NCT04852978

STATISTICAL ANALYSIS PLAN
VERSION: 2.0

Clinical Study Protocol 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

Compound:	REGN10933+REGN10987
Protocol Number:	R10933-10987-COV-2118
Clinical Phase:	Phase 2
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CRF	Case Report Form (electronic or paper)
CTCAE	Common Terminology Criteria for Adverse Events
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
ICF	Informed Consent Form
ID_{50}	50% Inhibitory Dilution
ICH	International Council for Harmonisation
IV	Intravenous
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PCSV	Potentially Clinically Significant Value
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Preferred Term
RBD	Receptor-Binding Domain
Regeneron	Regeneron Pharmaceuticals, Inc.
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous

SI	Standard International
SMQ	Standard MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
ULOQ	Upper Limit of Quantification
VNT	Viral Neutralizing Titer
WHO	World Health Organization

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R10933-10987-COV-2118 study. The current version of the SAP, version 2, was finalized after protocol amendment 5 to incorporate changes made to the protocol (see Section 1.2.6 for a summary of revisions).

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The original version of the analysis plan was issued prior to the first interim database lock.

1.1. Background/Rationale

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

The primary objectives are 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 and to evaluate the time interval between REGN10933+REGN10987 administration and Moderna mRNA-1273 vaccine administration to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2. To accomplish the first primary study objectives, REGN10933+REGN10987 will be evaluated using a 1200 mg dose level that has been authorized under Emergency Use Authorization (EUA) for the treatment and post-exposure prophylaxis of COVID-19 and for which clinical trial data (conducted prior to the emergence of omicron-lineage variants) indicate efficacy for pre-exposure prophylaxis of COVID-19 against susceptible variants (Table 1). The study is thus designed to mirror hypothetical clinical 'use case' scenarios, for which the two routes of administration of REGN10933+REGN10987, intravenous and subcutaneous, may be employed in close proximity to COVID-19 vaccination or, to accomplish the second primary objective, mimic waiting for vaccination for up to 6 months after a 1200 mg dose of REGN10933+REGN10987.

In this study, several additional dose levels below 1200 mg were to be administered at day 1 (Figure 1 and Figure 2). 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 was 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) lowered the likelihood of subjects becoming exposed to SARS-CoV-2 exposure during the study, which would confound the interpretation of results.

To summarize, 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 COVID-19 vaccines in the setting of REGN10933+REGN10987 therapy or prevention. Since 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) as 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.

1.2. Study Objectives

1.2.1. 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

1.2.2. 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

1.2.3. 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

1.2.4. Endpoints

Primary Endpoint

The primary endpoint is the 50% inhibitory dilution (ID50) 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.

This endpoint will be used in assessing both primary objectives.

Secondary Endpoints

- 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

Exploratory Endpoints

- 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

1.2.5. Modifications from the Statistical Section in the Final Protocol

Modifications in the Statistical Analysis Plan from the Statistical Section in the Final Protocol include the addition of Viral Neutralizing Titer and converted World Health Organization standard unit parameters as additional efficacy variables, further detailing of exclusion criteria for the Per Protocol Set and added exclusion details for the vaccine booster analysis set as subset of the Per Protocol Set.

1.2.6. Revision History for SAP Amendments

The revised SAP (version 2) is based on Protocol Amendment 5 dated January 28th 2022.

Summary of Changes from Version 1 to Version 2	
Change and Rationale for Change	**Sections changed**
Edits and additions, due to protocol amendment and for added clarity.	Section 1
Secondary and exploratory objectives and endpoint wording updated to match changes in protocol amendment	Section 1.2.2, 1.2.3, 1.2.4 Section 4.5.2 Section 4.5.3
Clarify timeframe for criteria 7 of the Per Protocol Set	Section 3.1
Vaccine Booster Analysis Set is defined	Section 3.5
Clarify that the pharmacokinetics analysis sets	Section 3.6

are defined for each study drug separately	
Clarify immunogenicity analysis sets and analysis of immunogenicity data	Section 3.7 Section 5.10.1, 5.10.2
Add clarification that medications reporting to include standardized medication name	Section 4.3
Safety periods updated to match protocol amendment and reflect optional vaccine booster dose	Section 4.6.1
Added tabulation of subjects who receive vaccine booster dose along with time from completion of primary series of vaccine	Section 5.6
In alignment to other studies within the REGEN-COV program, handling rule for values above the upper limit of quantification (ULOQ) to be set to the ULOQ	Section 5.7 Section 6.2
Noted an exploratory analysis that will be performed with data from a second neutralization assay and summarized in a separate report	Section 5.7.3
Addition of analyses for vaccine booster analysis set subjects	Section 5.7.6
Removal of text referencing noncompartmental analysis due to sampling schedule	Section 5.9
Schedule of events updated to reflect protocol amendment	Section 11.1

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

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.

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

Every effort was be made by the site to ensure balance of age (<65 years and ≥65 years) within each of the enrollment waves. At baseline (day 1), subjects were to be randomized to the corresponding study arms in each wave as described in Table 1.

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

Table 1: 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 US FDA EUA HCP Fact Sheet, 2021)
mAb=monoclonal antibody; SC=subcutaneous; IV=intravenous.

2.2. Sample Size and Power Considerations

This study planned 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 (resulting in 46 total Moderna mRNA-1273-alone subjects).

