Analysis Data Reviewer's Guide

ModernaTX, Inc.

Study mRNA-1273-P201 Part A

Analysis Data Reviewer's Guide

Contents

1. Introduction

1.1 Purpose

This document provides context for the analysis datasets and terminology that benefit from additional explanation beyond the Data Definition document (define.xml) for an individual study. In addition, this document provides a summary of ADaM conformance findings.

1.2 Acronyms

Acronym	Translation
AR	Adverse Reaction
DCO	Data Cut of date
mRNA	Messenger ribonucleic acid
PP	Per Protocol

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	•SDTM v1.4 •SDTM-IG v3.2
SDTM Controlled Terminology	CDISC SDTM Controlled Terminology, 2020-06-26
ADaM	•ADaM v2.1 •ADaM-IG v1.1
ADaM Controlled Terminology	CDISC ADaM Controlled Terminology, 2020-06-26
Data Definitions	Define-XML v2.0
TAUG (if applicable)	TAUG-VX 1.1
Medical Events Dictionary	MedDRA 23.0
Other standards (optional)	Guidance for Industry - Technical Specifications Document: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (October 2019)

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: mRNA-1273-P201

Protocol Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Protocol Versions: Amendment 1-6

Amendment 1, 18 May 2020:

The main purpose of this amendment is to incorporate the following modifications requested by the FDA Center for Biologics Evaluation and Research:

- Enhance monitoring of participants who are confirmed to have SARS-CoV-2 infection.
- Include a convalescent visit for participants with confirmed SARS-CoV-2 infection.
- Explore the mRNA-1273 vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection.
- Updated the Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to extend the follow-up to a full 12-month period after the second injection on Day 29 (Month 1).
- Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.

Amendment 2, 01 Jul 2020:

The main purpose of this amendment is to change the statistical analysis plan by removing interim analyses and defining the Primary Study Analysis and End of Study Analysis. The summary of changes table provided here describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Amendment 3, 02 Sep 2020:

The main purpose of this amendment is to clarify that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit. The summary of changes table describes the major changes made in Amendment 3 relative to Amendment 2, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Amendment 4, 15 Jan 2021:

Following authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA), this study amendment is designed to transition to Part B, the Open-Label Interventional Phase (Figure 3). Transitioning the study to Part B, Open-Label Interventional Phase permits all ongoing study participants to (a) be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA, and (b) the option to offer all ongoing study participants who request unblinding an opportunity to schedule a study visit to know their original group assignment (placebo vs. mRNA-1273 [50µg or 100µg vaccine]).

Part B, Open-label Interventional Phase, also provides the opportunity for study participants who previously received placebo, to request to receive 2 doses of the mRNA-1273 (100 µg) vaccine.

Participants who originally received 1 or 2 doses of mRNA-1273 (50µg or 100µg vaccine) during Part A, will have the opportunity to request to receive a single booster dose of mRNA-1273 (50 µg).

Amendment 5, 19 Feb 2021:

There is an urgent need for vaccination strategies against SARS-CoV2 that induce broader protection that includes variants such as B.1.351 to decrease morbidity and mortality. ModernaTX, Inc. is developing a mRNA vaccine (mRNA-1273.351) that is similar to the mRNA-1273 vaccine available under the Emergency Use Authorization (EUA), but in which the mRNA encodes for mutations included in the S protein of the B.1.351 variant.

This protocol amendment will add Part C to the protocol, which will be an amendment to investigate the proof of concept of a single dose booster of two dose levels of the mRNA-1273.351 variant and a mixture formulation of mRNA-1273/mRNA-1273.351 administered to approximately 60 participants who received primary vaccination during the mRNA-1273-P301 COVE study. The COVE study participants will be offered enrollment in this new site-specific sub study, Part C of mRNA-1273-P201, based on pre-determined eligibility criteria. If they choose to enroll in this protocol amendment, the participants will be discontinued from the mRNA-1273-P301 COVE study. The participants would have had to be originally randomized to the mRNA-1273 group and have previously received 2 doses of mRNA-1273, 28 days apart, to be enrolled in this amendment. The unblinding visit should also have occurred. In this protocol amendment, enrolled participants will be allocated 1:1:1 to receive a single intramuscular injection of mRNA-1273.351 (20 µg or 50 µg) or mRNA-1273/mRNA-1273.351 mixture (50 µg) as a booster injection.

Amendment 6, 22 Apr 2021:

This protocol amendment will add an analysis at the end of Part A. An analysis of safety and immunogenicity data will be performed after all participants have completed Part A of the study. All data collected in Part A of the study will be cleaned (ie, data that are as clean as possible) and locked and a report may be generated as needed.

