NCT04852978

IND: 148069 Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2 RANDOMIZED, OPEN-LABEL, PARALLEL GROUP STUDY TO ASSESS THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF MODERNA mRNA-1273 VACCINE ADMINISTERED WITH CASIRIVIMAB+IMDEVIMAB IN HEALTHY ADULT VOLUNTEERS

Compound:	Casirivimab+Imdevimab (REGN10933+REGN10987)
Clinical Phase:	2
Protocol Number:	R10933-10987-COV-2118
Protocol Version:	Amendment 5
Amendment 5 Date of Issue:	*See appended electronic signature page*
Amendment 4 Date of Issue:	21 Jul 2021
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AMENDMENT HISTORY

Amendment 5

Change	Rationale	Section(s) Changed
Sub-study has been included to allow subjects to opt to receive a booster dose of Moderna mRNA-1723 vaccine ≥5 months after completing the primary COVID-19 vaccination series and >35 days before the end of the main study (ie, until study day 345 for subjects in arms 1, 2, 3, 6a, 6c, 7 and 8 and until study day 331 for subjects in arms 4, 5, 6b, 6d and 9). One visit was added for pre-booster blood sample collection and booster dose administration and a second visit was added for post-booster blood sample collection. Nasopharyngeal swabs will be collected at each of the 2 visits.	To accommodate the updated CDC guidance for COVID-19 booster vaccines. To assess immune responses to the booster dose. To test for SARS-CoV-2 infection.	Section 2.3 Exploratory objectives Section 6.1 Study Description and Duration Section 8.3.3 Vaccine Deferral or Discontinuation Section 9.1 Schedule of Events, Table 3, Table 4, Table 5 and Table 6 Schedule of Events for the Moderna mRNA-1273 Vaccine Booster Sub-study [new] Section 9.1.1 Footnotes for the Schedule of Events Section 9.2.1.1 Informed Consent Section 9.2.10 Vaccine Booster Sub-Study (Optional) [new] Section 11.4.5 Adverse Events
Vaccine booster analysis set definition and analysis of sub-study vaccine booster text included in the protocol.	To define the vaccine booster analysis set and describe the possible analyses of the vaccine booster sub-study data.	Section 11.3.3 Vaccine Booster Analysis Set [new section] Section 11.4.5 Analysis of Sub-Study Vaccine Booster [new section]
The observation period definitions were clarified and a post-booster vaccination period was included.	To clarify the definitions of the different observation periods in the study.	Section 11.4.6.1 Adverse Events
Subjects will be allowed to receive COVID-19 booster vaccinations during the study. Subjects can choose to receive a third COVID-19 vaccine in the optional vaccine booster sub-study or receive COVID-19 vaccine boosters outside of the study which will then be recorded as a concomitant medication.	To accommodate the updated CDC guidance for COVID-19 booster vaccines.	Section 8.8.1 Prohibited Medications and Vaccines
Text on offering an additional vaccine to subjects in the affected arms if group-level study data identified vaccine interference from REGN10933+REGN10987 in one or more arms was removed.	An interim analysis which included wave 1 and 2 subjects, the arms where the dose of REGEN-COV is the highest and thus at greatest risk for vaccine interference showed only a small difference in neutralizing mAb binding. Thus, significant vaccine interference by REGEN-COV is unlikely.	Section 6.1 Study Description and Duration

Change	Rationale	Section(s) Changed
	The CDC guidance has changed to allow all subjects to receive booster doses of vaccines.	
The requirements for reporting of Grade ≥3 ISRs or Grade ≥2 hypersensitivity reactions related to Moderna mRNA-1273 administered as a concomitant medication outside of the study was included.	To clarify that Grade ≥3 ISRs and Grade ≥2 hypersensitivity reactions related to the Moderna mRNA-1273 vaccine administered outside the study should not be considered AESIs and do not require expedited reporting to the Sponsor.	Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Clarified that causality should be assessed in relation to the Moderna mRNA-1273 vaccine administered as part of the main study or sub-study, but not in relation to any vaccine administered as a concomitant medication outside of the study.	This clarification is now required because the Moderna mRNA-1273 booster shot administered as a concomitant medication is no longer prohibited.	Section 10.2.5 Causality.
Removed parenthetical referencing the post-vaccination period in describing SAE reporting, and clarified that any SAE assessed by the investigator as related to the study drug that occur subsequent to the reporting period should also be reported.	Reference to the reporting period being end of the post-vaccination period was removed because the naming logic of the safety period has changed and post-booster vaccination period has been added.	Section 10.1.1 General Guidelines
Risks for the Moderna mRNA-1273 vaccine were updated.	To align with the latest EUA Fact Sheet.	Section 3.3.2 Risk-Benefit for Moderna mRNA-1273 Vaccine
Text was added detailing mechanisms that could be implemented to ensure continuity of the study conduct and oversight due to COVID-19.	To explicitly detail temporary or alternative mechanisms that could be utilized due to the COVID-19 pandemic and to ensure appropriate documentation of any temporary or alternative mechanisms and deviation that may occur.	Section 9.1.
The risk-benefit information was updated to reflect the current investigator's brochure.	To provide current clinical data on REGN10933+REGN10987.	Section 3.3.1 Risk-Benefit for REGN10933+REGN10987.
Updates to relevant sections to include the current CDC guidelines, EUA for the Pfizer-BioNTech vaccine and Moderna COVID-19 vaccine fact sheet.	To include current CDC guidelines and Moderna COVID-19 vaccine fact sheet	Section 1 Introduction Section 3.2.1.2 Primary Objectives: Exploration of Time Intervals Section 3.3.2 Risk-Benefit for Moderna mRNA-1273 Vaccine
Updates to the background information, minor clarifications for consistency, and other minor typographical and administrative updates were made.	To include current CDC guidelines and include up to date references and to ensure	Throughout the document

Change	Rationale	Section(s) Changed
	clarity, accuracy, and consistency	

Amendment 4

Change	Rationale	Section(s) Changed
Five additional study arms have been included: • Two study arms, with a third concurrent control arm, will simulate vaccination up through approximately 6 months following REGN10933+REGN10987 administration. • One study arm, in addition to a concurrent control arm, will evaluate endogenous immune response to vaccination when the first vaccine dose is followed by REGN10933+REGN10987 administration 6 days later. Enrollment in these arms will occur as two additional waves (wave 3 and wave 4). In total, 106 additional subjects (30 per REGN10933+REGN10987 treatment arms, and 8 per control arms) will be enrolled. The justification for samples size was updated accordingly.	To better understand the temporal relationship between REGN10933+REGN10987 and Moderna mRNA-1723 vaccine with respect to endogenous immune response, by exploring larger time intervals between dosing, and by exploring the impact of immune "priming" prior to REGN10933+REGN10987 treatment on immunogenicity	Section 3.2.1.1 Primary Objectives: Potential Alteration of Endogenous Immune Responses Section 3.2.1.9 Use of Enrollment Waves Section 3.2.2 Rationale for Dose Selection Figure 1 Dose Administration by Study Arm Section 3.2.2.1 Study Arm 1 and Arm 9 (1200 mg IV) Section 3.2.2.2 Study Arm 2 (300 mg IV), Arm 3 (150 mg IV), Arm 7 (48 mg IV), and Arm 8 (12 mg IV) Table 1 Population Pharmacokinetics Modeling of Simulated Study Days Following 1200 mg IV Dose Section 3.2.2.3 Study Arm 4 (1200 mg SC) and Arm 5 (600 mg SC) Section 6.1 Study Description and Duration Figure 2 Study Flow Diagram (Enrollment Waves 1 and 2) Figure 3 Study Flow Diagram (Enrollment Waves 3 and 4) [new] Section 7.1 Number of Subjects Planned Section 8.5 Method of Enrollment and Treatment Assignment Table 2 Study Treatment Assignment Table 3 Schedule of Events for Study Arms 1, 2, 3, and 6a (Enrollment Wave 1) and Arms 7, 8, and 6c (Enrollment Waves 3) Table 4 Schedule of Events for Arms 4, 5, and 6b (Enrollment Wave 2) Table 5 Schedule of Events for Study Arms 9 and 6d (Enrollment Wave 4) [new]

Change	Rationale	Section(s) Changed
		Section 9.1.1 Footnotes for the Schedule of Events, #7, 10, and 11
Clinical history of myocarditis and/or pericarditis has been added as an exclusion criterion for study participation.	To ensure an appropriate risk-benefit profile for the target population	Section 7.2.2 Exclusion Criteria, #25 [new]
Definitions of safety observation periods, statistical analysis sets, and analysis plans were updated. In addition, it was updated that formal interim analysis may be performed.	To clarify methods of statistical analysis	Section 6.2 Planned Interim Analysis Section 11 Statistical Plan
Clarified that pregnancy testing is not required for women of childbearing potential (WOCBP) with documented bilateral tubal ligation.	To avoid unnecessary pregnancy testing	Section 9.1.1 Footnotes for the Schedules of Events
Risk-benefit information was updated to reflect the current investigator's brochure, as well as phase 3 clinical trials in the treatment and prevention of COVID-19.	To provide current clinical data on REGN10933+REGN10987	Section 3.3.1 Risk-Benefit for REGN10933+REGN10987
Updates to background information, minor clarifications for consistency, and other minor typographical and administrative updates were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 3

Change	Rationale	Section(s) Changed
Vital signs will be assessed at screening, as abnormal blood pressure at screening visit is an exclusion criterion (#12).	Updated to ensure accuracy of the Schedule of Events	Table 3 Schedule of Events for Study Arms 1, 2, 3, and 6a Table 4 Schedule of Events for Study Arms 4, 5, and 6b

Amendment 2

Change	Rationale	Section(s) Changed
Previously, it was specified that vaccine cards were to be dispensed to subjects only once their assigned study arm was deemed to have generated an appropriate vaccine response compared to the vaccine-only arm. This statement has been removed, and vaccine cards will be made available to **all** subjects upon receipt of the vaccine as per the current standard of care.	Based on site feedback; vaccine cards indicate receipt of the vaccine, rather than generation of an appropriate vaccine response.	Synopsis: Study Design Section 6.1 Study Description and Duration

Amendment 1

Change	Rationale	Section(s) Changed
Subjects with a positive serology test result for anti-SARS-CoV-2 antibodies **at screening**, tested either locally **or by a central laboratory**, will be excluded. Serology testing **at baseline** (central laboratory) will be used to exclude seropositive patients from the per-protocol set (PPS) for vaccine response analysis.	Due to limited supply of rapid serology test kits, local testing may not be operationally feasible.	Section 7.2.2 Exclusion Criteria, #2 Table 3 Schedule of Events for Study Arms 1, 2, 3, and 6a Table 4 Schedule of Events for Study Arms 4, 5, and 6b Section 9.1.1 Footnotes for Table 2 and Table 3 Schedule of Event, footnote #5
Procedural details regarding SARS-CoV-2 serology tests were updated.	Serology testing procedures were updated to remove unnecessary details or to ensure accuracy.	Section 9.2.1 Procedures Performed at the Screening/Baseline Visit Section 9.2.1.3 SARS-CoV-2 Serology
Subjects with positive SARS-CoV-2 **diagnostic test result** at any time prior to screening will be excluded from enrollment.	Previous exclusion criterion of positive SARS-CoV-2 **infection** needed to be updated for operational clarity.	Section 7.2.2 Exclusion Criteria, #3
Minor typographical and administrative updates	For accuracy and consistency	Throughout the protocol

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 19
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic data capture
EUA	Emergency Use Authorization
FBR	Future biomedical research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPS	Global Patient Safety
HDL	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
LDL	Low-density lipoprotein
LFIA	Lateral flow chromatographic immunoassay
mAb	Monoclonal antibody
mFAS	Modified full analysis set
MIS	Multisystem inflammatory syndrome
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PBMC	Peripheral blood mononuclear cell
PGx	Pharmacogenomics
PK	Pharmacokinetic
POC	Point of care
RBC	Red blood cell
RBD	Receptor binding domain
RBQM	Risk-Based Quality Monitoring
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
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Randomized, Open-Label, Parallel Group Study to Assess the Immunogenicity, Safety, and Tolerability of Moderna mRNA-1273 Vaccine Administered with Casirivimab+Imdevimab in Healthy Adult Volunteers
Site Locations	The study will be conducted in approximately 5 sites in the United States.
Principal Investigator	To be determined

Objectives

Primary

- To evaluate the extent of effect, if any, of REGN10933+REGN10987 administration on vaccine-induced neutralizing antibody responses to SARS-CoV-2 by Moderna mRNA-1273
- To evaluate the time interval required between REGN10933+REGN10987 administration and Moderna mRNA-1273 vaccination, to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2

Secondary

- To quantify the alteration of antigen specificity of vaccine-induced SARS-CoV-2 antibody responses when administered with different dose regimens of REGN10933+REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 and Moderna mRNA-1273 vaccine when administered in close succession
- To assess the concentrations of REGN10933 and REGN10987 in serum over time in subjects who receive REGN10933+REGN10987 and Moderna mRNA-1273 vaccine
- To evaluate the immunogenicity of REGN10933 and REGN10987 over time

Study Design

The study consists of 3 periods: a screening/baseline period, a vaccine response assessment period, and a follow-up period.

Subjects will be assessed for eligibility during the **screening/baseline period**, which may occur up to 21 days prior to day 1. To be eligible for the study, subjects must be confirmed negative for current or past SARS-CoV-2 infection by both RT-PCR and serology tests.

During this period, subjects will also be assigned to one of four different enrollment waves.

On day 1, subjects will be randomized to a study arm (1 of 12) within their assigned enrollment wave. Subjects randomized to study arms 1 through 5 or 7 through 9 will receive an IV infusion or SC injection of the study drug (REGN10933+REGN10987) on day 1 or day 7. Subjects in arms 6a to 6d (the control arms) will not receive any study drug. The first dose of the vaccine will be administered on day 1 or day 15, based on study arm assignment at randomization.

All subjects will receive the second dose of the vaccine 28 days after their first dose of the vaccine in accordance with the EUA Fact Sheet.

The **vaccine response assessment period** represents the time period of the primary analysis. For study arms 1, 2, 3, 7, 8, 6a, and 6c, this period includes up to study day 71; for study arms 4, 5, 9, 6b, and 6d, the period includes up to day 57. Following this assessment period, subjects will enter a **follow-up period** lasting up to 10 months.

Throughout the study, blood samples will be collected to assess whether the study drug impacts the ability of the vaccine to elicit neutralizing antibody titers against the SARS-CoV-2 S protein, and to understand any impact on vaccine-induced humoral and cellular immune responses to various S protein epitopes.

Subjects will also have blood samples taken at select visits for drug concentration, immunogenicity, and exploratory analyses, and will be monitored for AEs (including AESIs) during in-person visits. For subjects in study arms 4 and 5 (receiving the study drug and vaccine on the same day), a phone call will be made within 24 hours following study drug and vaccine administration on day 1 for AE collection.

The last study visit will take place approximately 1 year after the first dose of the vaccine.

Vaccine booster sub-study: All subjects will be offered an optional booster vaccination dose ≥5 months after completing the primary COVID-19 vaccination series and >35 days (ie, until study day 345 for subjects in arms 1, 2, 3, 6a, 6c, 7 and 8 and until study day 331 for subjects in arms 4, 5, 6b, 6d and 9) before the end of the main study. Blood samples for possible analysis will be collected pre- and post-booster administration.

Study Duration

The duration of the study is approximately 401 days or 387 days, depending on the study arm assignment and length of the screening period.

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

Up to approximately 286 subjects are planned to be enrolled.

Target Population

Eligible subjects for this study consist of healthy adult volunteers over 18 years of age who are negative at screening for both SARS-CoV-2 infection and endogenous anti-SARS-CoV-2 antibodies. A complete listing of eligibility criteria is provided in the main text.