The pooled standard deviation for the primary vaccine response endpoint of neutralizing antibody titer ID_{50} assessed 56 days after vaccination with Moderna mRNA 1273 (pooling across doses and age groups) is 0.30 (Anderson, 2020) (Jackson, 2020). With a sample size of 30 and 46 subjects per arm in combined study drug/vaccine and pooled vaccine-only arms, respectively, the half-widths of the 95% within-group confidence interval (CI) [ie, the minimal detectable difference] in this study are 0.11 and 0.09, 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. 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.

If 50% of subjects are excluded from the Per Protocol Analysis Set (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. 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. Note that it is not expected that 50% of subjects will be excluded from the Per Protcol Set (PPS); this precision statement is intended to be conservative.

Note that the mean decrease in neutralization titers in sera from recipients of the Moderna mRNA-1273 vaccine who were infected with South African variants (eg, B.1.351 v1, v2, and v3) was 1.44 in $\log_{10}$ scale (Garcia-Beltran, 2021). While this difference is not known to be clinically relevant, it provides a useful benchmark for results of this study. The vaccine still provided similar levels of protection against severe outcomes for infection with this variant (Chemaitelly, 2021).

2.3. Study Plan

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 of protocol.

Subjects will also have blood samples taken at select visits for drug concentration, immunogenicity, and exploratory analyses, and will be monitored for AEs [including Adverse Events of Special Interest (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.

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

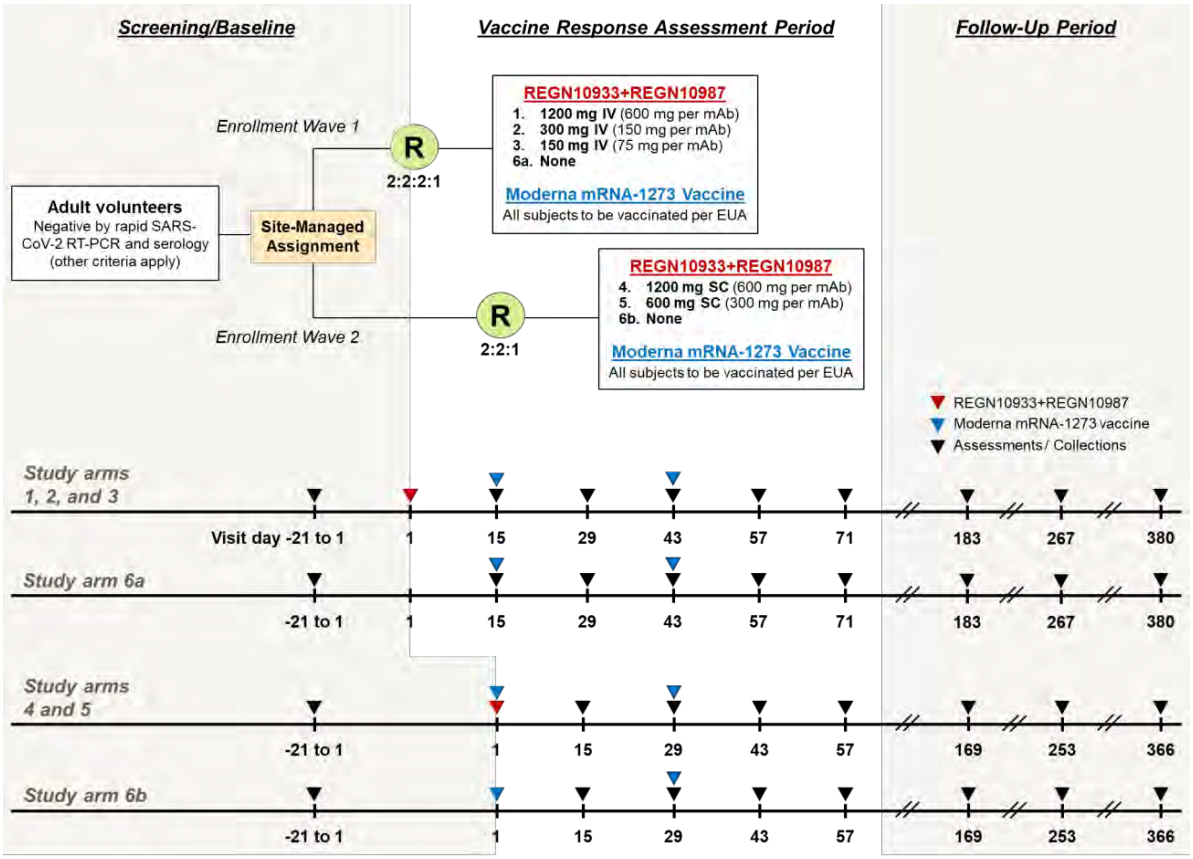
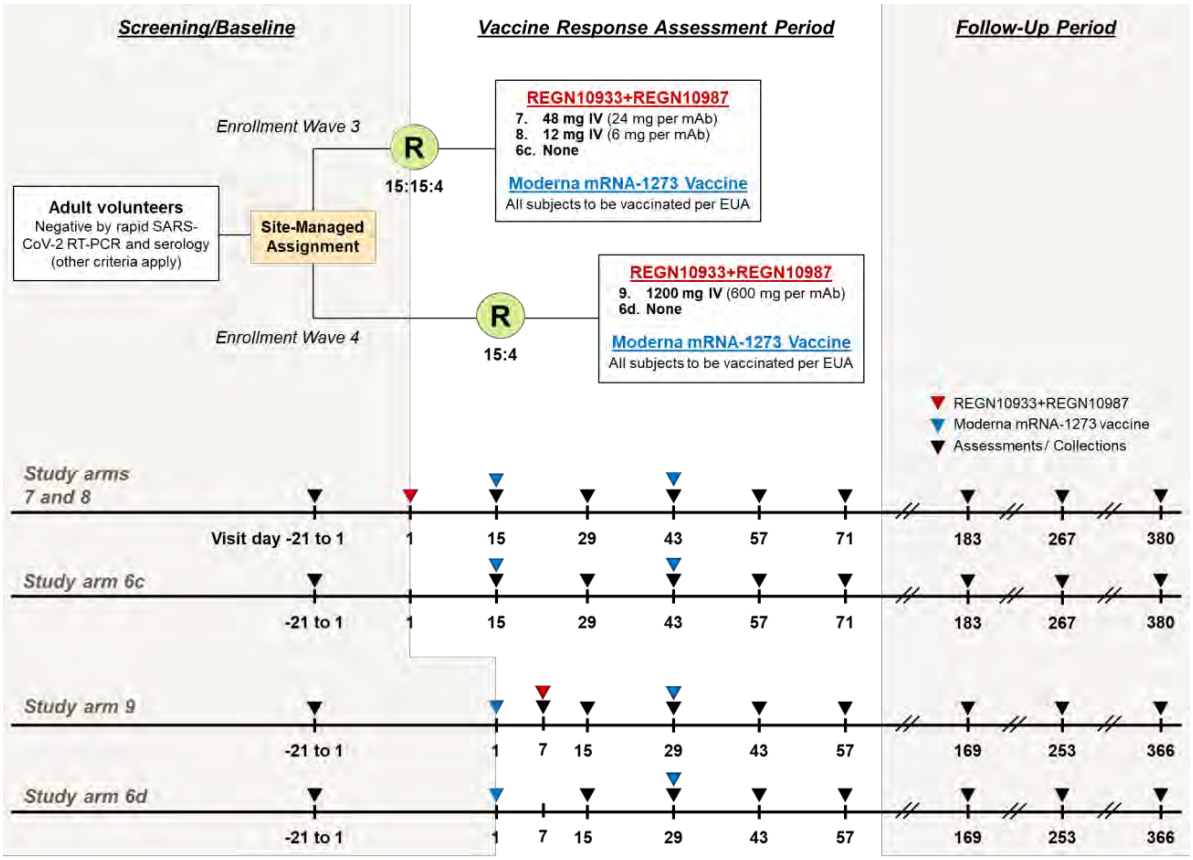