The summary of changes table provided here describes the major changes made in Amendment 6 relative to Amendment 5, including the sections modified and the corresponding rationales. The synopsis of Amendment 6 has been modified to correspond to changes in the body of the protocol.

2.2 Protocol Design in Relation to ADaM Concepts

Figure 1: Study Flow Schema (Part A, Blinded Phase)

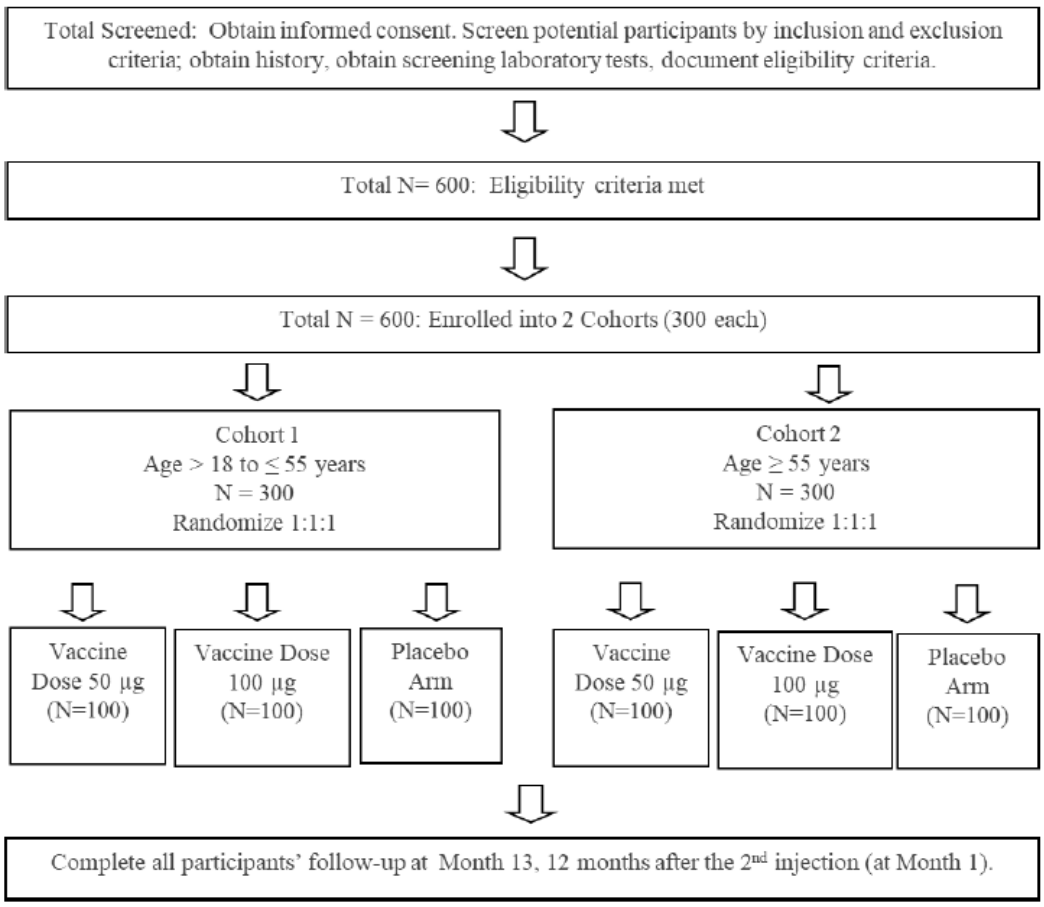
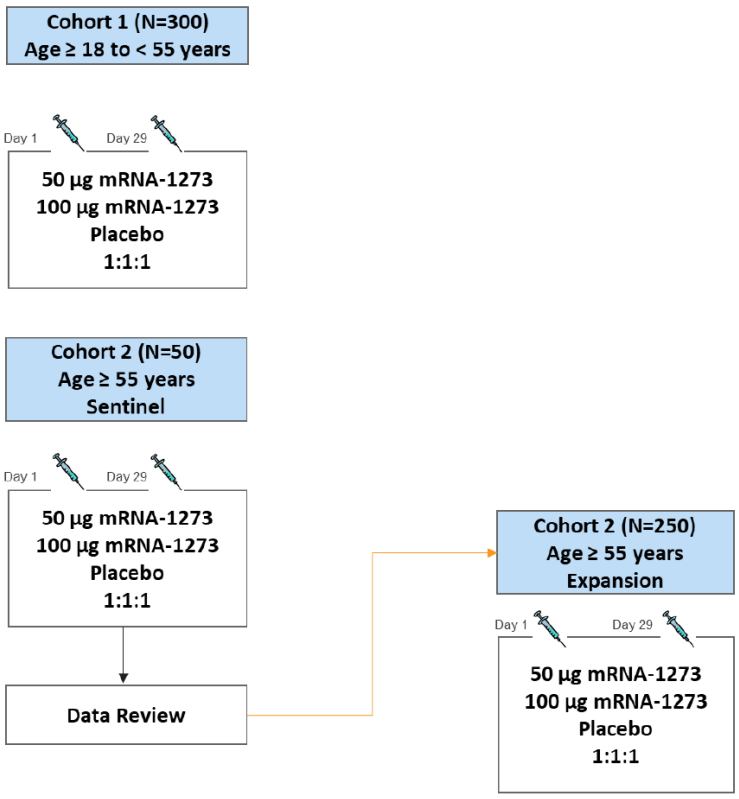