Every effort should made to enroll older subjects, such that 30% to 50% of subjects enrolled at each site are ≥65 years of age. Efforts should also be made to enroll subjects representative of the demographics (eg, race and ethnic distribution) of those at risk for COVID-19 in the region where the study site is located.

Treatments

Site-managed assignment. At screening, eligible subjects will be assigned to an enrollment wave. The enrollment waves are intended to avoid or minimize the potential for unused doses of Moderna mRNA-1273 COVID-19 vaccine. Every effort should be made by sites to avoid unused doses of vaccine.

Sites will manage the placement of subjects into each wave. Every effort should be made by the site to ensure balance of age (<65 years and ≥65 years) within each of the enrollment waves.

Randomization. At baseline (day 1), subjects will be randomized to the corresponding study arms in each wave. Randomization will be stratified by age (<65 years versus ≥65 years).

Study Arm	Random-ization Ratio	Targeted Enrollment	Co-administered REGN10933+REGN10987 Combination Therapy	Moderna mRNA-1273 Vaccine
Enrollment Wave 1				
1	2	30	1200 mg (600 mg of each mAb) IV on day 1	On day 15 and day 43
2	2	30	300 mg (150 mg of each mAb) IV on day 1	On day 15 and day 43
3	2	30	150 mg (75 mg of each mAb) IV on day 1	On day 15 and day 43
6a	1	15	None	On day 15 and day 43
Enrollment Wave 2				
4	2	30	1200 mg (600 mg of each mAb) SC on day 1	On day 1 and day 29
5	2	30	600 mg (300 mg of each mAb) SC on day 1	On day 1 and day 29
6b	1	15	None	On day 1 and day 29
Enrollment Wave 3				
7	15	30	48 mg (24 mg of each mAb) IV on day 1	On day 15 and day 43
8	15	30	12 mg (6 mg of each mAb) IV on day 1	On day 15 and day 43
6c	4	8	None	On day 15 and day 43
Enrollment Wave 4				
9	15	30	1200 mg (600 mg of each mAb) IV on day 7	On day 1 and day 29
6d	4	8	None	On day 1 and day 29

Endpoints

Primary

- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to the SARS-CoV-2 S protein assessed 56 days after the first dose of Moderna mRNA-1273 vaccine in individuals who receive high-dose (1200 mg) REGN10933+REGN10987 compared to vaccine alone
- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to the SARS-CoV-2 S protein assessed 56 days after the first dose of Moderna mRNA-1273 vaccine in individuals who receive submaximal dose levels of REGN10933+REGN10987 (less than 1200 mg) compared to vaccine alone

Secondary

- Absolute values, change from baseline, and percentage change from baseline in concentrations of vaccine-induced antibodies to the following SARS-CoV-2 antigens over time:
  - Anti-S protein
  - Anti-receptor binding domain (RBD)
  - Other S protein subdomains (including S1, S2, and NTD)
- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to SARS-CoV-2 S protein assessed over time
- Proportion of subjects with treatment-emergent adverse events (TEAEs) throughout the study
- Proportion of subjects with treatment-emergent serious adverse events (SAEs) throughout the study
- Proportion of subjects with infusion-related reactions (grade ≥2) to REGN10933+REGN10987 through day 4 post-infusion
- Proportion of subjects with injection site reactions (grade ≥3) to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 4 post-injection
- Proportion of subjects with hypersensitivity reactions (grade ≥2) to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 29 post-infusion or post-injection (as applicable)
- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity, as measured by anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to REGN10933 and REGN10987

Procedures and Assessments

Procedures and assessments will include the following:

- Nasopharyngeal (NP) swabs for SARS-CoV-2 rapid RT-PCR testing
- Blood collection for rapid serology testing and/or central serology testing
- Serum and whole blood collection for pharmacodynamic and exploratory analyses
- Blood collection for safety labs
- Pregnancy testing

Statistical Plan

Statistical Hypothesis

No statistical hypothesis testing is planned in this study. Analyses of immunogenicity, safety, tolerability, and other data will be descriptive and exploratory in nature.

Justification of Sample Size

This study plans to enroll up to approximately 286 subjects, in order to achieve a target enrollment of up to approximately 30 subjects per Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and 46 total Moderna mRNA-1273-alone subjects. Based on the calculations provided below, this sample size is considered appropriate to meet the aims of this phase 2 study, in that it is expected to provide adequate precision in quantifying the magnitude of effect for the primary endpoint, as well as allow for an assessment of the safety and tolerability of the Moderna mRNA-1273 vaccine when administered with REGN10933+REGN10987.

The assumed log10-scale standard deviation for the study is 0.30 log. This assumption is based on phase 1 data for the Moderna mRNA-1273 vaccine, taking the weighted average (ie, adjusting for sample sizes) across all doses (25,100, and 250 μg) and age groups (18 to 55, 56 to 70, and ≥71 years) for the neutralizing antibody titer ID50 endpoint at day 57 (Anderson, 2020) (Jackson, 2020). With a log-scale standard deviation of 0.30 for the primary endpoint and a sample size of 30 and 46 subjects per arm, the half-width of the 95% within-group confidence interval (CI) [ie, the minimal detectable difference] in this study is 0.11 log and 0.09 log respectively. For between-group comparisons, the half-width of the 95% between-group CI for any two Moderna mRNA-1273 + (REGN10933 and REGN10987) arms is 0.15 log. Additionally, the half-width of the 95% between-group CI in this study for any individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and the total Moderna mRNA-1273 alone subjects is 0.14 log.

The analysis set that will be used for assessment of vaccine response allows for subjects to be excluded from analysis if certain confounding criteria are met (see Section 11.3.1). If 50% of subjects are excluded from analysis (ie, 15 subjects are analyzed per individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and 23 total Moderna mRNA-1273 alone subjects are analyzed), the half-width of the 95% between-group CI for any two Moderna mRNA-1273 + (REGN10933 and REGN10987) arms is 0.22 log. Additionally, the half-width of the 95% between-group CI for any individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and Moderna mRNA-1273 alone subjects is 0.20 log. Under this scenario, the minimal detectable difference still remains substantially smaller than the decrease in neutralization titers observed in a separate study of sera from recipients of the Moderna mRNA-1273 vaccine who were infected with South African variants (eg, B.1.351 v1, v2, and v3) (Garcia-Beltran, 2021)

Statistical Analysis

Analysis of Primary Vaccine Response Endpoint

The primary endpoint is the 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to SARS-CoV-2 pseudovirus, assessed on 56 days after the first dose of the vaccine. The 56-day time point corresponds to study day 71 for study arms 1, 2, 3, 7, 8, 6a, and 6c, and study day 57 for study arms 4, 5, 9, 6b, and 6d.

An analysis of covariance (ANCOVA) model with treatment group as a fixed effect and age as a covariate will be fit to the data as the primary analysis.

The least squares mean estimates for the endpoint will be presented for each treatment group, as well as for the differences between treatment groups. Associated 95% CIs will also be reported for each treatment group and for between-group comparisons.

Data will be originally fitted in the log scale, and final outputs will be reported in geometric means and differences of the geometric means.

Accompanying descriptive analyses will also be provided. The analyses will be conducted based on the observed data with no imputation for missing data. Values below the limit of quantification (LOQ) will be set to half of LOQ.

Analysis of Secondary Vaccine Response Endpoints

The secondary endpoints will be analyzed in a similar manner as described for the primary endpoint.

For these secondary endpoints, the individual time points for assessments include all post-vaccine scheduled timepoints during the Vaccine Response Assessment Period as described in the Schedule of Events.

Accompanying descriptive analyses for each endpoint at each individual time points will also be provided.

Interim Analyses

Data will be reviewed periodically to provide an understanding of vaccine response in different study arms. Formal interim analysis may be conducted.

Timing of Primary and Final Analyses

The primary vaccine response analysis will be conducted as a first-step analysis after all subjects have finished the primary endpoint visit (ie, 56 days after the first dose of the vaccine), in order to estimate the levels of neutralizing antibodies in each study arm. This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis. The SAP will be issued prior to this analysis.

After all subjects finish 1-year of follow-up, a final study analysis will be conducted.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel RNA betacoronavirus, initially identified in patients experiencing atypical pneumonia in Wuhan City, China (Zhu, 2020) and later identified as the causative pathogen of coronavirus disease 2019 (COVID-19) (WHO, 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).

Over 200 COVID-19 vaccines are currently in preclinical or clinical development, and many of these employ mechanisms involving S protein neutralization (WHO, 2021). On 11 Dec 2020, the Food and Drug Administration (FDA) issued the first Emergency Use Authorization (EUA) for a COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine) in individuals ≥16 years old (FDA, 2020b). Similar authorizations were subsequently issued for mRNA-1273 (18 Dec 2020), a COVID-19 vaccine developed by Moderna, as well as a vaccine developed by Janssen Pharmaceuticals (27 Feb 2021), both in individuals ≥18 years old (Baden, 2020). On 03 Jan 2022, the EUA of the Pfizer-BioNTech vaccine was revised to include vaccination of individuals 5-11 years old who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise (FDA, 2022). Each of these vaccines elicit robust, dose-dependent neutralizing and other polyclonal antibodies against the S protein RBD (Polack, 2020) (Sadoff, 2021) (Jackson, 2020), and in phase 3 trials have shown over 90% (Pfizer-BioNTech, Moderna) and over 60% (Janssen) efficacy in preventing symptomatic COVID-19 illness compared with placebo (Baden, 2020) (Polack, 2020) (Sadoff, 2021).

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 a co-administered combination therapy, REGN10933+REGN10987 (casirivimab+imdevimab; also referred to by the proprietary name conditionally accepted by the FDA, REGEN-COV™) is being evaluated for the treatment and prevention of SARS-CoV-2 infection.

REGN10933+REGN10987 exhibits potent SARS-CoV-2 neutralization in pseudovirus assays using wildtype Spike (Baum, 2020), and Spike sequences found in several 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]) (REGEN-COV™ (casirivimab and imdevimab) [HCP Fact Sheet], 2022) (Weinreich, 2020) . The REGN10933+REGN10987 antibodies have significantly diminished potency and are not expected to be active against the recent Omicron variant (REGEN-COV™ (casirivimab and imdevimab) [HCP Fact Sheet], 2022).

The combination therapy is being evaluated for the treatment and prevention of SARS-CoV-2 infection, and in phase 3 clinical trials 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 3.3.1 additional information). REGN10933+REGN10987 (1200 mg IV or SC; 600 mg of each mAb) is currently authorized under EUA for the treatment of outpatients 12 years and older who are at high risk for developing severe COVID-19 (FDA, 2020a).

The Centers for Disease Control and Prevention (CDC) currently recommends deferring the receipt of a COVID-19 vaccine dose by 30 days following the use of passive antibody therapies for post-exposure prophylaxis and by 90 days following passive antibody therapies used for the treatment of COVID-19 (CDC, 2021). Currently, however, there are no published experimental data on potential pharmacodynamic interactions between anti-SARS-CoV-2 mAbs and COVID-19 vaccines to inform this recommendation. Empirical assessment of the potential immunological impact of mAb administration on COVID-19 vaccination is thus urgently needed.

This is a phase 2, randomized, open-label, parallel group study in healthy adult volunteers to assess the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine when administered with REGN10933+REGN10987. A central focus of the study will be to assess whether REGN10933+REGN10987 interferes with the ability of the Moderna mRNA-1273 vaccine to elicit neutralizing antibody titers against the SARS-CoV-2 S protein, and to gain a clearer mechanistic understanding of any observed alteration of vaccine-induced humoral and cellular immune responses to various S protein epitopes. The study is designed to replicate hypothetical clinical scenarios in which mAbs may be administered in conjunction with a COVID-19 vaccine, as well as simulate different time intervals between mAb and vaccine administration (using decreasing mAb dose concentrations as a proxy) to identify optimal dose timing in the event that interference with vaccine-induced immunity is observed. A detailed discussion of the rationale for the study design is provided in Section 3.2.

Additional background information on REGN10933+REGN10987 and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the extent of effect, if any, of REGN10933+REGN10987 administration on vaccine-induced neutralizing antibody responses to SARS-CoV-2 by Moderna mRNA-1273
- To evaluate the time interval required between REGN10933+REGN10987 administration and Moderna mRNA-1273 vaccination, to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2

2.2. Secondary Objectives

The secondary objectives of the study are:

- To quantify the alteration of antigen specificity of vaccine-induced SARS-CoV-2 antibody responses when administered with different dose regimens of REGN10933+REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 and Moderna mRNA-1273 vaccine when administered in close succession
- To assess the concentrations of REGN10933 and REGN10987 in serum over time in subjects who receive REGN10933+REGN10987 and Moderna mRNA-1273 vaccine
- To evaluate the immunogenicity of REGN10933 and REGN10987 over time

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore circulating T cell and B cell responses to SARS-CoV-2 antigens in subjects who receive both REGN10933+REGN10987 and Moderna mRNA-1273 vaccine versus those who receive the vaccine alone
- To explore the impact of REGN10933+REGN10987 as measured by the induction of vaccine-induced binding antibodies to SARS-CoV-2 receptor-binding domain (RBD) antigens post-Moderna mRNA-1273 vaccination that compete with the same epitopes recognized by REGN10933 and/or REGN10987
- To explore how REGN10933+REGN10987 alters vaccine-induced neutralizing antibody responses, induced by Moderna mRNA-1273 vaccine, against SARS-CoV-2 variants
- To characterize viral variants by sequencing SARS-CoV-2 in subjects who become infected post-baseline
- To explore the impact on vaccine responses and the mechanism of action of REGN10933+REGN10987 as measured by experimental laboratory assays and biomarkers after vaccination with Moderna mRNA-1273
- To explore biomarkers and genomic factors associated with safety and immune responses after exposure to REGN10933+REGN10987 and Moderna mRNA-1273
- To assess immune responses in subjects who receive booster vaccinations during the study

3. HYPOTHESES AND RATIONALE

3.1. Hypotheses

The clinical hypotheses of the study are that (1) REGN10933-REGN10987 does not alter the immunogenicity of Moderna mRNA-1273 vaccine and (2) REGN10933+REGN10987 and Moderna mRNA-1273, when administered in close succession, are well tolerated.

There is no statistical hypothesis in this descriptive study (Section 11.1).

3.2. Rationale

3.2.1. Rationale for Study Design

3.2.1.1. Primary Objectives: Potential Alteration of Endogenous Immune Responses

Monoclonal antibody therapies such as REGN10933+REGN10987 will continue to play an important role in COVID-19 treatment and/or prevention, even as COVID-19 vaccination becomes more widespread. There is a theoretical risk, however, that mAb treatments may alter the vaccine-induced immune responses, by binding to and thereby blocking key antigenic determinants that generate protective immunity. The primary objective of this study is thus to understand whether REGN10933+REGN10987, when administered in the setting of treatment or prevention of COVID-19, will alter the response to COVID-19 vaccines such as Moderna mRNA-1273.

To accomplish the primary study objective, REGN10933+REGN10987 will be evaluated using dose levels that have either been authorized under EUA for the treatment of COVID-19 and/or for which clinical trial data indicate efficacy in treating or preventing COVID-19 (Section 3.2.2). The study is thus designed to mirror hypothetical clinical 'use case' scenarios, for which the two administration modalities of REGN10933+REGN10987 may be employed in close proximity to COVID-19 vaccination or mimic waiting for vaccination for up to 6 months after a 1200 mg dose of REGEN-COV.

For the hypothetical treatment use case (ie, administration of REGN10933+REGN10987 1200 mg IV in a SARS-CoV-2-positive individual, followed by subsequent vaccination against future infection), Moderna mRNA-1273 will be administered 14 days after intravenous REGN10933+REGN10987. The use of an intervening period of time is based on public health recommendations to avoid COVID-19 vaccination during an active SARS-CoV-2 infection. The 14-day interval was selected to ensure adequate time for the distribution of REGN10933+REGN10987 from the plasma compartment into tissues.

