional information concerning the timing of vital sign collection.

9.2.4.2. Targeted Physical Examination

Targeted physical examination will include examination of the oropharynx, skin, heart, lungs. Other system will be examined based on complaints or concerns expressed by the subject.

9.2.4.3. Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded as defined in Section 8.7.

9.2.4.4. Adverse Events

Adverse events will be recorded at each visit indicated in the Schedule of Events (Table 3). This will include any adverse events that the subject is experiencing or has experienced since their last in-person or remote visit.

Adverse events should be obtained in an unsolicited fashion, allowing the subject and/or subject's parent(s) or guardian(s) to spontaneously report events. Solicitation of specific adverse events (eg, through the use of a checklist) should be avoided.

All adverse events will be recorded and reported in the eCRF (Section 10.1). In addition, signs and symptoms related to COVID-19 will be recorded as described in Section 9.2.4.5.

9.2.4.5. COVID-19 Signs and Symptoms

On each visit when adverse events are recorded (Section 9.2.4.4), subjects and/or their parent(s) or guardian(s) will be queried for any signs and symptoms associated with these adverse events that may be related to COVID-19, as defined by the Centers for Disease Control (CDC, 2021d).

For each sign or symptom, the start date, end date, and severity will be recorded (mild, moderate, severe) in the subject's medical record (source document). It is important to record this information in the source document, to ensure that the temporal dimensions of each sign or symptom are captured.

Subjects who experience signs or symptoms that are suspected to be related to COVID-19 will have an unscheduled visit to confirm SARS-CoV-2 infection, as described in Section 6.3. If the subject's SARS-CoV-2 test result is positive, all signs and symptoms that were captured in the source documents and are confirmed to be temporally related to the positive test result will be recorded on a separate eCRF (individual sign or symptom with start date and end date, and associated severity).

9.2.4.6. COVID-19-Related Medically-Attended Visits

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.

COVID-19-related medically-attended visits will be recorded in the eCRF. During each indicated collection visit (Table 3), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded. For subjects with confirmed SARS-CoV-2 infection will be queried for COVID-19-related medically-attended visits as described in Section 6.3.

At a minimum, the following details will be recorded:

- Nature of the visit (eg, hospitalization, emergency room visit)
- Date and length of visit
- Primary reason for the visit
  Note: the primary reason should also be recorded as an adverse event
- Respiratory rate
- Heart rate
- Peripheral capillary oxygen saturation (SpO_2)
- Oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2)
- Respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO)
- Systolic and diastolic blood pressure
- Requiring vasopressors (yes/no)
- Multiorgan dysfunction: Significant acute renal, hepatic, or neurologic dysfunction
- Multisystem inflammatory syndrome in children (MIS-C)
- Admission to an ICU

9.2.5. Laboratory Testing

Hematology, chemistry, and pregnancy testing samples will be analyzed by local laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 3. Tests will include:

Blood Chemistry

Sodium	Total protein, serum
Potassium	Creatinine
Chloride	Blood urea nitrogen (BUN)
Carbon dioxide	Aspartate aminotransferase (AST)
Calcium	Alanine aminotransferase (ALT)
Glucose	Total bilirubin
Albumin	

Hematology

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

Other Laboratory Tests

Urine pregnancy test will be performed for all women of childbearing potential (WOCBP) prior to administration of study drug and at end of study, regardless of pregnancy status. If urine pregnancy test is positive, a serum pregnancy test will be performed for confirmation.

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 drug concentration measurement will be collected at visits listed in Table 3. For information concerning unused samples and exploratory research, refer to Section 9.2.8.3.

9.2.7. Immunogenicity Measurements and Samples

Samples for immunogenicity assessments will be collected at the timepoints listed in Table 3. For information concerning unused samples and exploratory research, refer to Section 9.2.8.3.

9.2.8. Exploratory Biomarkers

9.2.8.1. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibody Responses

Antibodies against SARS-CoV-2 will be measured at baseline in all subjects. Antibodies may include, but may not be limited to, anti-S IgA and IgG and anti-N IgG antibodies measured using immunoassays. Anti-SARS-CoV-2 antibodies will be measured at timepoints post-baseline, as specified in the schedule of events, in order to explore the underlying prevalence of SARS-CoV-2 antibody positivity, and seroconversion (compared to baseline) in the study population with casirivimab+imdevimab. The assays used post-baseline to measure antibody immunity will have been demonstrated to not be susceptible to interference from casirivimab+imdevimab and may include but may not be limited to anti-N IgG immunoassays. Neutralization assays that detect anti-SARS-CoV-2 neutralizing antibodies may also be used to explore whether a positive anti-SARS-CoV-2 antibody response was comprised of functionally neutralizing antibodies.