Figure 2: Sentinel and Expansion Cohort Schema



3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Core Variables

Core variables are those that are represented across all/most analysis datasets.

Variable Name	Variable Description
STUDYID	Study Identifier
USUBJID	Unique Subject Identifier
SUBJID	Subject Identifier for the Study
SITEID	Study Site Identifier
COUNTRY	COUNTRY
AGE	Age
AGEU	Age Units
AGEGR1	Pooled Age Group 1

Variable Name	Variable Description
AGEGR1N	Pooled Age Group 1 (N)
AGEGR2	Pooled Age Group 2
AGEGR2N	Pooled Age Group 2 (N)
SEX	Sex
RACE	Race
RACESPY	Race Specify
ETHNIC	Ethnicity
RANDFL	Randomized Population Flag
SAFFL	Safety Population Flag
SAR1FL	First Solicited Safety Population Flag
SAR2FL	Second Solicited Safety Population Flag
SARAFL	Solicited Safety Population Flag
FASBABFL	Full Analysis Set bAb Population Flag
FASNABFL	Full Analysis Set nAb Population Flag
PPBABFL	Per Protocol bAb Population Flag
PPNABFL	Per Protocol nAb Population Flag
PPBD29FL	Per Protocol bAb Day 29 Flag
PPBD57FL	Per Protocol bAb Day 57 Flag
PPBD209FL	Per Protocol bAb Day 209 Flag
PPND29FL	Per Protocol nAb Day 29 Flag
PPND57FL	Per Protocol nAb Day 57 Flag
PPND209FL	Per Protocol nAb Day 209 Flag
FASNA2FL	FAS nAb 2 Population Flag
PPNAB2FL	PP nAb 2 Population Flag
PN2D29FL	Per Protocol nAb 2 Day 29 Flag
PN2D57FL	Per Protocol nAb 2 Day 57 Flag
PN2209FL	Per Protocol nAb 2 Day 209 Flag
COV19BL	Baseline COVID Infection
ELECSBL	Baseline Elecsys SARS CoV-2 Assay

Variable Name	Variable Description
COV19FL	COVID Infection Flag
SENTLFL	Sentinel Participant Flag
D29W7DFL	Day 29 Out of 7-Day Window Flag
TR01EDT	Date of Last Exposure in Period 01
TR01EDTM	Datetime of Last Exposure in Period 01
TR01SDT	Date of First Exposure in Period 01
TR01SDTM	Datetime of First Exposure in Period 01
TRT01A	Actual Treatment for Period 01
TRT01AN	Actual Treatment for Period 01 (N)
TRT01P	Planned Treatment for Period 01
TRT01PN	Planned Treatment for Period 01 (N)
TRTSDTM	Datetime of First Exposure to Treatment
TRTEDTM	Datetime of Last Exposure to Treatment
DVBABFL	Deviation Impact bAb Flag
DVNABFL	Deviation Impact nAb Flag
DOSE1FL	Vaccination 1 Flag
DOSE2DT	Date of Dose 2
DOSE2FL	Vaccination 2 Flag
DOS2DTM	Datetime of Dose 2
DOSEROFL	Dosing Error Flag

3.2 Treatment Variables

ARM versus TRTxxP

Are the values of ARM equivalent in meaning to values of TRT01P?

Yes: TRT01P are defined as Planned Treatment that is based on Randomized Number

ACTARM versus TRT01A

If TRT01A is used, then are the values of ACTARM equivalent in meaning to values of TRT01A?

Yes: Actual treatment is defined as

Dose Received	ACTARM/TRT01A
0	Placebo
>0 and <=75 ug	50 ug
>75	100 ug

Use of ADaM Treatment Variables in Analysis

Are both planned and actual treatment variables used in analysis?