Figure 2: Study Flow Diagram (Enrollment Waves 3 and 4)



3. ANALYSIS POPULATIONS

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

In this study, "as treated" is defined as: (1) subjects who receive study drug will be grouped in the vaccine + study drug combination arms (2) subjects who receive vaccine only will be grouped into the vaccine alone arm within the same randomization wave (e.g. for a subject randomized to arm 1 who receives vaccine only, they will be grouped into arm 6a).

3.1. Per Protocol Set Analysis Set (PPS)

The per protocol set (PPS) includes all randomized subjects who have received both doses of vaccine and who do not meet the following exclusion criteria:

1. Have a positive SARS-CoV-2 central serology result prior to the first dose of vaccine.
2. Receive a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) diagnostic test result for SARS-CoV-2 infection at any time point prior to the scheduled visit 56 days after the first dose of vaccine.
3. Receive any dose of investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, mAbs, hyperimmune globulin) outside of the study at any time point prior to the scheduled visit 56 days after the first dose of vaccine.
4. Receive any other vaccine within 28 days prior to the study to the scheduled visit 56 days after the first dose of Moderna mRNA-1273 vaccine administered as part of this study.

   Exception: seasonal influenza vaccine is only prohibited within 14 days before or after study drug administration, or within 14 days before or after Moderna mRNA-1273 vaccine administration.
5. Receive systemic medications that suppresses the immune system (for corticosteroids, ≥20 mg/day of prednisone equivalent) at any time point prior to the scheduled visit 56 days after the first dose of vaccine.
6. Receive IVIG or blood products at any time point prior to the scheduled visit 56 days after the first dose of vaccine.
7. Subjects with incomplete infusions or injections of study drug or vaccine at any time point prior to the scheduled visit 56 days after the first dose of vaccine.
8. Subjects with baseline neutralization antibody titer above the lower limit of quantification (LLOQ).

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

3.2. Modified Full Analysis Set (mFAS)

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).

3.3. Randomized Analysis Set

The randomized analysis set includes all randomized subjects; it is based on the treatment allocated by the IWRS (as randomized).

3.4. Safety Analysis Set (SAF)

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.

3.5. Vaccine Booster Analysis Set

The vaccine booster analysis set includes Per Protocol Set subjects who signed the optional sub-study informed consent, have been vaccinated with the study-provided vaccine booster and did not have an adverse event of COVID (Preferred Terms of 'COVID-19', 'Asymptomatic COVID-19', 'SARS-CoV-2 test positive', 'COVID-19 pneumonia') or a positive PCR test prior to the post-booster follow-up sample collection.