9.2.8.2. Serum and Plasma for Exploratory Research

Serum and plasma for exploratory research will be collected and banked from subjects with bodyweight >20 kg for exploratory research related to COVID-19, SARS-CoV-2, casirivimab+imdevimab, host and viral biological pathways, and other mechanisms related to safety, drug exposure, disease activity and clinical outcomes.

9.2.8.3. Unused and Residual Biological Samples

Any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up to 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to COVID-19, SARS-CoV-2, casirivimab+imdevimab, host and viral biological pathways, and other mechanisms related to safety, drug exposure, disease activity and clinical outcomes, or for assay development or validation, and/or for diagnostic test development or validation.

9.2.8.4. Viral Sequencing of Mid-Turbinate Nasal Swab Samples in SARS-CoV-2-Positive Subjects

In support of public health initiatives to track SARS-CoV-2 genetic variants, viral genome sequencing may be performed on SARS-CoV-2 viral nucleic acid isolated from nasal swab samples that have been confirmed positive for SARS-CoV-2.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The Investigator must promptly record all clinical events occurring during the study data collection, from the start of the pretreatment period to the end of on-treatment period (see Section 11.4.3.1). 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 an AE.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or parent, or by questioning the subject or parent at each study visit. Subjects and parents should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs 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 SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

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

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, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

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

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

Any SAE that may occur after the on-treatment period that the Investigator assesses as related to study drug should also be reported.

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

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed,

and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE eCRF, and retained at the study center and available upon request.

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

10.1.3. Events that Require Expedited Reporting to Sponsor

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

SAEs.

Adverse Events of Special Interest (AESI):

- Grade ≥3 injection-site reactions
- Grade ≥3 hypersensitivity reactions

  Note: refer to Table 4 for grading scale.
- Multisystem inflammatory syndrome in children (MIS-C)

  *Note: MIS-C is defined according to the CDC (CDC, 2021c). **All** of the following criteria must be met to qualify:*

  - *An individual aged <21 years presenting with fever (≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours)*
  - *Laboratory evidence of inflammation, including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin*
  - *Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)*
  - *No alternative plausible diagnoses*
  - *Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms*

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 study participants, during the study or within 8 months of the last dose of study drug. Any complication of pregnancy affecting a female subject, 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.

A pregnancy report form will be completed for each subject who becomes pregnant or is pregnant at the time the parent or guardian signs consent.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a subject 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 subject is a passenger).
- Is **life-threatening** – in the view of the Investigator, the subject 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 subject or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (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.

10.2.4. Severity

The severity of AEs (including test findings classified as AEs) and injection-site-related reactions will be graded using the current version of the NCI-CTCAE v5.0 (DCTD, 2017). The NCI-CTCAE severity grading systems for anaphylaxis, allergic reaction, and injection site reaction are specifically provided in Table 4.

Table 4: NCI-CTCAE Severity Grading (v5.0) for Anaphylaxis, Allergic Reaction, and Injection Site Reactions

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			Only grade 3, 4, and 5 are reportable as AESI[1]		
Anaphylaxis[2]	Not applicable	Not applicable	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Allergic reaction (hypersensitivity reaction)[3]	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Injection site reaction[4]	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

[1] See details in Section 10.1.3.

[2] Definition: A 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

[3] Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.

[4] Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

Source: (DCTD, 2017)

10.2.5. Causality

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

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation)
- Response to rechallenge (re-introduction of the drug)
- 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 subject at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the Sponsor in a timely fashion. The Sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Boards, and Investigators

During the study, the Sponsor and/or the contract research organization (CRO) will inform health authorities, 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.

Upon receipt of the Sponsor's notification of a SUSAR that occurred with the study drug, the Investigator will inform the Institutional Review Board (IRB) 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 IRB 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

No formal statistical hypothesis testing is planned in this study. The pharmacokinetics hypothesis for this study is defined in Section 3.2.3.1.

11.2. Justification of Sample Size

Analyses of PK, safety, tolerability, immunogenicity, and serology data will be descriptive. The sample size was chosen based on PK considerations and is consistent with early phase studies to assess PK.

At least 12 subjects are needed to enroll in each weight group (Group A: ≥10 kg to <40 kg, and Group B: ≥3 kg to <10 kg) to assess drug concentration. The study plans to enroll approximately 28 subjects in total.