Yes: Treatment Group Variables are used by each analysis set:

Treatment Group	Population Set
TRT01P	Randomized Set
TRT01A	Safety Set
TRT01A	Solicited Safety Set
TRT01P	Full Analysis Set
TRT01P	Per-Protocol Set

Use of ADaM Treatment Grouping Variables in Analysis

Are both planned and actual treatment grouping variables used in analysis?

No: There are no treatment grouping variables used in analysis

3.3 Subject Issues that Require Special Analysis Rules

Actual treatment group will be assigned if subject was treated with different treatment group as randomized. Subject with wrong treatment was documented and provided in Appendix A.

3.4 Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more analysis datasets?

Yes: Analysis Visit Window is used for Safety and Immunogenicity Analysis

Were unscheduled visits used in any analyses?

Yes: Unscheduled visits were used for Safety and Immunogenicity Analysis if they are not collected at scheduled visit and the following rule is used:

- If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

- If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Appendix B.

3.5 Imputation/Derivation Methods

If date imputation was performed, were there rules that were used in multiple analysis datasets?

Yes: Incomplete / missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix C.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (eg, <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (eg, >3000), the numeric values will be imputed by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

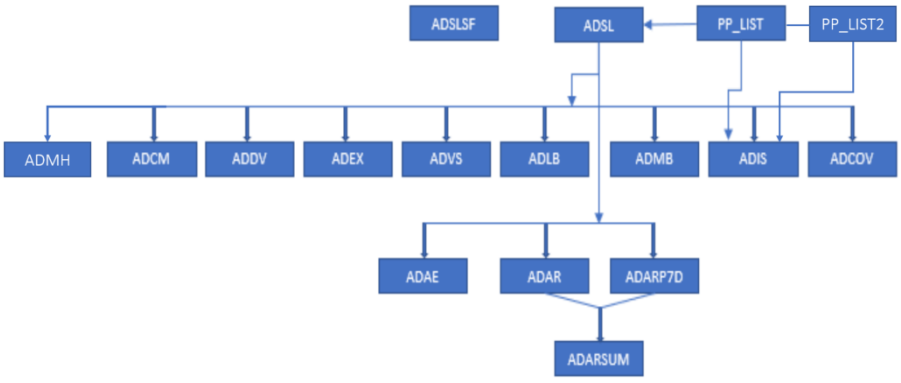
4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

There are no split datasets that required due to size constrains.

4.2 Data Dependencies

PP_LIST and PP_LIST2 were created first as intermediate datasets which means they are not included in ADaM data packages. ADSL was created after PP_LIST. All other datasets were created after ADSL to get core variables except ADSLSF (Screen Fail Subj-Level Analysis Dataset). ADARSUM (Solicited AR Summary Analysis Dataset) is derived directly from ADAR (Solicited AR Analysis Dataset) and ADARP7D (Solicited AR post D7 Analysis Dataset).



4.3 Intermediate Datasets

There are two intermediate datasets created:

PP_LIST (Per Protocol dataset from 1st viral Lot) and PP_LIST2 (Per Protocol dataset from all viral Lots) datasets were created as intermediate datasets because manual review process of major protocol deviations was needed before PP_LIST and PP_LIST2 were created. Then PP_LIST and PP_LIST2 were used to create ADIS.

There're two viral lots used for Serum SARS-CoV-2 Neutralizing Antibodies testing planned for *End of Part A Analysis*. The results by those 2 lots are generally comparable. However, LLOQ and ULOQ are different between results reported from those two lots, so for values close to the LLOQ/ULOQ, there could be sensitivities. Besides, the definition of seroconversion could be affected by the LLOQ value. As a result, the PPS analysis were conducted twice, a primary analysis was based on the 1st Lot only, by which the majority samples were tested, and a sensitivity analysis based on results reported using all lots. Hence, the PPS was defined for each analysis respectively. PP_LIST was defined based on the 1st lot, while PP_LIST2 was defined based on all Lots results.

PP_LIST is source data to derive ADSL.PPBABFL, ADSL.PPNABFL, ADIS.PPBABRFL and ADIS.PPNABRFL. PP_LIST2 is source data to derive ADSL. PPNAB2FL and ADIS.PPNA2RFL.