3.6. The Pharmacokinetic Analysis Set

The pharmacokinetics (PK) analysis sets (PKAS) are defined for each study drug separately and includes all subjects who received any study drug and who had at least 1 non-missing result following the first dose of the respective study drug. Subjects will be analyzed based on actual treatment received.

3.7. Immunogenicity Analysis Sets

The ADA analysis sets (AAS) are defined for each study drug separately and include all subjects who received any study drug (safety analysis set) and had at least one non-missing ADA result following the first dose of the respective study drug. The ADA analysis sets are based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis sets (NAbAS) are defined for each study drug separately and include all treated subjects that are included in the ADA analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAb analysis set. Subjects in the NAbAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Subjects in the NAbAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

4. ANALYSIS VARIABLES

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be obtained from the last available value up to the date of first dose of vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first).

The following demographic variables will be tabulated:

- Age (years)
- Age categories (≥18 to <45, ≥45 to <65, ≥65; and <65, and ≥65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Height
- Baseline BMI
- Baseline SARS-CoV-2 RT-PCR result (local lab)
- Baseline SARS-CoV-2 serology results (central lab)

Additional baseline characteristics will be included if needed.

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated System Organ Class (SOC) according to Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Prior / Concomitant Medication & Procedures

Medications will be coded to an ATC Level 4, associated ATC Level 2, and standardized medication name according to the Anatomical Therapeutic Chemical Classification System. Procedures will be coded to a PT and associated SOC according to MedDRA®.

Prior medications/procedures are defined as those that were started/performed prior to the first dose of vaccine or study drug (as applicable and whichever occurs first).

On-treatment medications/procedures are defined those taken (or continued to be taken)/ performed following the first dose of vaccine or study drug (as applicable and whichever occurs first).

4.4. Prohibited Medication and Vaccine During Study

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 analyses related to vaccine response (see Section 3.1).

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

  Exception: seasonal influenza vaccine is only prohibited within 14 days before or after study drug administration, or within 14 days before or after Moderna mRNA-1273 vaccine administration.
- Systemic medications that suppresses the immune system (for corticosteroids, ≥20 mg/day of prednisone equivalent), except for the treatment of COVID-19

4.5. Vaccine Response Variable

4.5.1. Primary Vaccine Response Variable

The primary endpoint is the 50% inhibitory dilution (ID50) neutralizing antibody titers of vaccine-induced neutralizing antibodies to SARS-CoV-2, assessed 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.

The Neutralizing Antibody Assay (IMMUNO-COV REGN2118) is a functional assay that detects the presence of specific neutralizing antibodies capable of inhibiting vesicular stomatitis virus (VSV)- SARS2-Fluc. Infection by VSV-SARS2-Fluc results in the expression of firefly luciferase within Vero cells overexpressing the Ace-2 receptor (Vero-Ace-2). Luciferase substrate (d-luciferin) is added to assay plates to allow for a luminescence readout. The total luminescence (relative light units, RLU) corresponds to the extent of infection by VSV-SARS2-Fluc. The ability of antibodies in human serum to block infection of Vero-Ace-2 cells by VSV-SARS2-Fluc by 50% serves as a proxy readout for antibodies capable of neutralizing SARS-CoV-2 infection.

4.5.2. Secondary Vaccine Response Variables

The secondary vaccine response variables in this study include:

- 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}) neutralizing antibody titers of vaccine-induced neutralizing antibodies to SARS-CoV-2 S protein assessed over time after the first dose of Moderna mRNA 1273 vaccine

The time points of the secondary vaccine response variables include 0, 6, 14, 28, 42, 56 days after the first dose of Moderna mRNA 1273 vaccine, except that day 56 is not applicable to the variable of 50% inhibitory dilution (ID_{50}) titers of vaccine-induced neutralizing antibodies to SARS-CoV-2. In addition, variables associated with 6 days after the first dose of Moderna mRNA 1273 vaccine are only applicable to study arms 6d and 9, which corresponds to study day 7 for these two arms. Variables will be reported in both BAU/mL and AU/mL units.

4.5.3. Exploratory Vaccine Response Variables

The exploratory vaccine response variables in this study include

- 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

The time points of the exploratory vaccine response variables include 0, 6, 14, 28, 42, 56 days after the first dose of Moderna mRNA 1273 vaccine. In addition, variables associated with 6 days after the first dose of Moderna mRNA 1273 vaccine are only applicable to study arms 6d and 9, which corresponds to study day 7 for these two arms.

4.5.4. Additional Vaccine Response Variables

World Health Organization (WHO) standard units (IU/mL) as well as Viral Neutralizing Titer (VNT) are collected and will be reported.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a PT and associated SOC according to the latest version of MedDRA®.

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 vaccine dose administration.
- The **primary series vaccination period** is defined as the time from the first vaccine dose administration to 28 days after the second vaccine dose administration, and in subjects receiving only one dose of the vaccine, 28 days after the first 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.

4.6.2. Adverse Events of Special Interest

AESIs are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. In this study, AESI are listed below (as provided in the protocol):

- 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)

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of blood chemistry, hematology, and urinalysis.