For the hypothetical prophylaxis use case (ie, administration of REGN10933+REGN10987 1200 mg SC in a SARS-CoV-2-negative individual for short-term protection against exposure, with administration of COVID-19 vaccination for long-term protection), REGN10933+REGN10987 will be administered on the same day as Moderna mRNA-1273. Simultaneous administration of both antibody therapy and vaccination has been used as effective post-exposure prophylaxis for several pathogens, including rabies virus and hepatitis A virus (Manning, 2008) (Nelson, 2018).

In addition to the above use case scenarios, the study will evaluate endogenous immune responses over time when 1200 mg IV of REGN10933+REGN10987 is administered 6 days after the first dose of Moderna mRNA-1273 (ie, study day 7). This interval was chosen to allow adequate

production and presentation of S protein antigens following vaccination and is thus intended to represent a scenario in which the immune system is "primed" prior to treatment with REGN10933+REGN10987. This will allow for assessment of safety of REGN10933+REGN10987 administration in close temporal proximity to vaccination. In the event REGN10933+REGN10987 is found to interfere with the endogenous immune response to vaccination when given prior to or concomitantly with vaccination, this will allow assessment of whether, in the prophylaxis setting, vaccination prior to REGN10933+REGN10987 administration will allow high risk subjects to receive both long term and short term protection from vaccination and REGN10933+REGN10987 administration followed shortly thereafter.

3.2.1.2. Primary Objectives: Exploration of Time Intervals

It is anticipated that REGN10933+REGN10987 will not alter the generation of endogenous, protective immune responses to Moderna mRNA-1273 vaccination. Vaccine responses are polyclonal, and the presence of mAb therapeutics may not alter neutralizing Ab generation to all S-protein epitopes. Additionally, we anticipate that presentation of peptides for T-cell priming will not be affected by mAb therapeutics. Finally, preliminary observations from subjects with SARS-CoV-2 infection in treatment trials of REGN10933+REGN10987 have demonstrated intact IgG responses to SARS-CoV-2 antigens.

However, it is possible that mAbs could meaningfully alter immune responses to vaccination. In light of this possibility, the other primary objective of this study is to understand the optimal time interval between mAb therapeutics and COVID-19 vaccinations. As a precautionary measure, the CDC has recommended a 90-day deferral period prior to vaccination in those who have received passive antibody therapy for COVID-19 treatment. The CDC has also recommended a 30-day deferral period prior to vaccination in those who have received passive antibody therapy for post-exposure prophylaxis. These recommendations were based on the estimated half-life of such products and the anticipated period of protection against infection when receiving anti-SARS-CoV-2 monoclonal antibodies for post-exposure prophylaxis or reinfection when receiving passive antibody therapy for treatment (CDC, 2021).

In this study, several additional doses levels below 1200 mg will be administered at day 1 (Figure 1 and Table 2). Sequentially lower dose levels were chosen as a means to vary the concentration of REGN10933+REGN10987 that exists at the time of Moderna mRNA-1273 vaccination. This method is intended to simulate various time intervals that could occur between administration of REGN10933+REGN10987 at 1200 mg and vaccination with Moderna mRNA-1273. This approach – altering the dose level rather than the time interval – was selected because REGN10933+REGN10987 concentration (and not time) is the key factor impacting the likelihood of altering vaccine responses. Moreover, the approach is operationally more feasible, and (by avoiding the need to test variable and potentially lengthy time intervals) lowers the likelihood of subjects becoming exposed to SARS-CoV-2 exposure during the study, which would confound the interpretation of results. Additional information regarding the selection of dose levels in this study is provided in Section 3.2.2.

Taken together, the primary objectives in this study are intended to provide information that may guide physicians and public health agencies in making evidence-based recommendations on the usage of the Moderna mRNA-1273 COVID-19 vaccine in the setting of REGN10933+REGN10987 therapy or prevention. As COVID-19 vaccines employing S protein

neutralization as their mode of action are likely to produce comparable antibody responses and protective immunity (an assumption supported by some initial experimental data for some vaccines (Garcia-Beltran, 2021) it is anticipated that the data generated from this study can potentially be extrapolated to the general case of S-protein-based COVID-19 vaccines given in the setting of mAbs targeting the S protein RBD.

3.2.1.3. Selection and Interpretation of Primary Endpoint

Although quantitative correlates of protective immunity against SARS-CoV-2 are not yet established, the presence of serum neutralizing antibodies has been shown to correlate with protection from viral reinfection for other respiratory viruses, including influenza virus (Verschoor, 2015) and respiratory syncytial virus (Kulkarni, 2018). Neutralizing antibody titers are accepted as a general functional biomarker of the endogenous ability to block viral infection of target cells in vivo (Jackson, 2020). In the absence of clear correlates of vaccine-induced protection against COVID-19, reduced neutralization can serve as a useful benchmark to interpret any observed impact of mAb therapy on the development of an immune response to Moderna mRNA-1273 vaccine. Accordingly, the primary objective will be assessed by quantifying endogenous neutralizing antibody titers following vaccination administered with or without REGN10933+REGN10987. While the threshold of SARS-CoV-2-neutralizing antibody titers associated with meaningful clinical efficacy in treating or preventing COVID-19 are currently unknown, this study is designed with a sufficient sample size to provide a minimal detectable difference of 0.15 log (refer to Section 11.2). This precision is considered adequate to meet the aims of this phase 2 study (ie, to both quantify the magnitude of effect for the primary endpoint and to allow assessment of the safety and tolerability of the Moderna mRNA-1273 vaccine when administered with REGN10933+REGN1098).

The primary endpoint will be assessed during the vaccine response assessment period, which includes the first 56 days after the first dose of Moderna mRNA-1273 (Section 4.1 and Section 6.1.1). SARS-CoV-2-neutralizing antibodies induced by Moderna mRNA-1273 vaccine can be detected as early as 2 weeks after the first vaccine dose, with titers peaking on day 36 (35 days after the first dose and one week after the second dose of the vaccine), and remaining at peak levels at day 57 and day 119 (pseudovirus serum neutralizing infectious dose 50 [ID_{50}] titers between 256 to 1024) (Jackson, 2020) (Widge, 2021). Assessing the primary endpoints after 56 days of the first dose of vaccine will thus maximize the ability to detect the effect of mAb administration on vaccine responses (Jackson, 2020). Additional analyses of neutralizing antibody titers at approximately 6 months, 9 months, and 1 year after vaccine administration will assess long-term/memory immune response to SARS-CoV-2 following vaccination with Moderna mRNA-1273.

An open-label design was chosen for this study, as it is considered appropriate and sufficient for achieving the primary objective, as well as the other pharmacodynamic objectives, of the study.

3.2.1.4. Selection of Moderna mRNA-1273 for Vaccine Response Analysis

The primary aim of this study is to evaluate the impact of REGN10933+REGN10987 on the induction of endogenous neutralizing immune responses to Moderna mRNA-1273. Moderna mRNA-1273 COVID-19 vaccine has demonstrated sufficient safety, tolerability and efficacy to receive EUA for active immunization against SARS-CoV-2 in individuals ≥18 years of age

(Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022). The vaccine was shown to elicit robust, dose-dependent neutralizing titers against full-length S protein and against the S protein RBD, when measured using a pseudotyped lentivirus (PsVNA) assay (Jackson, 2020), and in a phase 3 study of 30,420 volunteers, reduced the rates of symptomatic COVID-19 illness by over 90% compared to placebo (Baden, 2020). The robust neutralizing titers observed in clinical studies are anticipated to provide an opportunity for evaluating any impact of REGN10933+REGN10987 on immune response to vaccine. Any alteration of neutralization that may be observed in this trial will require further study.

3.2.1.5. Selection of Neutralizing Titer Assay

Serum neutralizing titers to Moderna mRNA-1273 vaccine will be assessed by a recombinant Vesicular Stomatitis Virus (rVSV) encoding SARS-CoV-2 S protein-based method (Vandergaast, 2020), similar to the assay reported in published reports of mRNA-1273 vaccine (Jackson, 2020) (Widge, 2021). The assay will be further validated with an additional anti-idiotype antibody step to block interference of REGN10933+REGN10987 in the measurement of the endogenous response to the vaccine. The impact of REGN10933+REGN10987 neutralizing Ab responses to S proteins from other viral variants may also be studied, if assays become available.

3.2.1.6. Secondary and Exploratory Analyses of Immune Response

It is possible that exogenous mAb treatments could skew or otherwise alter the antigen specificity of endogenous antibody responses elicited by Moderna mRNA-1273 vaccine. SARS-CoV-2 binding antibody assessments to S-protein trimer and S1 RBD will be performed using a Meso Scale Diagnostics (MSD) kit that has been used to measure neutralizing antibody responses in Phase 3 vaccine trials with Moderna mRNA-1273. The assay will be adapted with an anti-idiotype step to block the interference of REGN10933+REGN10987 with the measurement of endogenous antibodies.

In order to fully characterize the possible effects of REGN10933+REGN10987 on immune responses to Moderna mRNA-1273, we will evaluate cellular immune responses. Additional exploratory assays may be used to measure immunoglobulin titers to specific SARS-CoV-2 antigens (such as further epitope mapping of endogenous vaccine response) following vaccination. Similarly, B-cell responses following vaccination could reveal subtle immunologic effects of mAb therapy on vaccine response. To this end, the study will explore circulating B cell response specific to SARS-CoV-2 S trimer protein, RBD, and other spike subdomains. Additional analyses of T cell immune responses to Moderna mRNA-1273 in the presence of REGN10933+REGN10987 will also be performed and may reveal important mechanistic insights into any observed immune interaction.

Although the global emergence of variants has occurred only relatively recently in the history of the pandemic, emerging data suggest that they pose a significant threat to the clinical efficacy of some vaccines and therapies (AstraZeneca, 2021) (FDA, 2021). Recent evidence suggests that neutralizing humoral immunity induced by Moderna mRNA-1273 vaccination is reduced against specific SARS-CoV-2 variants (ie, B.1.351) (Garcia-Beltran, 2021). In this study, exploratory studies may be conducted to understand if REGN10933+REGN10987 alters the neutralization capacity seen with these viral variants after vaccination.

3.2.1.7. Study Population

The population for this study includes healthy volunteers who are both seronegative and RT-PCR negative for SARS-CoV-2 at screening/baseline, as this will maximize the ability to measure any effects of REGN10933+REGN10987 on immune responses to Moderna mRNA-1273 vaccine. Randomization will be stratified by age (<65 years versus ≥65 years), as older individuals may be less likely to have robust humoral immunity following vaccination and more likely to benefit from mAbs in the prevention or treatment of COVID-19.

3.2.1.8. Safety and Tolerability

REGN10933+REGN10987, when given concomitantly or in temporal proximity to Moderna mRNA-1273, is reasonably expected to be well-tolerated in healthy volunteers (see Section 3.1). Nevertheless, this study will evaluate safety and tolerability of REGN10933+REGN10987 and Moderna mRNA-1273, including assessment of IRR (REGN10933+REGN10987) as well as ISR and hypersensitivity reactions (REGN10933+REGN10987 and Moderna mRNA-1273; see Section 4).

As a precautionary safety measure, a follow-up phone call will be made within 24 hours after study drug and vaccine administration, for subjects receiving these concomitantly (see Section 9.2.2).

3.2.1.9. Use of Enrollment Waves

During the screening/baseline period, subjects will be assigned by each site to different enrollment waves, which are used to group study arms. The enrollment waves are staggered (eg, effort should be done so that study day 15 for wave 1 should occur on the same day as study day 1 for wave 2; see Figure 2). The primary intent of this staggering is to increase the number of study subjects who can be scheduled for vaccination on the same day at each site, and thus avoid or minimize the potential for unused doses of COVID-19 vaccine.

Although assignment to enrollment waves will be performed by the sites, assignment to study arms within each wave will occur via randomization. To minimize the potential for bias in study arm assignment, each wave will include a separate vaccine-only control arm, included as part of the randomization scheme. In addition, sites will be instructed to make every effort to balance assignment into each wave according to age, the baseline characteristic that is considered to have the greatest potential impact on susceptibility of mAb-mediated interference to vaccine response.

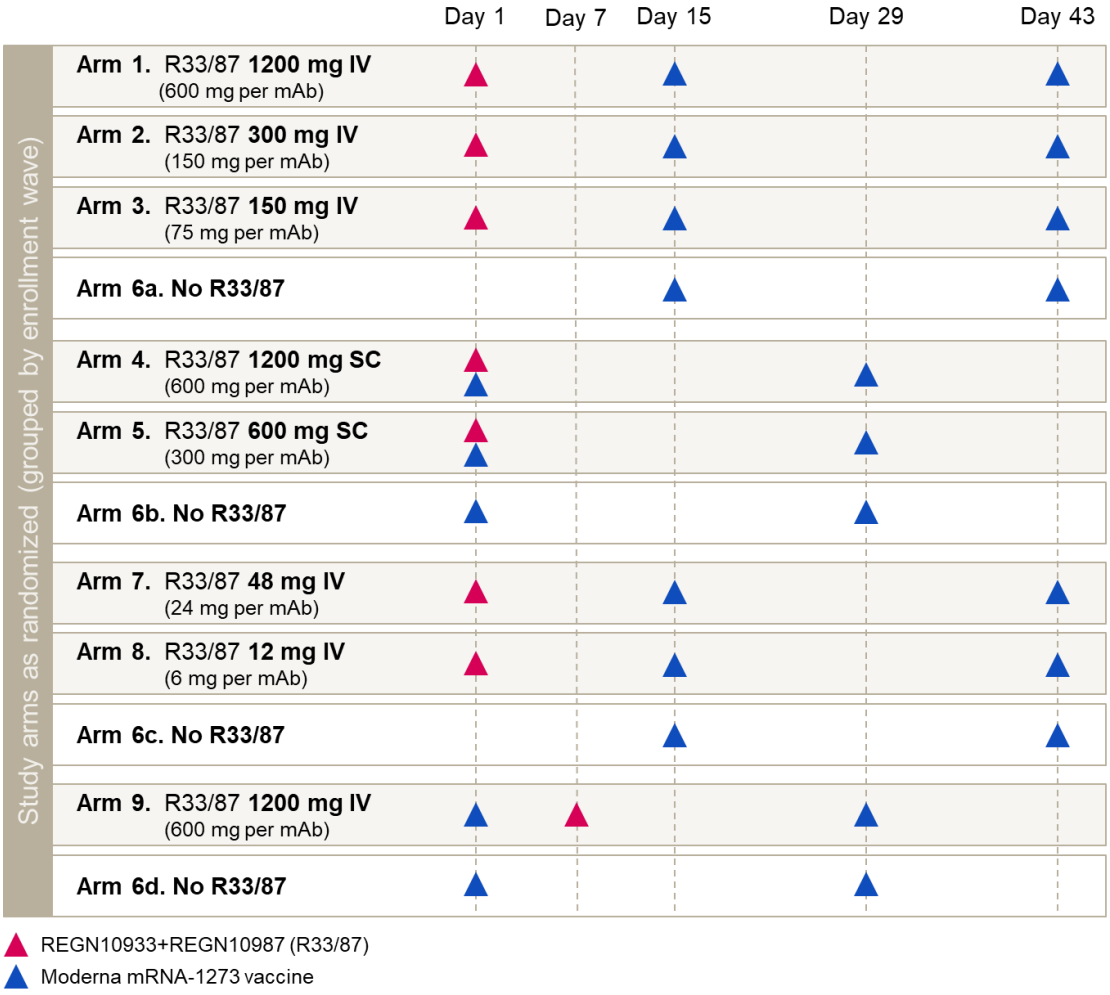
Refer to Section 8.5 for additional information on site-managed assignment to enrollment waves and subsequent randomization to study arms.