Table 4.3.1: Example output of PP Listing

Subject Identifier for the Study	Visit Timepoint	Dummy Visit Flag	Baseline COVID Infection	Received Vaccination #1	Received Vaccination #2	Vaccination #2 within window	Post-baseline COVID Infection	bAb result (for at least 1 assay)	nAb result (for at least 1 assay)	Serum bAb collection within window	Serum nAb collection within window
US2011004	Baseline	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y
US2011004	Day 29	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y
US2011004	Day 43	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y
US2011004	Day 57	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y
US2011004	Day 209	N	Not Detected	Y	Y	Y	N	Y	N	Y	N
US2011004	Day 394	Y	Not Detected	Y	Y	Y	N	N	N	N	N

Table 4.3.1: Example output of PP Listing (Continue)

Subject Identifier for the Study	Visit Timepoint	In bAb FAS	In nAb FAS	Exclusion from bAb due to major PD	Exclusion from nAb due to major PD	bAb PP flag at each visit	nAb PP flag at each visit	Reason exclusion from bAb PP	Reason exclusion from nAb PP
US2011004	Baseline	Y	Y	N	N	Y	Y		
US2011004	Day 29	Y	Y	N	N	Y	Y		
US2011004	Day 43	Y	Y	N	N	Y	Y		
US2011004	Day 57	Y	Y	N	N	Y	Y		
US2011004	Day 209	Y	Y	N	N	Y	N		There was no immunogenicity result at corresponding visit
US2011004	Day 394	Y	Y	N	N	N	N	There was no immunogenicity result at corresponding visit	There was no immunogenicity result at corresponding visit

Table 4.3.2: Example output of PP Listing2

Subject Identifier for the Study	Visit Timepoint	Dummy Visit Flag	Baseline COVID Infection	Received Vaccination #1	Received Vaccination #2	Vaccination #2 within window	Post-baseline COVID Infection	nAb result (for at least 1 assay)	Serum nAb collection within window	In nAb FAS 2	Exclusion from nAb due to major PD	nAb PP flag at each visit	MNET LLOQ ULOQ	MN50 LLOQ ULOQ
US2011004	Baseline	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y	40 - 1280	91.1 - 2031.87
US2011004	Day 29	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y	40 - 1280	91.1 - 2031.87
US2011004	Day 43	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y	40 - 1280	91.1 - 2031.87
US2011004	Day 57	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y	40 - 1280	91.1 - 2031.87
US2011004	Day 209	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y	160 - 1280	318.46 - 1917.83
US2011004	Day 394	Y	Not Detected	Y	Y	Y	N	N	N	Y	N	N		

5. Analysis Dataset Descriptions

5.1 Overview

Are data for screen failures, including data for run-in screening (for example, SDTM values of ARMCD='SCRNFAIL', or 'NOTASSGN') included in ADaM datasets? Yes

There is one screen failure ADaM dataset was created to support screen failure table. The screening failures are excluded from all other ADaM datasets.

Dataset	Dataset Label
ADSLSF	Screen Fail Subj-Level Analysis Dataset

Are data taken from an ongoing study?

Yes: Per protocol, the end of part A analysis of safety and immunogenicity data will be triggered after all participants have completed Participant Decision Visit / OL-D1 form. All data relevant to the end of part A analysis through Day 394 will be cleaned (data are as clean as possible).

For the end of part A analysis, subject-specific cut-off date is applied to all SDTM subject domains using DCO Algorithm provided IADCO.PDF

Do the analysis datasets support all protocol- and statistical analysis plan-specified objectives? Yes

Include all objectives listed in the protocol or SAP which are not supported in the analysis datasets and the reason for their absence. NA

5.2 Analysis Datasets

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject charac-teristics	PK /PD	Primary Objective	Structure
ADSL - Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			X			One record per subject
ADAE - Adverse Event Analysis Dataset	OCCURRENCE DATA STRUCTURE		X			X	One record per subject per adverse event
ADAR - Solicited AR Analysis Dataset	BASIC DATA STRUCTURE		X			X	One or more records per subject per analysis parameter per analysis timepoint
ADARP7D - Solicited AR post D7 Analysis Dataset	BASIC DATA STRUCTURE		X			X	One or more records per subject per analysis parameter per analysis timepoint
ADARSUM - Solicited AR Summary Analysis Dataset	BASIC DATA STRUCTURE		X			X	One or more records per subject per analysis parameter per analysis timepoint

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject charac-teristics	PK /PD	Primary Objective	Structure
ADCM - Concomitant Medication Analysis Dataset	OCCURRENCE DATA STRUCTURE			X			One record per subject per medication per medication start date
ADCOV - COVID-19 Analysis Dataset	BASIC DATA STRUCTURE		X				One or more records per subject per analysis parameter per analysis timepoint
ADDV - Deviation Analysis Dataset	OCCURRENCE DATA STRUCTURE			X			One record per subject per deviation
ADEX - Treatment Exposure Analysis Dataset	OCCURRENCE DATA STRUCTURE		X				One record per subject per administration
ADIS - Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE	X				X	One or more records per subject per analysis parameter per analysis timepoint