Samples for laboratory testing will be collected at visits according to the Schedule of Events (Appendix 11.1). Samples will be analyzed by a central laboratory. The clinical laboratory data consists of blood chemistry, hematology, urinalysis and other specified in section 9.2.5 of the protocol.

Clinical laboratory values will be presented in Standard International (SI) units.

Potentially clinically significant value (PCSV) ranges will be applied to the laboratory test values as applicable (see PCSV criteria in Appendix 11.2).

4.6.4. Vital Signs

Vital signs collected include temperature, blood pressure, heart rate, and respiratory rate. PCSV ranges will be applied to corresponding vital sign parameter values according to (see PCSV criteria in Appendix 11.2).

4.6.5. SARS-CoV-2 test results

SARS-CoV-2 rapid RT-PCR testing will be conducted using nasopharyngeal swabs throughout the study according to the specific Schedules of Events for each enrolment wave.

SARS-CoV-2 rapid RT-PCR will be performed at unscheduled or planned scheduled visits for subjects with signs or symptoms consistent with COVID-19 or those who obtain a positive SARS-CoV-2 RT-PCR test result from the study site or another testing location.

4.7. Pharmacokinetic Variables

The pharmacokinetic variables are the concentrations of REGN10933 and REGN10987 in serum and time when a sample was collected.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA response status, titer, and NAb status at nominal sampling time/visit. Serum samples for immunogenicity analysis will be collected at the timepoints outlined in the Schedule of Events (Appendix 11.1). Samples positive in the ADA assays will be further characterized for ADA titers and for the presence of NAb.

5. STATISTICAL METHODS

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be tabulated by treatment group and overall for the PPS, mFAS and SAF analysis sets.

Baseline is defined as the last available value prior to the first dose of Moderna mRNA-1273 vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first).

5.2. Medical History

Medical history will be tabulated by SOC and PT and by treatment group and overall for the SAF.

5.3. Prior/Concomitant Medications & Procedures

Prior medications and procedures will be tabulated by treatment group for the SAF.

Concomitant medications will be tabulated by treatment group for the entire study period for the SAF.

5.4. Prohibited Medications

Prohibited medications will be tabulated by treatment group for the SAF.

5.5. Subject Disposition

Subject counts within each analysis set by treatment group and total will be presented. Additionally, the following will be tabulated:

- Total number of screened subjects [defined as who signed the Informed Consent Form (ICF)]
- Number of randomized subjects and number and reasons for subjects not randomized.
- Number of subjects who discontinued from the study along with reason for study discontinuation

If applicable, a listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized will be provided.

5.6. Extent of Study Treatment Exposure and Compliance

The number of subjects whose infusion of REGN10933+REGN10987 or whose injection of vaccine was interrupted or incomplete will be tabulated by treatment group for the SAF.

The number of injections of primary series vaccine will be tabulated by treatment group for the SAF. Among those with more than one injection of vaccine, the time between first and second vaccination will be tabulated by treatment group for the SAF. The number of subjects with injections of booster vaccine will be tabulated by treatment group. Time from second injection of primary series vaccine to booster vaccine injection will be tabulated by treatment group for the SAF.

The extent of follow-up (completing visit 56 days after the first vaccine dose, visit 52 weeks after the first vaccine dose) will be tabulated by treatment group for the SAF.

5.7. Analysis of Vaccine Response Variables

For efficacy variables, baseline is defined as the last available value prior to the first dose of Moderna mRNA-1273 vaccine. The analyses will be conducted based on the observed data with no imputation for missing data. Values below the LLOQ will be set to half of LLOQ and values above the upper limit of quantification (ULOQ) will be set to the ULOQ.

5.7.1. Analysis of Primary Vaccine Response Variable

The primary endpoint is the 50% inhibitory dilution (ID_{50}) neutralizing antibody titers of vaccine-induced neutralizing antibodies to SARS-CoV-2, 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. For all analyses, the vaccine alone arms (i.e. arms 6a, 6b, 6c and 6d) will be pooled in the analysis.

An analysis of covariance (ANCOVA) model with treatment group as a fixed effect and age as a continuous covariate will be run in order to perform the primary analysis for the PPS. The least squares mean estimates and associated 95% confidence interval for the endpoint will be reported for each treatment group, as well as for the relative differences between each combination of Moderna mRNA-1273 vaccine and REGN10933+REGN10987 arm (i.e. arms 1 - 5, and 7 - 9) and the pooled vaccine alone group.

Data may be fitted in the log 2 scale, and final outputs of geometric means and relative differences of the geometric mean ratio will be reported through the back-transformation.

Let $\hat{\mu}_A$, $\hat{\mu}_B$ denote the least squares mean estimates and $\hat{\sigma}_A^2$, $\hat{\sigma}_B^2$, $\hat{\sigma}_{AB}$ denote the associated estimated variances and covariance for the endpoint of interest of treatment groups A and B, respectively.