3.2.2. Rationale for Dose Selection

This parallel group study will utilize 12 study arms, of which 8 will receive single-dose administration of REGN10933+REGN10987 and administration of the Moderna mRNA-1273 COVID-19 vaccine (Figure 1) before, after or concurrently with REGEN-COV administration. Study arms 6a, 6b, 6c and 6d will only receive the vaccine.

For all study arms that include IV administration of REGN10933+REGN10987 followed by Moderna mRNA-1723, a 14-day interval was chosen to ensure that mAb concentrations in serum are in the post-distribution phase, and therefore representative of concentrations in equilibrium with relevant peripheral tissues (ie, the site of a potential immune interaction).

Figure 1: Dose Administration by Study Arm



3.2.2.1. Study Arm 1 and Arm 9 (1200 mg IV)

REGN10933+REGN10987 1200 mg IV (600 mg per mAb) was selected as a potential use case scenario based on clinical efficacy data in treatment of COVID-19 (Section 3.3.1).

The rationale for study arm 9 (administration of REGN10933+REGN10987 after the first dose of Modern mRNA-1723 vaccine) is provided in Section 3.2.1.1.

3.2.2.2. Study Arm 2 (300 mg IV), Arm 3 (150 mg IV), Arm 7 (48 mg IV), and Arm 8 (12 mg IV)

As outlined in Section 3.2.1.3, one of the primary objectives of this study is to identify time intervals between administration of REGN10933+REGN10987 and Moderna mRNA-1273 that may mitigate any observed potential alteration of vaccine efficacy, and to utilize various dose levels as a means of simulating these time intervals. To this end, a preliminary population pharmacokinetics (PopPK) model was developed based on available REGN10933 and REGN10987 concentration data from studies COV-2067 and COV-2069. The PopPK model was

used to determine dose levels of REGN10933+REGN10987 that would achieve concentrations in serum on study day 15 (when Moderna mRNA-1723 is administered), that approximate particular time intervals following a 1200 mg IV dose (Section 3.2.1.2).

Table 1 provides the estimated time intervals for each of the study arms used for these anchoring analyses. As an example of this simulation, 300 mg IV of REGN10933+REGN10987 administered on day 1, followed by the administration of the first dose of Moderna mRNA-1723 on day 15, simulates a scenario in which an individual receives a single 1200 mg IV dose of REGN10933+REGN10987, and then begins their vaccination with Moderna mRNA-1723 approximately 60 days later.

Table 1: Population Pharmacokinetics Modeling of Simulated Study Days Following 1200 mg IV Dose

REGN10933+REGN10987 Dose Administered	Study Day of First Moderna mRNA-1723 Dose	Simulated Study Day Following 1200 mg IV Dose
300 mg IV (150 mg per mAb)	15	57
150 mg IV (75 mg per mAb)	15	85
48 mg IV (24 mg per mAb)	15	113
12 mg IV (6 mg per mAb)	15	169

3.2.2.3. Study Arm 4 (1200 mg SC) and Arm 5 (600 mg SC)

REGN10933+REGN10987 1200 mg SC (600 mg per mAb) was selected as a potential use case scenario based on clinical efficacy data in prevention of COVID-19. The 600 mg SC (300 per mAb) dose was also chosen as a potential use case, based on virologic efficacy observed at that dose level (Section 3.3.1). The rationale for concomitant administration of vaccine is provided in Section 3.2.1.1.

3.3. Risk-Benefit

Risk-benefit is provided separately for REGN10933+REGN10987 (Section 3.3.1), Moderna mRNA-1273 vaccine (Section 3.3.2), and REGN10933+REGN10987 administered with COVID-19 vaccines (Section 3.3.3).

3.3.1. Risk-Benefit for REGN10933+REGN10987

The anticipated risks and benefits of casirivimab and 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.

Intravenous Administration of Casirivimab+Imdevimab in Clinical Trials. In COV-2067, the phase 3 outpatient treatment trial, a single intravenous dose of casirivimab and 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 and imdevimab at 8000 mg and 2400 mg IV doses (Weinreich, 2021a).

Subcutaneous Administration of Casirivimab+Imdevimab in Clinical Trials. In COV-2069, the phase 3 prevention trial in those at high risk of infection by a household contact, a single subcutaneous dose of casirivimab and 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 and imdevimab (1200 mg) reduced (relative to placebo) progression to symptomatic disease by 31.5%, and reduced the duration of symptoms in those that developed symptomatic infections. Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (1%), but no injection-site reactions in the study were grade 3 or above (O'Brien, 2021a).

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

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

Identified Risks. As with other protein therapeutics, hypersensitivity reactions, including acute infusion-related reactions (IV administration) or injection site reactions (SC administration), may develop after study drug administration. Hypersensitivity reactions, including anaphylaxis, infusion-related reactions or injection site reactions, have been observed in patients who received REGN10933+REGN10987.

Potential or Theoretical Risks. The important potential risks of REGN10933+REGN10987 are the clinical consequences of immunogenicity, embryo-fetal toxicity and antiviral resistance.

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

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier and are present in breast milk; therefore,

the REGN10933+REGN10987 combination therapy have the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of REGN10933 and REGN10987, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of REGN10933 or REGN10987 was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of the combination of REGN10933+REGN10987 therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

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

REGN10933+REGN10987 combination therapy was strategically designed to be a combination therapy of 2 non-competing antibodies that can simultaneously bind distinct epitopes of the SARS-CoV-2 S protein to reduce the likelihood of antiviral resistance and provide coverage against circulating variants. However, there is a potential risk of treatment failure due to circulating or treatment-emergent SARS-CoV-2 variants that are resistant to REGN10933+REGN10987 combination.

Ongoing sequencing analyses of nasopharyngeal swab samples from sponsor-conducted clinical studies have found no evidence that the clinical use of REGN10933+REGN10987 leads to the selection of escape (treatment emergent) variants in REGN10933+REGN10987-binding epitopes, within the RBD, or other regions of the S protein.

The in vitro neutralization potency of REGN10933+REGN10987 and its individual components is continuously monitored against S protein variants, including VUS, variants identified in in vitro escape studies, and variants from publicly available SARS-CoV-2 genome data (eg, GISAID). REGN10933+REGN10987 demonstrates in vitro neutralization activity below the limit of quantitation against the Omicron variant, and it is unlikely that REGN10933+REGN10987 will be active against this variant. However, REGN10933+REGN10987 retains activity against the Alpha, Beta, Gamma, Delta, Epsilon, Iota, Kappa, and Mu variants. It is not known how in vitro neutralization data correlate with clinical outcomes.

Decisions regarding the use of REGN10933+REGN10987 should take into consideration what is known about the characteristics of circulating variants including regional or geographical differences and available information on REGN10933+REGN10987 susceptibility patterns.

There may also be a potential for the REGN10933+REGN10987 combination to interfere with an individual's endogenous immune response to either SARS-CoV-2 infection or to effectiveness of vaccination against COVID-19. Refer to Section 3.3.3 for more information.

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances Fc gamma receptor (FcγR)-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as

this may play a role in protecting against viral infection (Yasui, 2014), and 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 receiving REGN10933+REGN10987 will have safety follow-up assessments during the drug elimination period.

3.3.2. Risk-Benefit for Moderna mRNA-1273 Vaccine

Always refer to the latest EUA Fact Sheet (Moderna COVID-19 Vaccine [Patient Fact Sheet], 2022) . Information from the current version of the Fact Sheet (dated 07 January 2022) is provided below:

Benefit. In an ongoing clinical trial, Moderna mRNA-1273 vaccine has been shown to prevent COVID-19 following 2 doses given 1 month apart. The duration of protection against COVID-19 is currently unknown.

Risks.

There is a remote chance that the Moderna COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Moderna COVID-19 Vaccine. For this reason, the vaccination provider may ask the vaccine recipients to stay at the place where they received the vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of face and throat
- A fast heartbeat
- A bad rash all over body
- Dizziness and weakness

Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the Moderna COVID-19 Vaccine, more commonly in males under 40 years of age than among females and older males. In most of these people, symptoms began within a few days following receipt of the second dose of the Moderna COVID-19 Vaccine. The chance of having this occur is very low. The vaccine recipients should seek medical attention right away if they have any of the following symptoms after receiving the Moderna COVID-19 Vaccine:

- Chest pain
- Shortness of breath
- Feelings of having a fast-beating, fluttering, or pounding heart

Side effects that have been reported in a clinical trial with the Moderna COVID-19 Vaccine include:

- Injection site reactions: pain, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling (hardness), and redness

- General side effects: fatigue, headache, muscle pain, joint pain, chills, nausea and vomiting, fever and rash

Side effects that have been reported during post-authorization use of the Moderna COVID-19 Vaccine include:

- Severe allergic reactions
- Myocarditis (inflammation of the heart muscle)
- Pericarditis (inflammation of the lining outside the heart)
- Fainting in association with injection of the vaccine

These may not be all the possible side effects of the Moderna COVID-19 Vaccine. Serious and unexpected side effects may occur. The Moderna COVID-19 Vaccine is still being studied in clinical trials.

3.3.3. Risk-Benefit for REGN10933+REGN10987 Administered With COVID-19 Vaccines

To date, REGN10933+REGN10987 has not been studied systematically in the clinical development program with respect to concomitant (or temporally proximal) administration with vaccines (COVID-19 or otherwise). There are currently no published data on the safety and efficacy of COVID-19 vaccines in persons who received monoclonal antibodies as part of COVID-19 treatment. However, in a study of healthy adult subjects who received multiple SC doses of REGN10933+REGN10987 (R10933-10987-HV-2093), 54 subjects were noted (in blinded analysis) to have COVID-19 vaccination in close temporal proximity to study drug administration and thought to still be in therapeutic range for REGN10933+REGN10987. In this subset of subjects, no SAEs or hypersensitivity reactions were reported post vaccination. Similarly, study R10933-10987-COV-2069 (COV-2069) is a phase 3 randomized placebo-controlled trial assessing the safety and efficacy of REGN10933+REGN10987 in preventing COVID-19 after high risk exposure. During this study, 99 subjects received COVID-19 vaccination with few reported AE and no SAEs or hypersensitivity reactions. Although HV-2093 and COV-2069 were not systematically designed studies to assess vaccine-drug interaction, these results suggest that REGN10933+REGN10987 administered with a COVID-19 vaccine is reasonably expected to be well-tolerated in healthy adult subjects.

Little or no impact is anticipated on the safety profile of the REGN10933+REGN10987 combination when COVID-19 vaccine is given concomitantly or in temporal proximity, although safety and tolerability will nevertheless be evaluated in this study. Similarly, this study will also evaluate if concomitant administration (or administration in temporal proximity) may impact efficacy of COVID-19 vaccines to induce the desired immunologic response (positively or negatively).

All risks described in the sections above for individual treatments (Section 3.3.1 and Section 3.3.2) are considered relevant for the administration of REGN10933+REGN10987 and Moderna mRNA-1273 vaccine concomitantly or in temporal proximity. Theoretically, there may be a potential for the REGN10933+REGN10987 combination to interfere with an individual's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19 in such setting. The objective of this study is to determine if this theoretical risk is identified and, if so, to quantify the

risk. To mitigate the potential risk of such interference, an allowance is provided for subjects to receive additional vaccination if interference is identified (Section 6.1). Similarly, there could be risk of hypersensitivity reactions when REGN10933+REGN10987 is administered within close proximity of Moderna mRNA-1273 vaccine. In this study, the risk of hypersensitivity will be monitored closely during study visits. Theoretical risk of ADE also remains applicable. However, currently ADE has not come up as a safety concern for REGN10933+REGN10987 in the long-term safety follow-up in the ongoing clinical studies. We will continue to monitor ADE as a theoretical risk in this study like all other ongoing clinical studies.

Summary. In summary, based on prior experience with other human mAbs against exogenous targets, the available preclinical data for REGN10933+REGN10987 to date, and the unmet need for a SARS-CoV-2 therapy that can be given concomitantly (or in temporal proximity) to COVID-19 vaccination, it is the opinion of the Sponsor that the overall risk-benefit balance for REGN10933+REGN10987 given concomitantly with Moderna mRNA-1273 is acceptable to allow evaluation of this mAb combination in the adult population planned for this study.

4. ENDPOINTS

4.1. Primary Endpoints

The primary endpoints are:

- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to the SARS-CoV-2 S protein assessed 56 days after the first dose of Moderna mRNA-1273 vaccine in individuals who receive high-dose (1200 mg) REGN10933+REGN10987 compared to vaccine alone
- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to the SARS-CoV-2 S protein assessed 56 days after the first dose of Moderna mRNA-1273 vaccine in individuals who receive submaximal dose levels of REGN10933+REGN10987 (less than 1200 mg) compared to vaccine alone

4.2. Secondary Endpoints

The secondary endpoints are:

- Absolute values, change from baseline, and percentage change from baseline in concentrations of vaccine-induced antibodies to the following SARS-CoV-2 antigens over time:
  - Anti-S protein
  - Anti-RBD
  - Other S protein subdomains (including S1, S2, and NTD)
- 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to SARS-CoV-2 S protein assessed over time after the first dose of Moderna mRNA-1273 vaccine

- Proportion of subjects with treatment-emergent adverse events (TEAEs) throughout the study
- Proportion of subjects with treatment-emergent serious adverse events (SAEs) throughout the study
- Proportion of subjects with infusion-related reactions (grade ≥2) to REGN10933+REGN10987 through day 4 post-infusion
- Proportion of subjects with injection site reactions (grade ≥3) to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 4 post-injection
- Proportion of subjects with hypersensitivity reactions (grade ≥2) to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 29 post-infusion or post-injection (as applicable)
- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity, as measured by anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to REGN10933 and REGN10987

4.3. Exploratory Endpoints

The exploratory endpoints are:

- Absolute percentages, change, and percentage change from baseline of blood-derived memory T cell responses specific to SARS-CoV-2 viral peptides over time
- Absolute percentages, change, and percentage change from baseline of blood-derived B cell responses specific to SARS-CoV-2 S protein, RBD, and other S protein subdomains over time
- Viral variant characteristics of SARS-CoV-2 in subjects who become infected post-baseline

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Pharmacodynamic and Other Biomarker Variables

Primary, secondary, and exploratory endpoint variables may include, but are not limited to, the following: parameters reported in neutralization antibody titer assays to SARS-CoV-2 variants, binding antibody assays to SARS-CoV-2 antigens, virus-specific T cell and B cell assays, assays for detection of antibodies binding to RBD elicited post-vaccination that compete with REGN10933 and/or REGN10987, virology tests, and virus sequencing for variant determination.

5.3. Safety Variables

Safety variables include recording, measurements, or laboratory test results for individual subjects of the following: Adverse events (AEs), vital signs (including temperature, blood pressure, heart rate, and respiratory rate), targeted physical examination findings, and results of laboratory tests (including hematology, blood chemistry, urinalysis, and pregnancy test).

5.4. Pharmacokinetic Variables

The variables are the concentration of REGN10933 and REGN10987 in serum, and time. Samples will be collected at the visits specified in the Schedules of Events (Section 9.1).

5.5. Immunogenicity Variables

The study drug immunogenicity variables are ADA status, titer, NAb status, and time point/visit. Samples will be collected at the visits specified in the Schedules of Events (Section 9.1).

6. STUDY DESIGN

This study is a phase 2, randomized, open-label, parallel group study in healthy adult volunteers to assess the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine when administered with REGN10933+REGN10987.

6.1. Study Description and Duration

The study consists of 3 periods: a screening/baseline period, a vaccine response assessment period, and a follow-up period. The study design is depicted in Figure 2 and Figure 3; study treatment assignment is depicted in Figure 1. The Schedules of Events can be found in Table 3 (enrollment wave 1 [study arms 1, 2, 3, and 6a] and enrollment wave 3 [arms 7, 8, and 6c]), Table 4 (enrollment wave 2 [study arms 4, 5, and 6b]), and Figure 3 (enrollment wave 4 [arms 9 and 6d]).