Dataset - Dataset Label	Class	Efficacy	Safety	Baseline or other subject charac-teristics	PK /PD	Primary Objective	Structure
ADLB - Laboratory Analysis Dataset	BASIC DATA STRUCTURE		X			X	One or more records per subject per analysis parameter per analysis timepoint
ADMB - Microbiology Analysis Dataset	BASIC DATA STRUCTURE	X					One or more records per subject per analysis parameter per analysis timepoint
ADMH - Medical History Analysis Dataset	OCCURRENCE DATA STRUCTURE		X	X			One record per subject per medical history
ADSLSF - Screen Fail Subj-Level Analysis Dataset	ADAM OTHER			X			One record per screen failed subject
ADVS - Vital Signs Analysis Dataset	BASIC DATA STRUCTURE		X			X	One or more records per subject per analysis parameter per analysis timepoint

5.2.1 ADSL - Subject-Level Analysis Dataset

In addition to supporting all analyses, ADSL contains variables to also support baseline characteristics and disposition analyses. The common variables are defined in ADSL and copied

into other analysis datasets as needed. All subjects in DM, except of screen failures, were included in ADSL.

ADSL.UICF - Updated Informed Consent (Y/N) is the variable for Part A Completed (Y/N)

5.2.2 ADAR - Solicited AR Analysis Dataset

ADAR contains symptom data that are derived from SDTM.FACE (Daily Symptom within 7 days after each vaccine) and SDTM.VS (Fever if VS.VSTPTNUM<=7). It is based on one record per subject (SUBJID), per symptom (PARAMCD), per timepoint (ATPT), per vaccine reference (ATPTREF), per evaluator (FAEVAL = 'STUDY SUBJECT' or 'INVESTIGATOR' if data source is from FACE). PARAM represented each symptom reported by either subject via e-Diary or investigator via CRF (see Table 5.2.2). Pooled Analysis Timepoint Variable (ATPTGR1) is created to set worse ATOXGR flag (ANL01FL) per subject, per symptom, per vaccination (Table 5.2.2.1 screen captured sample data).

Table 5.2.2 – List of Symptom Data Source

PARAMCD	PARAM	DATA SOURCE
PAIN	Pain	e-Diary/CRF
ERYTHDIA	Erythema Longest Diameter (mm)	e-Diary/CRF
SWELLDIA	Swelling Longest Diameter (mm)	e-Diary/CRF
FEVER	Fever (C)	e-Diary/CRF
ARTHRALG	Arthralgia	e-Diary/CRF
CHILLS	Chills	e-Diary/CRF
FATIGUE	Fatigue	e-Diary/CRF
HEADACHE	Headache	e-Diary/CRF
NAUSEA	Nausea/Vomiting	e-Diary/CRF
MYALGIA	Myalgia	e-Diary/CRF
LYMPHOCC	Lymphadenopathy Occurrence	e-Diary/CRF
RASHOCC	Rash Occurrence	e-Diary/CRF
LYMPH	Lymphadenopathy	CRF
RASH	Rash	CRF

Table 5.2.2.1

SUBJID	ATPT	ATPTREF	ATPTGR1	PARAMCD	ATOXGR	FAEVAL	ANL01FL
US2021058	DAY 1, 1 HOUR AFTER VACCINATION (AT STUDY CLINIC)	Vaccination 2	DAY 1	MYALGIA	Grade 0	STUDY SUBJECT	
US2021058	DAY 1, AFTER VACCINATION (AT HOME)	Vaccination 2	DAY 1	MYALGIA	Grade 3	INVESTIGATOR	
US2021058	DAY 1, AFTER VACCINATION (AT HOME)	Vaccination 2	DAY 1	MYALGIA	Grade 3	STUDY SUBJECT	Y
US2021058	DAY 2	Vaccination 2	DAY 2	MYALGIA	Grade 3	INVESTIGATOR	
US2021058	DAY 2	Vaccination 2	DAY 2	MYALGIA	Grade 3	STUDY SUBJECT	Y
US2021058	DAY 3	Vaccination 2	DAY 3	MYALGIA	Grade 3	INVESTIGATOR	Y
US2021058	DAY 3	Vaccination 2	DAY 3	MYALGIA	Grade 1	STUDY SUBJECT	

5.2.3 ADARP7D - Solicited AR post D7 Analysis Dataset

ADARP7D has the same data structure as ADAR, data are derived from SDTM.FACE (Daily Symptom within 7 days), SDTM.FAAE (Daily Symptom last and beyond day 7) and SDTM.VS.