Geometric means and associated 95% confidence intervals for treatment groups A and B will be calculated as:

$$2^{\hat{\mu}_A}, (2^{\hat{\mu}_A - t_{df,\alpha} \times \hat{\sigma}_A}, 2^{\hat{\mu}_A + t_{df,\alpha} \times \hat{\sigma}_A}),$$

and

$$2^{\hat{\mu}_B}, (2^{\hat{\mu}_B - t_{df,\alpha} \times \hat{\sigma}_B}, 2^{\hat{\mu}_B + t_{df,\alpha} \times \hat{\sigma}_B}).$$

Relative difference of the geometric mean ratio and associated 95% confidence interval for treatment groups A and B will be calculated as:

$$(2^{\hat{\mu}_A-\hat{\mu}_B}-1)\times 100\%,\left(\left(2^{(\hat{\mu}_A-\hat{\mu}_B)-t_{d,f,\alpha}\times\sqrt{\hat{\sigma}_A^2-2\hat{\sigma}_{AB}+\hat{\sigma}_B^2}}-1\right)\times 100\%,\left(2^{(\hat{\mu}_A-\hat{\mu}_B)+t_{d,f,\alpha}\times\sqrt{\hat{\sigma}_A^2-2\hat{\sigma}_{AB}+\hat{\sigma}_B^2}}-1\right)\times 100\%\right).$$

5.7.2. Analysis of Secondary Vaccine Response Variables

Secondary vaccine response variables will also be analyzed using an ANCOVA model with treatment group as a fixed effect and age as a covariate in the model using the Per Protocol Analysis Set.

The least square means estimates as well as the relative difference of these estimates between each combination of Moderna mRNA-1273 vaccine and REGN10933+REGN10987 group and the pooled vaccine alone group will be provided along with the associated 95% confidence interval.

Data may be fitted in the log scale, and final outputs will be back-transformed to the original scale using the same method as described for the primary endpoint (see Section 5.7.1).

For concentrations of vaccine-induced antibodies to the following SARS-CoV-2 antigens, if a log transformation is needed, modelling will use a log transformation with base 10:

- Anti-S protein
- Anti-RBD
- Other S protein subdomains (including S1, S2, and NTD)

For variables listed below, if a log transformation is needed, modelling will use a log transformation with base 2:

- 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

Numerical summaries of observed value, change from baseline, and percentage change from baseline will also be tabulated.

5.7.3. Analysis of Exploratory Vaccine Response Variables

Exploratory vaccine response variables will be analyzed in a similar manner as described for the secondary vaccine response variables.

Accompanying descriptive analyses will be provided to all (primary/secondary/exploratory) vaccine response variables.

The distribution of endpoint variables will be checked to ensure ANCOVA type analyses are appropriate. If such modeling is deemed not appropriate, only raw data descriptions will be provided.

On limited numbers of samples, an exploratory analysis will be performed with data from a second neutralization assay that will be summarized in a separate report.

5.7.4. Analysis of Additional Vaccine Response Variables

VNT and WHO standard units will be analyzed in a similar manner as described for the primary vaccine response variable. Efficacy variables may also be explored using the mFAS.

5.7.5. Supplementary and Subgroup Analyses

Supplementary analysis:

In order to assess the consistency of results due to concurrent randomization, analyses of the primary vaccine response variable may be performed separately within waves 1, 2 and within waves 3, 4, respectively.

Subgroup analysis:

The following subgroup analysis may be performed in Per Protocol Analysis Set in order to assess the consistency of results:

- age groups: <65 vs ≥65 (if applicable)
- gender: male vs female

5.7.6. Analysis of sub-study vaccine booster administration

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

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed within the SAF population.

5.8.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of MedDRA®. Coding will be to lowest level terms. The PT and the primary SOC will be listed.

All adverse events will be provided in a listing. Listing of deaths and other SAEs will also be provided.

Tabulations by treatment group will include the following:

<u>All periods combined</u>

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC and PT and Severity
- Serious TEAEs by SOC and PT
- Study Drug Related TEAEs by SOC and PT
- Vaccine Related TEAEs by SOC and PT
- Study Drug Related Infusion Related Reaction TEAEs by SOC and PT

- Study Drug Related Injection Site Reaction TEAEs by SOC and PT
- Vaccine Related Injection Site Reaction TEAEs by SOC and PT
- Study Drug Related Hypersensitivity Reaction TEAEs by SOC and PT
- Vaccine Related Hypersensitivity Reaction TEAEs by SOC and PT
- Treatment-Emergent AESIs by SOC and PT
- TEAEs leading to permanent discontinuation of vaccine by SOC and PT
- TEAEs leading to permanent discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT

Pre-vaccination period

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC and PT and Severity
- Serious TEAEs by SOC and PT
- Study Drug Related TEAEs by SOC and PT
- Study Drug Related Infusion Related Reaction TEAEs by SOC and PT
- Study Drug Related Injection Site Reaction TEAEs by SOC and PT
- Study Drug Related Hypersensitivity Reaction TEAEs by SOC and PT
- TEAEs leading to permanent discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT

Primary series vaccination period and Post-booster vaccination period

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC and PT and Severity
- Serious TEAEs by SOC and PT
- Study Drug Related TEAEs by SOC and PT
- Vaccine Related TEAEs by SOC and PT
- Study Drug Related Infusion Related Reaction TEAEs by SOC and PT
- Study Drug Related Injection Site Reaction TEAEs by SOC and PT
- Vaccine Related Injection Site Reaction TEAEs by SOC and PT
- Study Drug Related Hypersensitivity Reaction TEAEs by SOC and PT
- Vaccine Related Hypersensitivity Reaction TEAEs by SOC and PT

- TEAEs leading to permanent discontinuation of vaccine by SOC and PT
- TEAEs leading to permanent discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT

5.8.2. Clinical Laboratory Measurements

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

Number and percentage of subjects with potentially clinically significant value (PCSV) at any post-randomization time point will be tabulated 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.