Subjects will be assessed for eligibility during the **screening/baseline period**, which may occur up to 21 days prior to day 1. To be eligible for the study, subjects must be confirmed negative for current or past SARS-CoV-2 infection by both RT-PCR and serology tests (refer Section 7.2.2 for exclusion criteria).

During this period, subjects will also be assigned to an enrollment wave, as described in Section 8.5).

On day 1, eligible subjects will be randomized to a study arm (1 of 12) within their assigned enrollment wave. Subjects randomized to study arms 1 through 5 or 7 through 9 will receive an IV infusion or SC injection of the study drug (REGN10933+REGN10987) on day 1 or day 7. Subjects in arms 6a to 6d (the control arms) will not receive any study drug. The first dose of the vaccine will be administered on day 1 or day 15, based on study arm assignment at randomization (Figure 1).

All subjects will receive the second dose of the vaccine 28 days after their first dose of the vaccine in accordance with the EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022) (refer to Section 3.2.1 for rationale). Refer to Section 8.5 for more information on dose levels and timing of administration.

The **vaccine response assessment period** represents the time period of the primary analysis (Section 4.1). For study arms 1, 2, 3, 7, 8, 6a, and 6c, this period includes up to study day 71; for study arms 4, 5, 9, 6b, and 6d, the period includes up to day 57. Following this assessment period, subjects will enter a **follow-up period** lasting up to 10 months.

Throughout the study, blood samples will be collected to assess whether the study drug impacts the ability of the vaccine to elicit neutralizing antibody titers against the SARS-CoV-2 S protein, and to understand any impact on vaccine-induced humoral and cellular immune responses to various S protein epitopes. Additional details are provided in Section 9.2.3.

Subjects will also have blood samples taken at select visits for drug concentration, immunogenicity, and exploratory analyses, and will be monitored for AEs (including AESIs) during in-person visits (refer to Section 10.1 for recording and reporting requirements). For subjects in study arms 4 and 5 (receiving the study drug and vaccine on the same day), a phone call will be made within 24 hours following study drug and vaccine administration on day 1 for AE collection.

The last study visit will take place approximately 1 year after the first dose of the vaccine.

Vaccine booster sub-study. All subjects who have not already received the COVID-19 vaccine booster will be offered an optional booster vaccination dose ≥5 months after completing the primary COVID-19 vaccination series and >35 days (ie, until study day 345 for subjects in arms 1, 2, 3, 6a, 6c, 7 and 8 and until study day 331 for subjects in arms 4, 5, 6b, 6d and 9) before the end of the main study. Blood samples for possible analysis will be collected pre- and post-booster administration.

Figure 2: Study Flow Diagram (Enrollment Waves 1 and 2)

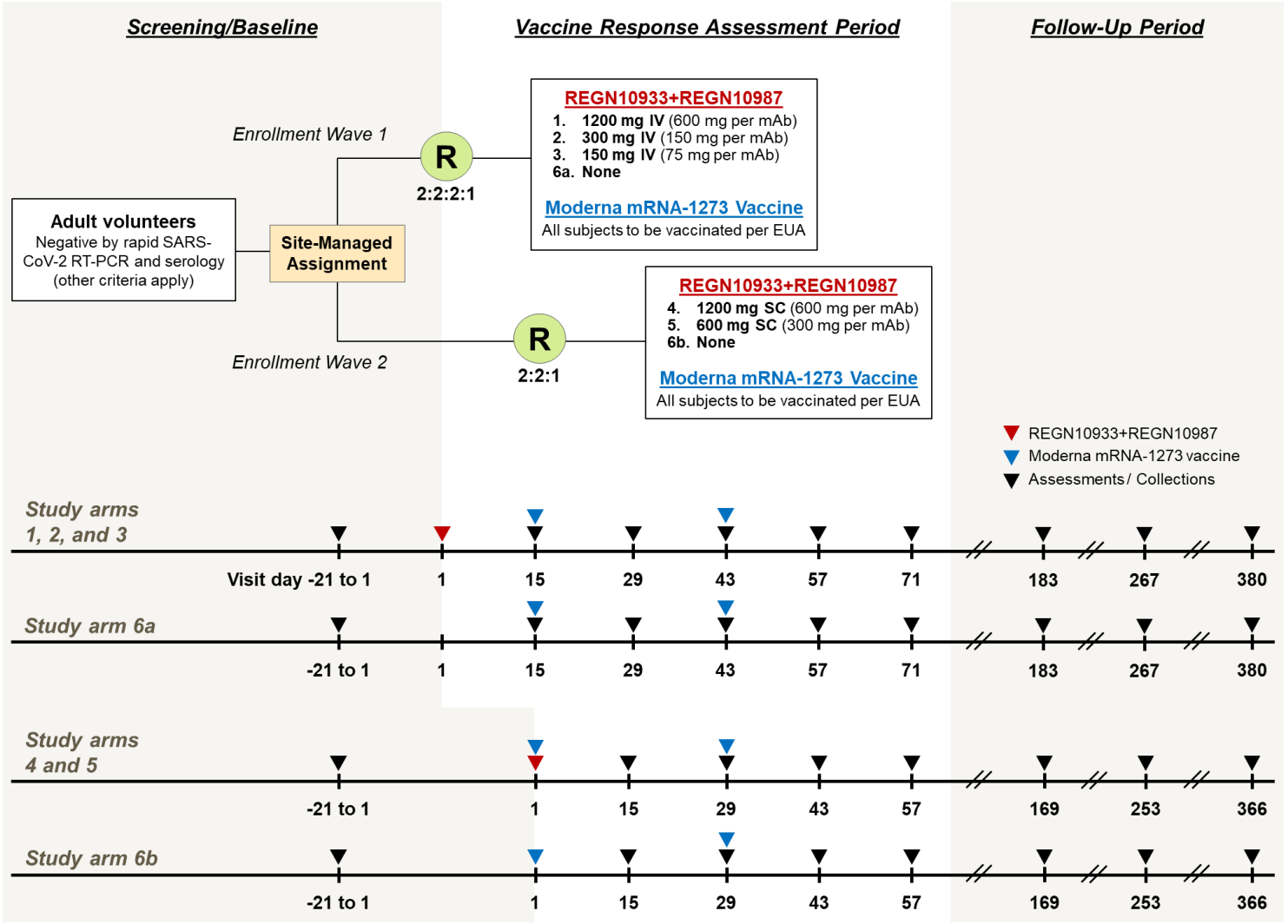
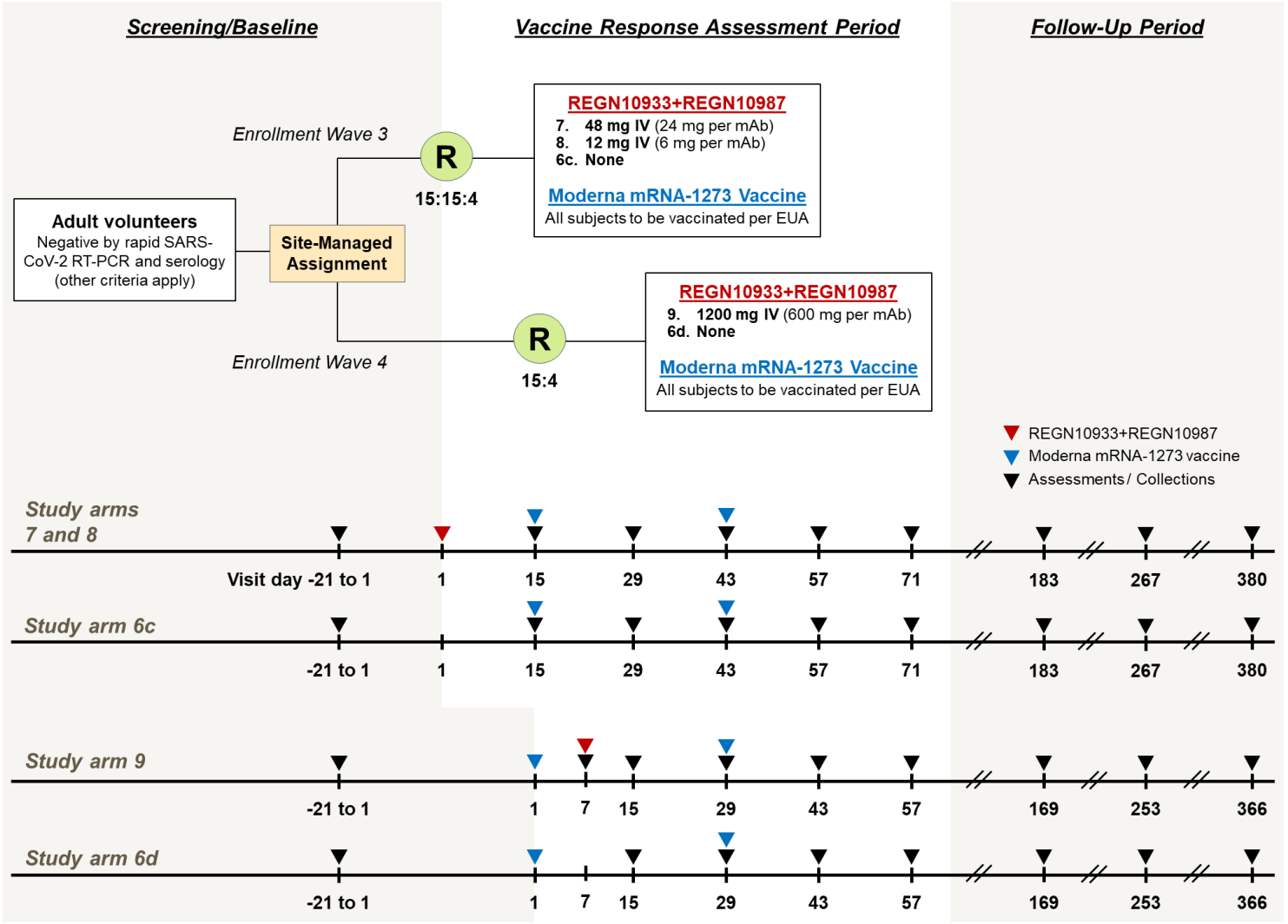


Figure 3: Study Flow Diagram (Enrollment Waves 3 and 4)



6.1.1. Risk Minimization for SARS-CoV-2 Infection and Transmission

To minimize the risk of acquiring or transmitting SARS-CoV-2 infection during the study, subjects will be asked to comply with all precautionary measures related to COVID-19 stipulated within site policies and local public health guidelines or requirements.

Subjects 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 positive SARS-CoV-2 testing results or symptoms/signs potentially related to COVID-19. Subjects presenting with acute illness should be medically managed according to local standard of care and per the discretion of the treating physician. Refer to Section 8.3.3 for additional guidance concerning COVID-19 vaccine deferral or discontinuation.

Subjects with laboratory confirmed SARS-CoV-2 infection should be informed as soon as possible, and should undergo medical isolation per local guidelines and CDC guidance on medical isolation (CDC, 2021) , to prevent contact with others and reduce the risk of further transmission.

6.1.2. Sample Collection and Visit Scheduling for Subjects with Suspected COVID-19 Symptoms or Positive SARS-CoV-2 Test

For subjects with signs or symptoms consistent with COVID-19, or those who obtain a positive SARS-CoV-2 RT-PCR test result from another testing location, every effort should be made to obtain a sample for SARS-CoV-2 rapid RT-PCR testing as soon as possible, either during an unscheduled visit or during a planned schedule visit (whichever is sooner). All subjects with suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection will continue to follow their respective Schedule of Events (Section 9.1), as feasible according to local guidelines, site policies, and/or CDC guidance on medical isolation (CDC, 2021) . Every effort should be made to obtain subsequent rapid RT-PCR testing samples as indicated in the Schedule of Events as feasible according to local guidelines, site policies, and/or CDC guidance on medical isolation (CDC, 2021) . Every effort should be made to obtain subsequent rapid RT-PCR testing samples as indicated in the Schedule of Events. These samples will be banked for viral sequencing.

6.1.3. Study Stopping Rules

A Regeneron team will monitor the safety data on an ongoing basis to assess the risk-benefit profile of REGN10933+REGN10987 administered with Moderna mRNA-1273 vaccine. The team may be comprised of the medical/study director, a Global Patient Safety representative, representatives from Biostatistics and Data Management, Clinical Operations, and Regulatory Affairs.

The monitoring team will also include at least 2 medical officers from the National Institutes of Health (NIH). One officer will serve as the primary representative, with a second officer serving as an alternate representative as needed.

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 Regeneron Safety Oversight Committee (RSOC), which will include senior clinical, regulatory, and pharmacovigilance leaders at Regeneron. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

Reasons for premature withdrawal from the study are described in Section 7.3. Study drug and vaccine discontinuation rules are described in Section 8.3.2 and Section 8.3.3.

6.1.4. 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).

6.2. Planned Interim Analysis

Formal interim analysis may be conducted. The Sponsor may view and report on the data as it is accumulated.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

Up to approximately 286 subjects are planned to be enrolled. Refer to Section 11.2 for the justification of sample size.

7.2. Study Population

Eligible subjects for this study consist of healthy adult volunteers who are between 18 years to 90 years of age (inclusive) who are negative at screening for both SARS-CoV-2 infection and endogenous anti-SARS-CoV-2 antibodies.

Every effort should made to enroll older subjects, such that 30% to 50% of subjects enrolled at each site are ≥65 years of age. Efforts should also be made to enroll subjects representative of the demographics (eg, race and ethnic distribution) of those at risk for COVID-19 in the region where the study site is located.

7.2.1. Inclusion Criteria

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

1. 18 years to 90 years of age (inclusive) at the signing of informed consent
2. Healthy or has chronic medical condition(s) that is (are) stable and well-controlled in the opinion of the investigator and that are not likely to require significant medical intervention through the end of study
3. Willing and able to comply with study visits and study-related procedures, including compliance with site precautionary requirements related to SARS-CoV-2 infection and transmission
4. Willing and able to provide signed informed consent

7.2.2. Exclusion Criteria

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

1. Positive RT-PCR test result for SARS-CoV-2 infection at screening and/or baseline
2. Positive serology test result for anti-SARS-CoV-2 antibodies at screening
3. COVID-19 diagnosis, positive SARS-CoV-2 diagnostic test result, or positive SARS-CoV-2 serology test result at any time prior to screening
4. Previously received an investigational, authorized, or approved coronavirus vaccine (eg, SARS-CoV-2 vaccine, MERS-CoV vaccine)
5. Currently enrolled in, or has plans to enroll in, any interventional study to prevent or treat COVID-19
6. Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, mAbs, hyperimmune globulin)
7. Received intravenous immunoglobulin (IVIG) or blood products in the last 3 months
8. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by study participation
9. History of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric or neurological disease, as assessed by the investigator, that may confound the results of the study or pose an additional risk to the subject by study participation
10. Medically attended acute illness or hospitalization (ie, >24 hours) for any reason within 30 days prior to screening
11. History of heart failure hospitalization, diagnosis of a myocardial infarction, stroke, transient ischemic attack, unstable angina, percutaneous or surgical revascularization procedure (coronary, carotid, or peripheral vascular), or intracardiac device placement (eg, pacemaker) within 6 months prior to screening
12. Abnormal blood pressure (BP) at screening visit, as defined by diastolic BP >100 mm Hg and/or systolic BP >160 mm Hg

    Note: Blood pressure measurements may be repeated once during screening
13. Active bleeding disorder considered a contraindication to subcutaneous or intramuscular injection or phlebotomy
14. Regular alcohol consumption consistent with alcohol dependence or addiction, in the opinion of the investigator
15. Any malignancy within the past 5 years, except for basal cell or squamous epithelial cell carcinomas of the skin or carcinoma in situ of the cervix or anus, that have been resected, with no evidence of metastatic disease for 3 years

16. Immunosuppressive or immunodeficient state, asplenia or recurrent severe infections that, in the opinion of the investigator may confound the results of the study or pose an additional risk to the subject by study participation
17. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to screening (for corticosteroids, ≥20 mg/day of prednisone equivalent)
18. 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.
19. Known allergy or hypersensitivity to components of the study drug or vaccine
20. Treatment with another investigational drug within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to screening
21. Member of the clinical site study team and/or immediate family
22. Pregnant or breastfeeding women
23. Women of childbearing potential (WOCBP)[1] who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment and for at least 6 months after REGN10933+REGN10987 administration

    Highly effective contraceptive measures include:

    - Abstinence[2,3]
    - Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
    - Bilateral tubal ligation

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

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

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

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

24. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug follow-up period and for 6 months after REGN10933+REGN10987 administration: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for up to 6 months after REGN10933+REGN10987 administration.
25. Clinical history of myocarditis and/or pericarditis.