Data from SDTM.FACE are copied to ADARP7D only if the same subject and symptom records (Toxicity Grade >0) are found from SDTM.FAAE (see table 5.2.3.1).

Table 5.2.3.1

STUDYID	USUBJID	ATPTREF	ATPT	PARAM	ATOXGR	SRCDOM	FAEVAL
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 2	Arthralgia	Grade 1	FACE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 3	Arthralgia	Grade 2	FACE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 4	Arthralgia	Grade 1	FACE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 5	Arthralgia	Grade 1	FACE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 7	Arthralgia	Grade 1	FACE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 8	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 9	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 10	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 11	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 12	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 13	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 14	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 15	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 16	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 17	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 18	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 19	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 20	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 21	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 22	Arthralgia	Grade 1	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 23	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 24	Arthralgia	Grade 2	FAAE	STUDY SUBJECT
mRNA-1273-P201	mRNA-1273-P201-US201-1123	Vaccination 1	DAY 25	Arthralgia	Grade 1	FAAE	STUDY SUBJECT

A set of records selection flag variables are created to support different analysis (see table 5.2.3.2)

Table 5.2.3.2

ANL01FL	Set to 'Y' if PARAMCD in ('PAIN' or 'ERYTHDIA' or 'SWELLDIA', 'LYMPH')
ANL02FL	Set to 'Y' if the records satisfied both criteria met: 1. ANL01FL = 'Y' 2. the smallest ATPTGR1N >=8 per subject per symptom (PARAMCD) per vaccination (ATPTREF)
ANL03FL	Set to blank if PARAMCD in (MEDTAK, MEDTAKT And MEDTAKP) Set to 'Y' by selecting the first record with maximum non-missing AVALC (Y>N) per subject per PARAM per vaccination (ATPTREF) per ATPT if PARAMCD in (RASHOCC, LYMPHOCC) Set to 'Y' by selecting the first record with maximum non-missing ATOXGRN per subject per PARAM per vaccination (ATPTREF) per ATPT, otherwise Note: Please select the one where FAEVAL='STUDY SUBJECT' or missing for FEVER) if there are two records per day with different FAEVAL
ANL04FL	Set to 'Y' to all records per subject per ATPTREF per PARAM if the smallest ATPTGR1N<8 and the largest ATPTGR1N>=8
ANL05FL	Set 'Y' to all records with correspondent PARAMCD where PARACT1='LOCAL' and records at ATPTN=7 and ATPTN=8 per subject per ATPTREF per PARAMCD
ANL06FL	Set to 'Y' to all records correspondent PARAMCD where PARACT1= 'LOCAL' and any of below criteria met per subject per ATPTREF per PARAMCD 1. Have no record at ATPTN=7 2. Have record at ATPTN=7 but have no record at ATPTN=8.

	Symptom Occurred within Day 7							Symptom Occurred after Day 7						ANLXXFL
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	
Case 1							X	X							ANL05FL
Case 2							X		X						ANL06FL
Case 2						X		X							
Case 2						X			X						
Case 3									X						ANL02FL
Case 3									X						
Case 7								X	X						

5.2.4 ADARSUM - Solicited AR Summary Analysis Dataset

ADARSUM includes summary data of ADAR and ADARP7D. They contain

a. Topline symptom grade within 7 days after each vaccine that is derived from ADAR. One record per subject (SUBJID), per symptom (PARAMCD), worse grade (ATOXGR) and per vaccine from Day 1 to Day 7 (ATPTREF).
b. Total number of days with symptom grade > 0 that are derived from both ADAR and ADARP7D. One record per subject (SUBJID), per symptom (PARAMCD), and per vaccine (ATPTREF).

5.2.5 ADCOV - COVID-19 Analysis Dataset

ADCOV contains COVID-19 symptom data from SDTM.FAOT, COVID-19 EXPOSURE' from SDTM.ER and SDTM.SS where SSCAT is not 'SAFETY CALL'.

5.2.6 ADIS - Immunogenicity Analysis Dataset

ADIS dataset was created to support Summary of Binding/Neutralized Antibody Levels analysis. Log10 transformed parameters (see Table 5.2.7.1) were derived to support GMT and GMFR.