5.8.3. Vital Signs

Vital signs (temperature, blood pressure, heart rate, and respiratory rate) will be tabulated by baseline and change from baseline to each scheduled assessment time with descriptive statistics. Graphs of mean (+/- SE) value may be provided.

5.9. Analysis of Pharmacokinetic Data

The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups. No formal statistical hypothesis testing will be performed.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category, and maximum titer observed in subjects in the ADA analysis sets.

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

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

The ADA category of each positive subject is classified as:

- Treatment-boosted – A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value

- Treatment-emergent – A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Subjects that are treatment-emergent will be further categorized as follows:
  - Persistent – A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period (based on nominal sampling time), with no ADA-negative results in-between, regardless of any missing samples
  - Transient – Not persistent or indeterminate, regardless of any missing samples
  - Indeterminate – A positive result in the ADA assay at the last collection time point only, regardless of any missing samples.

The maximum titer category of each subject is classified as:

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

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative subjects
- Number (n) and percent (%) of pre-existing subjects
- Number (n) and percent (%) of treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects

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

5.10.2. Analysis of NAb Data

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

- Negative: Samples tested negative in the ADA assays, or samples positive in the ADA assays but tested negative in the NAb assays, or ADA-positive results without Nab analysis results.
- Positive: Samples tested positive in the NAb assays.

5.10.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to REGN10933 and REGN10987 will be explored by treatment groups. Plots of individual REGN10933 and REGN10987 concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category and NAb status on these profiles.

5.10.3.2. Immunogenicity and Safety and Exposure

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category
- NAb positive

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of the first dose of Moderna mRNA-1273 vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first).

6.2. Data Handling Convention for Vaccine Response Variables

Values below the LLOQ will be set to half of LLOQ and values above the upper limit of quantification (ULOQ) will be set to the ULOQ. If two or more measurements correspond to the same visit, the lowest value will be used.

6.3. Data Handling Convention for Missing Data

Adverse Event

If the severity of a TEAE is missing, it will be classified as severe in the frequency tables by intensity of TEAEs.

If the assessment of relationship of a TEAE to either Moderna mRNA-1273 vaccine or REGN10933+REGN10987 is missing, following rules will be applied

- If the relationship to Moderna mRNA-1273 vaccine is missing, the TEAE will be classified as related to Moderna mRNA-1273 vaccine if the TEAE occurs after the first dose of vaccine
- If the relationship to REGN10933+REGN10987 is missing, the TEAE will be classified as related to REGN10933+REGN10987 if the TEAE occurs after the REGN10933+REGN10987 administration

If the start time of an AE is completely missing, it will be assumed to have occurred on the time of the first dose of Moderna mRNA-1273 vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first). When the partial AE time information does not indicate that in which period (pre-treatment/pre-vaccination/vaccination/post-vaccination) the AE starts, the following rules will be applied (1) if the AE could happen either in pre-treatment or pre-vaccination periods, the AE will be classified to the pre-vaccination period (applicable to arms 1, 2, 3, 4, 5, 7, 8); (2) if the AE could happen either in pre-treatment or vaccination periods, the AE will be classified to the vaccination period (applicable to arms 6a – 6d and 9); (3) if the AE could happen either in pre-vaccination or vaccination periods, the AE will be classified to the vaccination period (applicable to arms 1, 2, 3, 4, 5, 7, 8); (4) if the AE could happen either in vaccination or post-vaccination periods, the AE will be classified to the vaccination period. If the end date of the AE is missing, then the date of the last follow-up will be used for imputation.

Medication/Procedure

If a medication time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first dose of Moderna mRNA-1273 vaccine

or REGN10933+REGN10987 (as applicable and whichever occurs first), it will be considered as concomitant medication/procedure by imputing the start time on the time of first dose of Moderna mRNA-1273 vaccine or REGN10933+REGN10987 (as applicable and whichever occurs first).

Potentially Clinically Significant Values

If a subject has a missing baseline value, this subject will be grouped in the category "normal/missing at baseline."

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSV is >0.5 giga/L or >ULN if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be tabulated or taken into account in the computation of PCSVs.

6.4. Analysis Windows

Assessments repeatedly collected during the study will be defined by the eCRF visit label for temporal tabulations and subject listings.

6.5. Unscheduled Assessments

For safety variables unscheduled visit measurements may be used to determine abnormal values, and PCSVs.

7. INTERIM ANALYSIS

An interim analysis may be conducted after subjects within common enrollment waves have completed the primary endpoint visit (ie, 56 days after the first dose of the vaccine). Such analyses represent an interim analyses of the primary endpoint variable and is not considered the final analysis of the primary endpoint.

8. TIMING OF PRIMARY AND FINAL ANALYSES

The primary vaccine response analysis will be conducted after all subjects have finished the primary endpoint visit (ie, 56 days after the first dose of the vaccine). This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis.

After all subjects finish 1-year of follow-up, the final long-term vaccine response, safety and biomarker data from this study will be reported.

9. SOFTWARE

All statistical analyses will be done using SAS version 9.4 and R 3.5.3 or higher.