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 drug or vaccine are discussed in Section 8.3.

7.4. Replacement of Subjects

Subjects who do not receive their first dose of Moderna mRNA-1273 vaccine as assigned may be replaced.

8. STUDY DRUG AND COVID-19 VACCINE

8.1. Investigational Treatment (Study Drug)

In this study, the study drug (REGN10933+REGN10987) will be administered intravenously or subcutaneously as described in Section 8.5. Instructions on dose preparation are provided in the pharmacy manual. Refer to Section 9.2.2 for information on drug administration.

8.2. COVID-19 Vaccine

In this study, the vaccine (Moderna mRNA-1273) will be prepared and administered as described in the latest EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022). Refer to Section 8.5 for dose levels and method of treatment allocation; refer to Section 9.2.2 for information on vaccine administration.

8.3. Dose Modification and Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual subject is not allowed for REGN10933+REGN10987 or Moderna mRNA-1273.

8.3.2. Study Drug Discontinuation

Subjects receiving REGN10933+REGN10987 will receive a single dose of the study drug; study drug discontinuation is not applicable.

8.3.3. Vaccine Deferral or Discontinuation

In subjects who become infected, the timing of vaccine administration (either the first dose, second dose, or booster dose, as applicable) should be deferred according to the most recent CDC guidance (CDC, 2021) . Subjects who become pregnant will be counseled accordingly.

For applicable vaccine discontinuation rules, always refer to the latest Moderna mRNA-1273 vaccine EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022).

Vaccination will be permanently stopped or not administered in the event of:

- Serious or severe allergic reactions (grade ≥3) considered related to REGN10933+REGN10987 or Moderna mRNA-1273 vaccine

  Note: In case of mild to moderate allergic reactions (grade ≤2) considered related to REGN10933+REGN10987 or Moderna mRNA-1273 vaccine, vaccine discontinuation is up to the investigator's discretion.

- Subject withdrawal of consent

Subjects who permanently discontinue from Moderna mRNA-1273 vaccine should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study follow up visits per the Schedule of Events.

Subjects who permanently discontinue and who opt to withdraw from the study will be asked to complete study assessments described in Section 9.1.2.

If a subject requires a prohibited medication (Section 8.8.1) at any time during the study, the principal investigator should contact the Sponsor medical monitor (except for illness requiring prompt treatment). Based on the discussions, vaccination may either be continued or permanently discontinued.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous Infusion Reactions to the Study Drug

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.1) and graded using the grading scales as instructed in Section 10.2.4.

8.4.1.1. Interruption of the Intravenous Infusion

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

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

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

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

8.4.1.2. Termination of the Intravenous Infusion

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

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

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

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.4.2. Acute Injection Reactions to the Study Drug

8.4.2.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.1) 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.

8.4.2.2. Local Injection Site Reactions

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

8.4.3. Acute Injection Reactions to the Vaccine

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the vaccine. Always refer to the latest EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022) for additional information.

8.5. Method of Enrollment and Treatment Assignment

Site-managed assignment. At screening, eligible subjects will be assigned to an enrollment wave. The enrollment waves are intended to avoid or minimize the potential for unused doses of Moderna mRNA-1273 COVID-19 vaccine (refer to Section 3.2.1 for additional rationale). Every effort should be made by sites to avoid unused doses of vaccine.

Sites will manage the placement of subjects into each wave. Every effort should be made by the site to ensure balance of age (<65 years and ≥65 years) within each of the enrollment waves.

Randomization. At baseline (day 1), subjects will be randomized to the corresponding study arms in each wave as described in Table 2.

Randomization will be performed according to a computer-generated randomization scheme provided by an interactive web response system (IWRS) to a designated study pharmacist or a qualified designee.

Randomization will be stratified by age (<65 years versus ≥65 years).

Table 2: Study Treatment Assignment

Study Arm	Random-ization Ratio	Targeted Enrollment	Co-administered REGN10933+REGN10987 Combination Therapy	Moderna mRNA-1273 Vaccine*
Enrollment Wave 1				
1	2	30	1200 mg (600 mg of each mAb) IV on day 1	On day 15 and day 43
2	2	30	300 mg (150 mg of each mAb) IV on day 1	On day 15 and day 43
3	2	30	150 mg (75 mg of each mAb) IV on day 1	On day 15 and day 43
6a	1	15	None	On day 15 and day 43
Enrollment Wave 2				
4	2	30	1200 mg (600 mg of each mAb) SC on day 1	On day 1 and day 29
5	2	30	600 mg (300 mg of each mAb) SC on day 1	On day 1 and day 29
6b	1	15	None	On day 1 and day 29
Enrollment Wave 3				
7	15	30	48 mg (24 mg of each mAb) IV on day 1	On day 15 and day 43
8	15	30	12 mg (6 mg of each mAb) IV on day 1	On day 15 and day 43
6c	4	8	None	On day 15 and day 43
Enrollment Wave 4				
9	15	30	1200 mg (600 mg of each mAb) IV on day 7	On day 1 and day 29
6d	4	8	None	On day 1 and day 29

*Moderna mRNA-1273 vaccine will be administered as described on the EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022).
mAb=monoclonal antibody; SC=subcutaneous; IV=intravenous.

8.6. Blinding

This is an open-label study without blinding.

8.7. Logistics and Accountability for Study Drug and Vaccine

8.7.1. Packaging, Labeling, and Storage

Study Drug (REGN10933+REGN10987)

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.

Vaccine (Moderna mRNA-1273)

Vaccine will labeled and stored as described on the EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022).

8.7.2. Supply and Disposition of Study Drug

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.

8.7.3. Study Drug and Vaccine Accountability

All study drug and vaccine accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug and vaccine. 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.

8.7.4. Study Drug and Vaccine Compliance

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

8.8. Concomitant Medications

Any treatment administered from the time of the first dose of Moderna mRNA-1273 Vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first) to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.8.1. Prohibited Medications and Vaccines

The use of the following concomitant medications and vaccines may not require withdrawal of the participant from the study but may determine a subject's evaluability in the per-protocol analyses (Section 11.3):

- Investigational drugs
- Investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, mAbs, hyperimmune globulin)
- Any vaccine within 28 days prior to or after study drug administration, other than Moderna mRNA-1273 vaccine administered as part of this study

  Exceptions:
  - seasonal influenza vaccine is only prohibited within 14 days before or after study drug administration, or within 14 days before or after mRNA-1273 vaccine administration.
  - COVID-19 vaccine booster vaccinations are permitted. Subjects may receive a single booster vaccination (i.e. third COVID-19 vaccine administration) in the optional Vaccine Booster Sub-study (Section 6.1). COVID-19 vaccination boosters received outside of the study are permitted and should be recorded as a concomitant medication.

- Systemic medications that suppresses the immune system (as described in Section 7.2.2 #17), except for the treatment of COVID-19

8.8.2. Permitted Medications

Other than the prohibited medications and vaccines listed in Section 8.8.1, treatment with concomitant medications is permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor. Any medications used by the study subject should be captured in the concomitant medication eCRF.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

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Table 3: Schedule of Events for Arms 1, 2, 3, and 6a (Enrollment Wave 1) and Arms 7, 8, and 6c (Enrollment Wave 3)

Visit Period	Screening/Baseline				Vaccine Response Assessment					Follow-Up				
Study Day	-21 to 1				15[1]	29	43[1]	57	71	183	267	380	Unscheduled Visit	ET
	Screening	Pre-dose	Dose[1]	Post-Dose										
Days After the First Vaccine Dose						*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)					-1 to +3	±2	-1 to +3	±2	±2	±7	±14	±14		
Screening/Baseline and Key Laboratory Testing														
Inclusion/exclusion	X	X												
Informed consent	X													
Informed consent for optional FBR sub-study[2]	X													
Informed consent for optional PGx sub-study[2]	X													
Medical history	X													
Demographics	X													
Height and weight	X													
Pregnancy test (WOCBP)[3]	X[3]	X[3]			X		X						X	
SARS-CoV-2 rapid (local/POC) RT-PCR[4]	X[4]	X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	
SARS-CoV-2 rapid serology[5]	X[5]	X[5]												
SARS-CoV-2 serology (central lab)[5]		X[5]											X	
Enrollment Wave and Treatment Assignment														
Site-managed assignment[6]	X[6]													
Randomization[6]		X[6]												
Study Drug and Vaccine Administration														
REGN10933+REGN10987 (arms 1, 2, 3, 7, and 8 only)[7]			X[7]											
Moderna mRNA-1273 vaccine (arms 1, 2, 3, 7, 8, 6a, and 6c)[7]					X[7]		X[7]							
Biomarkers														
Serum for SARS-CoV-2 neutralization[8]		X			X	X	X	X	X	X	X	X	X	X
Serum for serology characterization[8]		X			X	X	X	X	X	X	X	X	X	X
Whole blood for PBMCs[8]		X			X	X	X	X	X	X	X	X	X	X
Serum for exploratory research		X			X	X	X	X	X	X	X	X	X	X
Plasma for exploratory research		X			X	X	X	X	X	X	X	X	X	X
Safety														
Vital signs[9]	X	X[9]		X[9]	X[9]		X[9]							
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Targeted physical examination	X													
Laboratory Testing (Central Lab)														
Hematology		X			X		X		X	X			X	X
Blood Chemistry		X			X		X		X	X			X	X
Urinalysis		X											X	
Drug concentrations and Immunogenicity														
Drug concentration (PK) sample[10]		X[10]		X[10]	X	X	X	X	X	X				
Immunogenicity (ADA) sample[11]		X[11]				X				X				
Pharmacogenomics (Optional)														
Whole Blood for DNA		X[2]												
Vaccine Booster Sub-Study (Optional)[13]														
Informed consent for vaccine booster sub-study[2]					Refer to Table 6.									

Visit Period	Screening/Baseline				Vaccine Response Assessment					Follow-Up			Unscheduled Visit	ET
Study Day	-21 to 1				15[1]	29	43[1]	57	71	183	267	380		
	Screening	Pre-dose	Dose[1]	Post-Dose										
Days After the First Vaccine Dose						*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)					-1 to +3	±2	-1 to +3	±2	±2	±7	±14	±14		
Sample collection and assessments														

Table 4: Schedule of Events for Arms 4, 5, and 6b (Enrollment Wave 2)

Visit Period	Screening/Baseline				Vaccine Response Assessment				Follow-Up			Unscheduled Visit	ET
Study Day	-21 to 1				15	29[1]	43	57	169	253	366		
	Screening	Pre-dose	Dose[1]	Post-Dose									
Days After the First Vaccine Dose					*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)					±2	-1 to +3	±2	±2	±7	±14	±14		
Screening/Baseline and Key Laboratory Testing													
Inclusion/exclusion	X	X											
Informed consent	X												
Informed consent for optional FBR sub-study[2]	X												
Informed consent for optional PGx sub-study[2]	X												
Medical history	X												
Demographics	X												
Height and weight	X												
Pregnancy test (WOCBP)[3]	X[3]	X[3]				X[3]						X	
SARS-CoV-2 rapid (local/POC) RT-PCR[4]	X[4]	X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	
SARS-CoV-2 rapid serology[5]	X[5]	X[5]											
SARS-CoV-2 serology (central lab)[5]		X[5]										X	
Enrollment Wave and Treatment Assignment													
Site-managed assignment[6]	X[6]												
Randomization[6]		X[6]											
Study Drug and Vaccine Administration													
REGN10933+REGN10987 (arms 4 and 5 only)[7]			X[7]										
Moderna mRNA-1273 vaccine (arms 4, 5, and 6b)[7]			X[7]			X[7]							
Biomarkers													
Serum for SARS-CoV2 neutralization[8]		X			X	X	X	X	X	X	X	X	X
Serum for serology characterization[8]		X			X	X	X	X	X	X	X	X	X
Whole blood for PBMCs[8]		X			X	X	X	X	X	X	X	X	X
Serum for exploratory research		X			X	X	X	X	X	X	X	X	X
Plasma for exploratory research		X			X	X	X	X	X	X	X	X	X
Safety													
Vital signs[9]	X	X[9]		X[9]		X[9]							
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Targeted physical examination	X												
Laboratory Testing (Central Lab)													
Hematology		X				X		X	X			X	X
Blood Chemistry		X				X		X	X			X	X
Urinalysis		X										X	
Drug concentrations and Immunogenicity													
Drug concentration (PK) sample[10]		X[10]		X[10]	X	X	X	X	X				
Immunogenicity (ADA) sample[11]		X[11]				X			X				
Pharmacogenomics (Optional)													
Whole Blood for DNA		X[2]											

Visit Period	Screening/Baseline				Vaccine Response Assessment				Follow-Up			Unscheduled Visit	ET
Study Day	-21 to 1				15	29[1]	43	57	169	253	366		
	Screening	Pre-dose	Dose[1]	Post-Dose									
Days After the First Vaccine Dose					*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)					±2	-1 to +3	±2	±2	±7	±14	±14		
Vaccine Booster Sub-Study (Optional)[14]													
Informed consent for vaccine booster sub-study[2]					Refer to Table 6.								
Sample collection and assessments													

Table 5: Schedule of Events for Study Arms 9 and 6d (Enrollment Wave 4)

Visit Period	Screening/Baseline				Vaccine Response Assessment							Follow-Up			Unscheduled Visit	ET
Study Day	-21 to 1				7			15	29[1]	43	57	169	253	366		
	Screening	Pre-dose	Dose[1]	Post-Dose	Pre-dose	Dose[1]	Post-Dose									
Days After the First Vaccine Dose								*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)								±2	-1 to +3	±2	±2	±7	±14	±14		
Screening/Baseline and Key Laboratory Testing																
Inclusion/exclusion	X	X														
Informed consent	X															
Informed consent for optional FBR sub-study[2]	X															
Informed consent for optional PGx sub-study[2]	X															
Medical history	X															
Demographics	X															
Height and weight	X															
Pregnancy test (WOCBP)[3]	X[3]	X[3]			X[3]				X[3]						X	
SARS-CoV-2 rapid (local/POC) RT-PCR[4]	X[4]	X[4]			X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	
SARS-CoV-2 rapid serology[5]	X[5]	X[5]														
SARS-CoV-2 serology (central lab)[5]		X[5]			X										X	
Enrollment Wave and Treatment Assignment																
Site-managed assignment[6]	X[6]															
Randomization[6]		X[6]														
Study Drug and Vaccine Administration																
REGN10933+REGN10987 (arm 9 only)[7]						X[7]										
Moderna mRNA-1273 vaccine (arms 9 and 6d)[7]			X[7]						X[7]							
Biomarkers																
Serum for SARS-CoV2 neutralization[8]		X			X			X	X	X	X	X	X	X	X	X
Serum for serology characterization[8]		X			X			X	X	X	X	X	X	X	X	X
Whole blood for PBMCs[8]		X			X			X	X	X	X	X	X	X	X	X
Serum for exploratory research		X			X			X	X	X	X	X	X	X	X	X
Plasma for exploratory research		X			X			X	X	X	X	X	X	X	X	X
Safety																
Vital signs[9]	X	X[9]		X[9]	X[9]		X[9]		X[9]							
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Targeted physical examination	X															
Laboratory Testing (Central Lab)																
Hematology		X			X				X		X	X			X	X
Blood Chemistry		X			X				X		X	X			X	X
Urinalysis		X													X	
Drug concentrations and Immunogenicity																
Drug concentration (PK) sample[10]					X[10]		X[10]	X	X	X	X	X				
Immunogenicity (ADA) sample[11]					X[11]							X				
Pharmacogenomics (Optional)																
Whole Blood for DNA		X[2]														
Vaccine Booster Sub-Study (Optional)[14]																