The sample size may be adjusted if planned SC dosing of casirivimab+imdevimab does not achieve concentrations in serum similar to, or higher than, that observed in adults (≥18 years of age) after casirivimab+imdevimab 1200 mg (600 mg per mAb) SC administration. PK will be evaluated on an ongoing basis to determine if dose adjustments are needed and whether more subjects are needed for analysis.

11.3. Analysis Sets

11.3.1. Safety Analysis Set

The safety analysis set (SAF) includes all subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.2. Pharmacokinetic Analysis Set

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

11.3.3. Immunogenicity Analysis Sets

The ADA analysis sets (AAS) include all subjects who received any study drug and had at least one non-missing ADA result following the first dose of the study drug. The AAS is based on the actual treatment received (as treated).

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

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects 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. Subject Disposition

The following will be provided:

- The total number of screened subjects whose parent(s) or guardian signed the ICF
- The total number of subjects who discontinued the study, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by weight group and by all subjects combined.

11.4.3. Safety Analysis

11.4.3.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from the parent(s)/guardian(s) signing the ICF to before study drug administration.
- The on-treatment 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 subjects with at least 1 TEAE by SOC and 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)

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

11.4.3.2. 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 subjects with a potentially clinically significant value (PCSV) at any post-study drug administration time point will be summarized for each clinical laboratory test for all subjects and separately for subjects 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.

11.4.3.3. Treatment Exposure

The duration of study treatment exposure will be defined as 28 days after the last dose for a subject in SAF.

11.4.3.4. Treatment Compliance

Subject treatment compliance is not applicable for this study, since the study drug is administered once at the site and will be the same as treatment exposure.

11.4.4. Pharmacokinetics

11.4.4.1. Analysis of Drug Concentration Data

Analysis will be performed according to two groups:

- Group A: body weight ≥10 kg to <40 kg
- Group B: body weight ≥3 kg to <10 kg

The concentrations of total casirivimab and total imdevimab over time will be summarized by descriptive statistics for each weight group.

Subjects who test positive for SARS-CoV-2 infection during the treatment period may be analyzed separately from the PK analysis population.

Stratification of the analysis may be performed if subjects receive a treatment that has the potential to impact the pharmacokinetics of casirivimab+imdevimab (eg, IVIG)

No formal statistical hypothesis testing will be performed.

11.4.5. Analysis of Immunogenicity Data

11.4.5.1. Analysis of ADA Data

The immunogenicity variables described in Section 5.4 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category, and maximum titer observed in patients in the ADA analysis sets.

The ADA status of each patient 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 patient is classified as one of the following:

- 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
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent may be further categorized.

The maximum titer category of each patient is classified as:

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

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

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.

11.4.5.2. Analysis of NAb Data

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis sets will be provided by treatment groups. The NAb status is categorized as follows:

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

11.4.6. Other Analyses

The number and percentage of baseline seronegative subjects with post-baseline anti-SARS-CoV-2 positive serology will be summarized for the entire study period.

The number and percentage of subjects with COVID-19-related MAVs will be summarized for the entire study period.

11.5. Interim Analysis

No formal interim analysis is planned. Interim reviews of PK and safety data may be performed before subjects complete the end of 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, AEs, 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) system.

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

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

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

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects 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 subject records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

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

12.2.3. Case Report Form Requirements

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

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

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the Sponsor 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, eCRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the Investigator's institution.

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the Investigator. This signed declaration accompanies each set of subject 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 and Assent

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

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

It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject and his/her parent(s) or legal guardian(s) prior to the subject'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 subject and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the subject's parent(s) or legal guardian(s) and the same Investigator or designee who explained the ICF.

In the case of more than one parent or guardian, local law must be observed in deciding whether 1 or both parent's/guardian's consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason the other parent or guardian did not sign. The subject may also be required to sign and date the ICF, as determined by the IRB and in accordance with the local regulations and requirements.

- Subjects who can write but cannot read will have the assent form read to them before writing their name on the form.
- Subjects who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that informed assent was given.

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

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 and assent form must be reviewed and updated appropriately. All study subjects and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the subject to continue in the study. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject's parent(s) or legal guardian(s).

13.3. Subjects Confidentiality and Data Protection

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

The subject '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

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

- The protocol, ICF, and any other materials to be provided to the subjects (eg, advertising) before any subject 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 subject, in which case the IRB 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 should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB approval letter with a current list of the IRB 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 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 - 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 subject 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 subjects required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' 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 2a, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Pediatric Subjects Under 12 Years of Age 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. 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 2a, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Pediatric Subjects Under 12 Years of Age

Protocol Number: R10933-10987-COV-2121

Protocol Version: Amendment 2

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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