10. REFERENCES

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11. APPENDIX

11.1. Schedule of Events

Table 2: 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			Unscheduled Visit	ET
Study Day	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	15[1]	29	43[1]	57	71	183	267	380		
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	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	15[1]	29	43[1]	57	71	183	267	380		
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 3: 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	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	15	29[1]	43	57	169	253	366		
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	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	15	29[1]	43	57	169	253	366		
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 4: 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	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	Pre-dose	7 Dose[1]	Post-Dose	15	29[1]	43	57	169	253	366		
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[3]														
Vaccine Booster Sub-Study (Optional)[14]																

Visit Period	Screening/Baseline				Vaccine Response Assessment							Follow-Up			Unscheduled Visit	ET
Study Day	Screening	-21 to 1 Pre-dose	Dose[1]	Post-Dose	Pre-dose	7 Dose[1]	Post-Dose	15	29[1]	43	57	169	253	366		
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[3]					Refer to Table 6.											
Sample collection and assessments																

Table 5: 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

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 (Protocol Section 9.2.10), optional future biomedical research sub-study (Protocol Section 9.2.8), and optional pharmacogenomics sub-study (Protocol 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 Protocol 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 Protocol 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 postbaseline, the samples will be banked for viral sequencing.
   Additional information is provided in Protocol 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 Protocol 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 Protocol Section 8.5.
7. Note that not all subjects will receive study drug at randomization. Refer to Protocol Section 8.5 and Protocol 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 Protocol 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 Protocol Section 9.2.3.1, Protocol 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 Protocol Section 10.1.1.

13. For Arms 1, 2, 3, 6a, 6c, 7 and 8: 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. For Arms 4, 5, 6b, 6d, and 9: 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.

11.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
AST	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008
Total Bilirubin	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Concept paper on DILI – FDA draft Guidance Oct 2008 Internal DILI WG Oct 2008
Conjugated bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN, and baseline Total Bilirubin ≤ 35% or TBILI ≤1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤ 3 ULN or TBILI ≤ 2ULN	Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008
CPK	>3 and ≤ 10 ULN and baseline ≤ 3ULN >10 ULN and baseline ≤10ULN	FDA Feb 2005 Am J Cardio April 2006
Creatinine	≥150 µmol/L (Adults) or ≥ULN (if ULN≥150 µmol/L) and baseline < 150 µmol/L or <ULN (if ULN≥150 µmol/L) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994 3 independent criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	FDA draft guidance 2010 Four independent criteria
Uric Acid Hyperuricemia: Hypouricemia:	>408 µmol/L or >ULN (if ULN≥408 µmol/L) and baseline ≤408 µmol/L or ≤ULN (if ULN≥408 µmol/L) <120 µmol/L or <LLN (if LLN≤120 µmol/L) and baseline ≥ 120 µmol/L or ≥LLN (if LLN≤120 µmol/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	<80 mmol/L or <LLN (if LLN≤80 mmol/L) and baseline ≥ 80 mmol/L or ≥LLN (if LLN≤80 mmol/L) >115 mmol/L or >ULN (if ULN≥115 mmol/L) and baseline ≤ 115 mmol/L or ≤ULN (if ULN≥115 mmol/L)	Two independent criteria
Sodium Hyponatremia: Hypernatremia:	≤129 mmol/L or ≤LLN (if LLN≤129 mmol/L) and baseline > 129 mmol/L or >LLN (if LLN≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L or <LLN (if LLN≤3 mmol/L) and baseline ≥ 3 mmol/L or ≥LLN (if LLN≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN≥5.5 mmol/L)	FDA Feb 2005. Two independent criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN≥7.74 mmol/L) and baseline < 7.74 mmol/L or <ULN (if ULN≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN≥4.6 mmol/L) and baseline < 4.6 mmol/L or <ULN (if ULN≥4.6 mmol/L)	Threshold for therapeutic intervention
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	FDA Sept 2005
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black) ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	Increase in WBC: not relevant.
Lymphocytes	>4.0 Giga/L or >ULN (if ULN≥4.0 Giga/L) and baseline ≤ 4.0 Giga/L or ≤ULN (if ULN≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991.

Parameter	PCSV For Studies in healthy subjects only	Comments
Monocytes	>0.7 Giga/L or >ULN (if ULN≥0.7 Giga/L) and baseline ≤ 0.7 Giga/L or ≤ULN (if ULN≥0.7 Giga/L)	
Basophils	>0.1 Giga/L or >ULN (if ULN≥0.1 Giga/L) and baseline ≤ 0.1 Giga/L or ≤ULN (if ULN≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L or ≤LLN (if LLN≤115 g/L) and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN≤95 g/L) and baseline > 95 g/L or >LLN (if LLN≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN≥185 g/L) and baseline <185 g/L or <ULN (if ULN≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN≥165 g/L) and baseline < 165 g/L or <ULN (if ULN≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent.
Hematocrit	≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male; ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN≤0.32v/v) for Female ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male; ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female	Two Criteria are independent
RBC	≥6 Tera/L or ≥ULN (if ULN≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN≥6 Tera/L)	

Parameter	PCSV For Studies in healthy subjects only	Comments
Platelets	<100 Giga/L or <LLN (if LLN≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN≥700 Giga/L) and baseline < 700 Giga/L or <ULN (if ULN≥700 Giga/L)	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING
Weight	≥ 5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

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