Visit Period	Screening/Baseline				Vaccine Response Assessment							Follow-Up			Unscheduled Visit	ET
Study Day	-21 to 1				7			15	29[1]	43	57	169	253	366		
	Screening	Pre-dose	Dose[1]	Post-Dose	Pre-dose	Dose[1]	Post-Dose									
Days After the First Vaccine Dose								*14*	*28*	*42*	*56*	*168*	*252*	*365*		
Window (day)								±2	-1 to +3	±2	±2	±7	±14	±14		
Informed consent for vaccine booster sub-study[2]					Refer to Table 6.											
Sample collection and assessments																

Table 6: Schedule of Events for the Moderna mRNA-1273 Vaccine Booster Sub-Study

Visit	Vaccine Booster Administration			Post-Booster Follow-Up
	Pre-Dose	Dose[1]	Post-Dose	
Visit Window	*≥5 months after the second dose of the vaccine (primary series), and >35 days before end of the main study*			*28 days ±7 days after the vaccine booster*
Informed consent for the booster sub-study[2]	X			
Moderna mRNA-1273 vaccine booster shot		X		
Pregnancy test (WOCBP)[3]	X			
SARS-CoV-2 rapid (local/POC) RT-PCR[4]	X[4]			X[4]
Adverse events[12]	X	X	X	X
Drug concentration (PK) sample[10]	X			X
Serum for exploratory research	X			X
Plasma for exploratory research	X			X
Whole blood for PBMCs[8]	X			X

9.1.1. Footnotes for the Schedules of Events

1. Throughout the study, study drug and/or vaccine administration will occur after all samples have been collected and all assessments have been performed.
2. Separate consent is required for participation in the optional vaccine booster sub-study (Section 9.2.10), optional future biomedical research sub-study (Section 9.2.8), and optional pharmacogenomics sub-study (Section 9.2.9). For subjects consenting to the genomics sub-study, the blood sample for genomic DNA should be collected at baseline (day 1) but may be collected at any visit.
3. All women of childbearing potential (WOCBP), with the exception of women with documented bilateral tubal ligation, will require pregnancy testing at screening, prior to study drug administration, and prior to COVID-19 vaccine administration. If a urine pregnancy test result is positive, a serum pregnancy test will be performed for confirmation. Subjects with confirmed pregnancy (by serum test) at screening will not be randomized. If the screening visit occurs on the same day as the baseline visit on day 1, pregnancy testing does not need to be repeated. Subjects with confirmed pregnancy at post-baseline dosing visits will be counseled according to Section 8.3.3.
4. If the screening visit occurs on the same day as the baseline visit on day 1, SARS-CoV-2-rapid RT-PCR test does not need to be repeated. Nasopharyngeal swabs will be used for rapid RT-PCR testing. Refer to Section 6.1.2 for more information on sample collection and visit scheduling for subjects with suspected COVID-19 or positive RT-PCR test result.

   Post-baseline samples only: If the rapid RT-PCR test is positive at any time point post-baseline, the samples will be banked for viral sequencing.

   Additional information is provided in Section 9.2.1.2.
5. If a rapid serology test is used at the screening visit, and screening occurs on the same day as the baseline visit, the rapid serology test does not need to be repeated at baseline. Additional information about the rapid serology test is provided in Section 9.2.1.3.

   At screening, if the rapid serology test is not available locally, a rapid test may be performed at a central laboratory to determine eligibility, and a repeat of the test is not required at baseline.
6. Subjects will receive site-managed assignment (at screening) and randomized treatment assignment (at baseline on day 1) according to Section 8.5.
7. Note that not all subjects will receive study drug at randomization. Refer to Section 8.5 and Figure 1 for more information.

   Study arms 4 and 5: Subjects assigned to study arms 4 and 5 will receive both the study drug and vaccine on day 1. The study drug will be administered first, followed by the vaccine. There must be a minimum of 2 hours waiting period between administration of the study drug and subsequent vaccine administration. Approximately 24 hours after completion of the study drug and vaccine administration on day 1, subjects will be followed up by telephone for safety. Subjects should be monitored for at least 1 hour after study drug or vaccine administration.

Study arms 6a, 6b, 6c, and 6d only: Subjects assigned to one of these study arms will not receive study drug. These subjects will receive the vaccine only. These subjects should be monitored for at least 30 minutes after vaccine administration.

Refer to Section 9.2.2 for additional information concerning administration and monitoring requirements following study drug and/or vaccine administration.

8. Serology characterization assays will be used to assess antibodies against various SARS-CoV-2 antigens including: S protein, RBD, S1, and N protein. Refer to Section 9.2.3.1, Section 9.2.3.2, and Section 9.2.3.3 for more information on procedures and assays related to vaccine response assessment.
9. Vital signs, including temperature, blood pressure, heart rate, and respiratory rate will be collected prior to and 30 minutes following each administration of the study drug or vaccine primary series (first and second dose) as described in Section 9.2.4.1.
10. Actual dosing time and drug concentration sample collection times will be recorded.

    Study arms 1, 2, 3, 7, 8, and 9 (receiving IV infusion of study drug): At the indicated visit, blood for assessment of drug concentration in serum will be taken prior to dosing and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.

    Study arms 4 and 5 (receiving SC injection of study drug): At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing. The post-dose blood collection should occur at least 1 hour after study drug administration.

    Study arms 6a, 6b, 6c, and 6d (receiving no study drug): No blood for assessment of drug concentration in serum will be collected.
11. The window for pre-dose ADA sample collection should be as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times will be recorded.

    Study arms 6a, 6b, 6c, and 6d (receiving no study drug): No blood for ADA assessment will be collected.
12. Adverse events will be continuously monitored as described in Section 10.1.1.
13. <u>For Arms 1, 2, 3, 6a, 6c, 7 and 8:</u> For subjects receiving their COVID-19 vaccine booster as part of the sub-study, the vaccine booster may be administered at any time from 5 months after their second vaccine dose until study day 345. The *actual date* the subject received their second vaccine dose should be used (as opposed to using study day 43) to determine when the booster window should begin.
14. <u>For Arms 4, 5, 6b, 6d, and 9:</u> For subjects receiving their COVID-19 booster as part of the sub-study, the vaccine booster may be administered at any time from 5 months after their second vaccine dose until study day 331. The *actual date* the subject received their second vaccine dose should be used (as opposed to using study day 29) to determine when the booster window should begin.

9.1.2. Early Termination Visit

Subjects who are withdrawn from the study before the primary endpoint visit (56 days after the first dose of the vaccine; **day 71** for study arms 1, 2, 3, 6a, 7, 8, and 6c, and **day 57** for study arms 4, 5, 6b, 9, and 6d) will be asked to return to the clinic once for an **early termination (ET) visit** consisting of the end of study assessments (as described in the respective Schedules of Events).

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, or for any other reason, as warranted.

9.2. Study Procedures

9.2.1. Procedures Performed at the Screening/Baseline Visit

Procedures to be performed for the purpose of determining study eligibility or characterizing the baseline population include: medical history, demographics (including age, sex, race, weight, height), and SARS-CoV-2 RT-PCR and serology tests.

9.2.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. Additional informed consent must be obtained if subjects choose to participate in the optional vaccine booster sub-study (Section 9.2.10), optional future biomedical research sub-study (refer to Section 9.2.8), or optional pharmacogenomics sub-study (refer to Section 9.2.9).

9.2.1.2. SARS-CoV-2 Rapid RT-PCR

At screening, the investigator or designee will verify that the subject has tested negative for SARS-CoV-2 by a rapid RT-PCR test. Historical test results will not be accepted.

Subjects will also be tested for SARS-CoV-2 infection by the rapid RT-PCR test using nasopharyngeal (NP) swabs throughout the study according to the respective Schedules of Events. Any post-baseline virology samples that test positive for SARS-CoV-2 will be banked for viral sequencing Section 9.2.3.4.

9.2.1.3. SARS-CoV-2 Serology

The investigator or designee will verify that the subject has tested negative for circulating SARS-CoV-2-specific antibodies by a SARS-CoV-2 antibody test.

The diagnostic antibody test may be performed using a rapid lateral flow chromatographic immunoassay (LFIA) intended for the qualitative detection and differentiation of IgM and IgG antibodies to SARS-CoV-2. If the LFIA assay is not available locally, the rapid LFIA test at the central laboratory will be used to determine study eligibility.

9.2.2. Study Drug and Vaccine Administration and Post-Administration Monitoring

Refer to Section 8.5 for treatment assignments.

SC and IM Injection Administration

All subjects allocated to a SC regimen will receive either 4 (study arm 4) or 2 (study arm 5) injections of study drug on the day of administration. It is recommended that SC injection sites should be chosen among the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs. During study drug administration, each injection must be given in a different anatomical location (1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc).

All subjects will receive each Moderna mRNA-1273 vaccination dose through a single IM injection in the deltoid muscle (CDC, 2021) .

Subjects should receive all doses of Moderna mRNA-1273 vaccine as assigned and as described in the EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022).

Study arms 4 and 5 only: Subjects will receive both study drug and vaccine on day 1. The study drug will be administered first, followed by the vaccine. There must be a minimum of 2 hours waiting period between administration of the study drug and subsequent vaccine. Administration of the individual regimens should be performed as described above.

Post-administration monitoring of study drug and vaccine

Study arms 1 through 5 and 7 through 9: Subjects should be monitored for at least 1 hour after study drug or vaccine administration. Vaccine recipients should be monitored for the occurrence of acute reactions according to the latest CDC guidelines (CDC, 2021) . For study arms 4 and 5 (receiving study drug and vaccine on the same day), approximately 24 hours after completion of the study drug and vaccine administration on day 1, subjects will be followed up by telephone for safety.

Study arms 6a, 6b, 6c and 6d: Subjects assigned to each of these study arms will not receive study drug during this study. These subjects should be monitored for at least 30 minutes after vaccine administration.

9.2.3. Pharmacodynamic and Exploratory Biomarker Procedures

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

Note that any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to how the study drugs work and to study SARS-CoV-2, COVID-19, and immune responses to SARS-CoV-2 vaccination.

9.2.3.1. SARS-CoV-2 Neutralization Assays

Vaccine induced neutralizing antibody titers will be characterized using an assay to measure the ability of serum antibodies to block SARS-CoV-2 S protein-mediated infection of cells in vitro. (Vandergaast, 2020). Because REGN10933+REGN10987 will neutralize infection in this assay, anti-idiotype antibodies that block REGN10933 and REGN10987 neutralizing activity will be added, allowing for detection of vaccine-induced neutralizing antibodies generated in vivo post-vaccination. The ID_{50} (serum dilution that inhibits by 50% the transfection signal detected in

positive control wells) of neutralizing antibodies tested will be compared between the vaccine-only arm and each REGN10933+REGN10987 treatment group at time points in the Schedules of Events to measure the induction of neutralizing activity to the SARS-CoV-2 S protein.

9.2.3.2. SARS-CoV-2 Serology Characterization Assays

Serum binding antibodies to SARS-CoV-2 S protein trimer, RBD and other SARS-CoV-2 subdomains (including S1 and nucleocapsid) will be assessed as secondary and exploratory objectives of this study. To explore whether or not mRNA-1273 vaccine-mediated humoral immunity to SARS-CoV-2 is affected by the administration of REGN10933+REGN10987, serological immunoassays will be used to detect antibodies against the SARS-CoV-2 S protein and subdomains at time points in the Schedules of Events. Because REGN10933+REGN10987 will interfere with these measurements, an anti-idiotype antibody that blocks REGN10933+REGN10987 will be included in the assay, allowing for detection of endogenous serum antibodies generated in vivo post-vaccination. Additional serological characterization related to antibody recognition of viral variants and further delineation of the epitope repertoire of vaccine-induced antibodies may be done if technically feasible and assays become available.

9.2.3.3. Cellular Immunity Assays

PBMCs will be processed at a central lab and may be stored for analysis. Both B cell and T cell immune responses will be studied. Assays for B cell responses may include, but not be limited to, quantification by flow-cytometry of circulating antigen-specific B cells or plasma cells using labeled S protein trimer, RBD and other SARS-CoV-2 subdomains, and quantification of SARS-CoV-2 specific antibody responses in either primary ELISPOT assays or re-stimulation assays followed by ELISPOT. Studies focused on T cell responses may include, but may not be limited to, flow cytometry with isolated PBMCs to characterize immune subsets, quantify SARS-CoV-2 specific T cell responses via ex vivo peptide stimulation assays with downstream flow cytometry and/or cytokine measurements. Cell profiling may include bulk RNA (transcriptome) sequencing, and T cell receptor or B cell receptor RNA or DNA sequencing.

9.2.3.4. Viral Sequencing

In order to monitor for possible SARS-CoV-2 infection post-REGN10933+REGN10987 treatment and/or post-vaccination and potential resistance, NP swabs will be collected for SARS-CoV-2 RT-PCR testing at timepoints designated in the Schedules of Events. Viral genome sequencing will be performed on available post-baseline viral nucleic acid samples with a positive RT-PCR test result. Sequencing analyses will consist of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

Viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 or the mRNA-1273 vaccine will be evaluated in nonclinical work separate from this protocol.

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

9.2.3.5. Serum and Plasma for Exploratory Research

Changes in circulating concentrations of serum/plasma biomarkers associated with COVID-19, SARS-CoV-2, REGN10933+REGN10987, vaccine-induced immunity, vaccine-drug interactions, host and viral biological pathways, and other mechanisms related to disease activity and clinical

outcome may be assessed in volunteers post-REGN10933+REGN10987 treatment and/or vaccination. The association between changes in biomarkers with clinical endpoints may be evaluated.

9.2.4. Safety Procedures

9.2.4.1. Vital Signs

Vital signs will include temperature, blood pressure, heart 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.

Vital signs will be collected prior to and approximately 30 minutes following each administration of the study drug or vaccine primary series (first and second vaccine dose). Vital signs may also be collected as needed, according to local standard of care and as per the discretion of the investigator.

Blood pressure measurements may be repeated once during screening.

9.2.4.2. Adverse Events Monitoring

Adverse events listed in Section 10.1.1 will be recorded.

9.2.4.3. Concomitant Medications

Concomitant medications (as defined in Section 9.2.4.3) will be recorded.

9.2.4.4. Pregnancy Test

Urine pregnancy test will be performed for WOCBP at the time periods described in the Schedules of Events. If urine pregnancy test is positive, a serum pregnancy test will be performed for confirmation, and subjects should be counseled as described in Section 8.3.3.

9.2.4.5. Targeted Physical Examination

Targeted physical examination is required and will include examination of the oropharynx, skin, heart, lungs, and any other system(s) depending on complaints or concerns expressed by the subject.

9.2.5. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Samples for laboratory testing will be collected at visits according to the Schedules of Events.

Tests will include:

Blood Chemistry

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

**low-density lipoprotein (LDL) and high-density lipoprotein (HDL).*

Hematology

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

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Refer to Section 9.2.1.2 for information on the SARS-CoV-2 rapid RT-PCR test.

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.

9.2.6. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in the Schedules of Events.

9.2.7. Immunogenicity Measurements and Samples

Samples for study drug immunogenicity (ADA and NAb) assessment will be collected at time points listed in the Schedules of Events.

9.2.8. Future Biomedical Research (Optional)

Subjects who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.9. Pharmacogenomic Analysis (Optional)

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

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN10933+REGN10987, SARS-CoV-2 vaccination, other COVID-19 clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of COVID-19 as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, SARS-CoV-2 vaccination or COVID-19.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

9.2.10. Vaccine Booster Sub-Study (Optional)

Subjects who have not already received the COVID-19 vaccine booster and who agree to participate in the vaccine booster sub-study will be required to consent to this optional sub-study before collection of the pre-dose blood sample and administration of the booster vaccination dose. Another blood sample will be collected approximately 28 days after the vaccine booster. These blood samples may be analyzed to supplement data regarding the potential immunological impact of mAb administration on COVID-19 vaccination.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

In this study, the following TEAEs will be recorded:

- Treatment-emergent AEs throughout the study
- Treatment-emergent SAEs throughout the study
- Treatment-emergent AESIs (defined in Section 10.1.3)

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of the post-vaccination observation period (see Section 11.4.6.1). 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 by questioning the subject at each study visit. Subjects 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 10.1.4. 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, 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 10.1.4 for definitions).

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

Any SAE that may occur subsequent to the reporting period 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 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 CRF. 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 CRF, and retained at the study center and available upon request.

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

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **Treatment-emergent SAEs**.
- **Treatment-emergent AESI** (serious and nonserious), defined as**:**
  - Grade ≥2 infusion-related reactions to REGN10933+REGN10987 through day 4
  - Grade ≥3 injection-site reactions to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 4 post-injection
  - Grade ≥2 hypersensitivity reactions to REGN10933+REGN10987 or each dose of Moderna mRNA-1273 vaccine through day 29 post-infusion or post-injection (as applicable)

- If subjects experience Grade ≥ 3 ISRs or Grade ≥2 hypersensitivity reactions related to Moderna mRNA-1273 **administered as a concomitant medication outside of the study**, these events are NOT to be considered as AESIs and do not require expedited reporting to Sponsor
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female, for 6 months after REGN10933+REGN10987 administration. Any complication of pregnancy affecting a female study 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.

10.1.4. Reporting Adverse Events Following Vaccination

It is advised that healthcare providers administering Moderna mRNA-1273 vaccine should comply with CDC requirements for AE reporting, as outlined in the EUA Fact Sheet (Moderna COVID-19 Vaccine [HCP Fact Sheet], 2022).

The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event,
- Serious adverse events* (irrespective of attribution to vaccination),
- Cases of Multisystem Inflammatory Syndrome (MIS) in adults, and
- Cases of COVID-19 that result in hospitalization or death.

**Serious adverse events are defined as: Death; A life-threatening adverse event; Inpatient hospitalization or prolongation of existing hospitalization; A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; A congenital anomaly/birth defect; An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.*

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.

AESI are defined for this study in Section 10.1.3.

10.2.4. Severity

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

Treatment-emergent AEs, SAEs, or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 7. The grading systems for anaphylaxis, allergic reaction (hypersensitivity), infusion-related reaction, and injection-site reaction are provided in Table 8.

Table 7: NCI-CTCAE (v5.0) Severity Grading System for Adverse Events: General Guideline

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

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

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

Table 8: NCI-CTCAE (v5.0) Severity Grading System for Anaphylaxis, Allergic Reactions, Infusion-Related Reactions, and Injection Site Reactions

Grade	CTCAE Term			
	Anaphylaxis[1]	**Allergic Reaction** *(hypersensitivity)*[2]	**Infusion-Related Reaction**[3]	**Injection-Site Reaction**[4]
1	N/A	Systemic intervention not indicated	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
2	N/A	Oral intervention indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Pain; lipodystrophy; edema; phlebitis
3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Ulceration or necrosis; severe tissue damage; operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death	Death	Death

[1] Disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death

[2] Disorder characterized by an adverse local or general response from exposure to an allergen.

[3] Disorder characterized by adverse reaction to the infusion of pharmacological or biological substances

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

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the study drug and/or vaccine administered as part of the study caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. Causality should be assessed separately for the study drug and for the vaccine. 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 vs time study drug and/or vaccine was administered
- Nature of the reactions: immediate vs long term
- Clinical and pathological features of the events
- Existing information about study drug and/or vaccine and the same class of drugs or vaccines
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Subject's medical and social history

Causality to the study drug and/or vaccine (including study drug and/or vaccine administration):

- **Related:**
  - The AE follows a reasonable temporal sequence from the study drug and/or vaccine administered as part of the study, and cannot be reasonably explained by the nature of the reaction, subject's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from the study drug and/or vaccine administered as part of the study, and is a known reaction to the drug or vaccine under study or its classes, or is predicted by known pharmacology.
- **Not Related:**
  - The AE does not follow a reasonable sequence from the study drug and/or vaccine administered as part of the study, or can be reasonably explained by the nature of the reaction, subject'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, subject's clinical state (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, subject'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, GPS; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board, 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 REGN10933+REGN10987, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the Sponsor’s notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB) unless delegated to the Sponsor.

Event expectedness for study drug REGN10933+REGN10987 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 statistical hypothesis testing is planned in this study. Analyses of immunogenicity, safety, tolerability, and other data will be descriptive and exploratory in nature.

11.2. Justification of Sample Size

This study plans to enroll up to approximately 286 subjects, in order to achieve a target enrollment of up to approximately 30 subjects per Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and 46 total Moderna mRNA-1273-alone subjects. Based on the calculations provided below, this sample size is considered appropriate to meet the aims of this phase 2 study, in that it is expected to provide adequate precision in quantifying the magnitude of effect for the primary endpoint, as well as allow for an assessment of the safety and tolerability of the Moderna mRNA-1273 vaccine when administered with REGN10933+REGN10987.

The assumed $\log_{10}$-scale standard deviation for the study is 0.30 log. This assumption is based on phase 1 data for the Moderna mRNA-1273 vaccine, taking the weighted average (ie, adjusting for sample sizes) across all doses (25,100, and 250 µg) and age groups (18 to 55, 56 to 70, and ≥71 years) for the neutralizing antibody titer ID_{50} endpoint at day 57 (Anderson, 2020) (Jackson, 2020). With a log-scale standard deviation of 0.30 for the primary endpoint and a sample size of 30 and 46 subjects per arm (in combined study drug/vaccine and vaccine-only arms, respectively), the half-width of the 95% within-group confidence interval (CI) [ie, the minimal detectable difference] in this study is 0.11 log and 0.09 log, respectively. For between-group comparisons, the half-width of the 95% between-group CI for any two Moderna mRNA-1273 + (REGN10933 and REGN10987) arms is 0.15 log. Additionally, the half-width of the 95% between-group CI in this study for any individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and the total Moderna mRNA-1273 alone subjects is 0.14 log.

The analysis set that will be used for assessment of vaccine response allows for subjects to be excluded from analysis if certain confounding criteria are met (see Section 11.3.1). If 50% of subjects are excluded from analysis (ie, 15 subjects are analyzed per individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and 23 total Moderna mRNA-1273 alone subjects are analyzed), the half-width of the 95% between group CI for any two Moderna mRNA-1273 + (REGN10933 and REGN10987) arms is 0.22 log. Additionally, the half-width of the 95% between group CI for any individual Moderna mRNA-1273 + (REGN10933 and REGN10987) arm and Moderna mRNA-1273 alone subjects is 0.20 log. Under this scenario, the minimal detectable difference still remains substantially smaller than the decrease in neutralization titers observed in a separate study of sera from recipients of the Moderna mRNA-1273 vaccine who were infected with South African variants (eg, B.1.351 v1, v2, and v3) (Garcia-Beltran, 2021)

11.3. Analysis Sets

11.3.1. Vaccine Response Analysis Sets

The **modified full analysis set (mFAS)** includes all randomized subjects who have been vaccinated with at least one dose and have a negative serology test result from the central laboratory test at baseline; it is based on the treatment received (as treated).

The **per protocol set (PPS)** includes all randomized subjects who have been vaccinated with at least one dose and do not meet the PPS exclusion criteria; it is based on the treatment received (as treated).

The PPS excludes subjects who:

- Receive positive SARS-CoV-2 serology result based on central laboratory test at baseline
- Do not receive the second dose of the vaccine
- Receive a positive diagnostic test result for SARS-CoV-2 infection before 56 days after the first dose of the vaccine
- Receive any dose of a coronavirus vaccine (refer to Section 8.8.1) outside of the study within 56 days after the first dose of the vaccine
- Receive systemic immunosuppressants or immune-modifying drugs within 56 days after the first dose of the vaccine
- Receive IVIG or blood products within 56 days after the first dose of the vaccine

The SAP will document the finalized exclusion criteria for the PPS.

The PPS is the primary analysis set for assessing vaccine response.

11.3.2. Safety Analysis Set

The **safety analysis set (SAF)** includes all randomized subjects who have been vaccinated with at least one dose or 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.

11.3.3. Vaccine Booster Analysis Set

The **vaccine booster analysis set** includes all randomized subjects who signed the optional sub-study informed consent and have been vaccinated with the study provided vaccine booster; it is based on the treatment received (as treated).

11.3.4. Pharmacokinetic Analysis Set

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

11.3.5. Immunogenicity Analysis Sets

The ADA analysis sets include all subjects who received any study drug and had at least 1 non-missing ADA result from the ADA assays after first dose of study drug.

The NAb analysis sets include all subjects who received any study drug and who are either negative in the ADA assays or positive for ADA with at least one non-missing result in the NAb assays after first dose of the study drug. Subjects who are negative in the ADA assays are set to negative in the NAb analysis sets.

Subjects will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of 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 who have signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- The total number of subjects who discontinued from study treatment, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

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

11.4.3. Analysis of Primary Vaccine Response Endpoint

The primary endpoint is the 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to SARS-CoV-2 pseudovirus, assessed on 56 days after the first dose of the vaccine (ie, the vaccine response assessment period). The 56-day time point corresponds to study day 71 for study arms 1, 2, 3, 7, 8, 6a, and 6c, and study day 57 for study arms 4, 5, 9, 6b, and 6d.

An analysis of covariance (ANCOVA) model with treatment group as a fixed effect and age as a covariate will be fit to the data as the primary analysis.

The least squares mean estimates for the endpoint will be presented for each treatment group, as well as for the differences between treatment groups. Associated 95% confidence intervals will also be reported for each treatment group and for between-group comparisons.

Data will be fitted in the log scale, and final outputs will be reported in geometric means and differences of the geometric means.

Accompanying descriptive analyses will also be provided. The analyses will be conducted based on the observed data with no imputation for missing data. Values below the limit of quantification (LOQ) will be set to half of LOQ.

11.4.4. Analysis of Secondary Vaccine Response Endpoints

The secondary endpoints will be analyzed in a similar manner as described for the primary endpoint.

For these secondary endpoints, the individual time points for assessments include all post-vaccine scheduled timepoints during the Vaccine Response Assessment Period as described in the Schedule of Events (Section 9.1). Accompanying descriptive analyses for each endpoint at each individual time points will also be provided.

11.4.5. Analysis of Sub-Study Vaccine Booster

Possible analysis includes assessment of vaccine immune responses over time among the vaccine booster analysis set. Accompanying descriptive statistics at individual time points will also be provided.

11.4.6. Safety Analysis

11.4.6.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The **pre-vaccination period** is defined as the time from study drug administration to the first primary series vaccine dose administration.
- The **primary series vaccination period** is defined as the time from the first primary series vaccine dose administration to 28 days after the second primary series vaccine dose administration, and in subjects receiving only one dose of the primary series vaccine, 28 days after the first primary series vaccine dose administration.
- The **post primary series-vaccination period** is defined as the time from the end of the primary series vaccination period to the end of the follow-up period in subjects who do not receive the sub-study provided vaccine booster. In subjects who receive the sub-study provided vaccine booster dose, the post-primary series vaccination period is defined as the time from the end of the primary series vaccination period to the administration of the sub-study provided vaccine booster.
- The **post-booster vaccination period**: is defined as the time from the sub-study provided vaccine booster to the end of the follow-up period.

Treatment-emergent adverse events are defined as those that are not present at the time of the first dose of Moderna mRNA-1273 Vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first) or represent the exacerbation of a pre-existing condition during the observation period.

Analysis

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

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of subjects with at least 1 TEAE by SOC and PT
- The number (n) and percentage (%) of subjects with at least 1 treatment-emergent serious adverse events (SAEs) by SOC and PT
- The number (n) and percentage (%) of subjects with at least 1 infusion-related reactions (grade ≥2) through day 4 by PT
- The number (n) and percentage (%) of subjects with at least 1 injection-site reactions (grade ≥3) through day 4 by PT
- The number (n) and percentage (%) of subjects with at least 1 hypersensitivity reactions (grade ≥2) through day 29 by PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- Treatment related TEAEs , presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and SAEs will be summarized by treatment group.

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

11.4.6.2. Other Safety

Vital Signs

Vital signs (temperature, blood pressure, heart rate, and respiratory 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-randomization 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.

11.4.6.3. Treatment Exposure

The derived variables, the summary tables and listings to be used to illustrate the extent of exposure to the investigational drug (characterized according to the number of subjects exposed, the duration of exposure and the dose to which they were exposed).

The associated medications in interaction studies or in studies where associated medication is specified as part of the investigational drug.

11.4.6.4. Treatment Compliance

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

11.4.7. Pharmacokinetics

11.4.7.1. Analysis of Drug Concentration Data

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

11.4.8. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate. Details of the exposure-response analyses will be documented separately.

11.4.9. Analysis of Immunogenicity Data

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

ADA response categories:

- ADA negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, or a positive assay response at baseline, with all post first dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when the baseline results are negative or missing. Treatment-emergent responses will be further characterized as Persistent, Indeterminate, or Transient.
- Treatment-boosted ADA response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

Titer categories (Maximum Titer values)

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

The following analysis will be provided:

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

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

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

11.5. Interim Analysis

Formal interim analysis may be conducted.

11.6. Timing of Primary and Final Analyses

The primary vaccine response analysis will be conducted as a first-step analysis after all subjects have finished the primary endpoint visit (ie, 56 days after the first dose of the vaccine, at study days listed in Section 11.4.3), in order to estimate the levels of neutralizing antibodies in each study arm. This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis. The SAP will be issued prior to this analysis.

After all subjects finish 1-year of follow-up, a final study analysis will be conducted.

11.7. 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, physical examination findings) will be done using internationally recognized and accepted dictionaries.

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

12.1.2. Electronic Systems

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

- IWRS system: randomization, study drug supply
- EDC system and 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 CRF 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 CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be

completed for each and every subject enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the CRFs. After review of the clinical data for each subject, the investigator must provide an electronic signature. A copy of each subject CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

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

12.3. Audits and Inspections

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB 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 CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the Sponsor before

discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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 prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

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

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

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

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 CRFs or other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor (eg, signed ICF) must be kept in strict confidence.

The 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/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

- The investigator has received all items and information necessary to perform the study, but has not enrolled any 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 2 RANDOMIZED, OPEN-LABEL, PARALLEL GROUP STUDY TO ASSESS THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF MODERNA mRNA-1273 VACCINE ADMINISTERED WITH CASIRIVIMAB+IMDEVIMAB IN HEALTHY ADULT VOLUNTEERS 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 2 Randomized, Open-Label, Parallel Group Study to Assess the Immunogenicity, Safety, and Tolerability of Moderna mRNA-1273 Vaccine Administered with Casirivimab+Imdevimab in Healthy Adult Volunteers

Protocol Number: R10933-10987-COV-2118

Protocol Version: Amendment 5

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

VV-RIM-00182647-1.0 Approved - 28 Jan 2022 GMT-5:00

Signature Page for VV-RIM-00182647 v1.0

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