The GMT and geometric mean (GM) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers or levels within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers or levels for subject i at time points j and k, $j \neq k$

5.2.7 ADMB - Microbiology Analysis Dataset

ADMB contains both RT-PCR test results and other microbiology data that is derived from SDT.MB. It is based on one record per subject (SUBJID), per parameter (PARAMCD) and per timepoint (AVISIT).

5.2.8 ADSLSF - Screen Fail Subj-Level Analysis Dataset

ADSLSF was created for Summary of Subject Screen Failure tables, which contains subject id and reasons of screen failure only, the detail information can be retrieved from SDTM.DM /SUPPDM and SDTM.DS.

6. Data Conformance Summary

6.1 Conformance Inputs

Was a validator used to evaluate conformance?	**Yes**
If yes, specify the version(s) of the validation rules:	**Pinnacle 21 Enterprise version 4.2.0** **Validation Engine version 1907.2**
Were sponsor-defined validation rules used to evaluate conformance?	**No**
If yes, describe any significant sponsor-defined validation rules:	**n/a**
(Text or table here. If significant amount, include as an appendix)	
Were the ADaM datasets evaluated in relation to define.xml?	**Yes**
Was define.xml evaluated?	**Yes**
Provide any additional compliance evaluation information:	

6.2 Issues Summary

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0019	COMPLFL subject-population flag value is null	Error	ADSL	555 (92.50%)	This is due to study is still ongoing

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0253	Record key from SDTM AE is not traceable to ADaM ADAE (not enough ADAE recs)	Error	AE	78 (12.17%)	Any solicited AR captured in AE form has been moved to either ADAR (within 7 days after each vaccine) or ADARP7D (last or after 7 days after each vaccine) unless it meets the criteria for SAE or lasts beyond 7 days post injection, but SDTM.AE is flagged such record as SUPPAE.REMOVEFL=Y instead of remove
AD0279	ASEVN value != 1, 2, 3, or null	Error	ADAE	1 (0.18%)	Per protocol, AR analysis is based both AESEV and AETOXGR, ASEV is created for such type analysis
AD0304	Only some of these variables are present and populated: SMQ06NAM,SMQ06CD,SMQ06SC	Error	ADAE	31 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ14NAM,SMQ14CD,SMQ14SC	Error	ADAE	9 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ10NAM,SMQ10CD,SMQ10SC	Error	ADAE	2 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ07NAM,SMQ07CD,SMQ07SC	Error	ADAE	3 (100.00%)	SMQXXCD is permissible variable, accept current setting

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0304	Only some of these variables are present and populated: SMQ11NAM,SMQ11CD,SMQ11SC	Error	ADAE	7 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ01NAM,SMQ01CD,SMQ01SC	Error	ADAE	24 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ02NAM,SMQ02CD,SMQ02SC	Error	ADAE	2 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ03NAM,SMQ03CD,SMQ03SC	Error	ADAE	26 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ13NAM,SMQ13CD,SMQ13SC	Error	ADAE	3 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ09NAM,SMQ09CD,SMQ09SC	Error	ADAE	1 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ01NAM,SMQ01CD,SMQ01SC	Error	ADMH	2 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD0304	Only some of these variables are present and populated: SMQ06NAM,SMQ06CD,SMQ06SC	Error	ADMH	321 (100.00%)	SMQXXCD is permissible variable, accept current setting

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0304	Only some of these variables are present and populated: SMQ02NAM,SMQ02CD,SMQ02SC	Error	ADMH	125 (100.00%)	SMQXXCD is permissible variable, accept current setting
AD1012	Secondary custom variable is present, but its primary variable is not present	Warning	ADMH	3 (60.00%)	False positive message
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADAR	757 (0.68%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADARSUM	144 (0.65%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADCM	19 (0.83%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADCOV	84 (0.63%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADDV	11 (1.07%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADEX	8 (0.67%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADIS	225 (0.68%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADLB	131 (0.35%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADMB	273 (0.66%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADMH	8 (0.33%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADSL	4 (0.67%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADVS	286 (0.68%)	RACE = "MULTIPLE" because patient checked more than one race. RACE = "OTHER" because data was captured from CRF
DD0024	Invalid Term in codelist 'Action Taken with Study Treatment' for variable 'AEACN'	Warning	DEFINE	1 (100.00%)	'DOSE DELAY ' was captured from CRF
DD0099	Extended value for AnalysisReason	Warning	DEFINE	2 (100.00%)	No issues found. accepted current setting
DD0100	Extended value for AnalysisPurpose	Warning	DEFINE	2 (100.00%)	No issues found. accepted current setting

7. Submission of Programs

All programs for analysis datasets and primary and secondary efficacy results are submitted. They were all created on a SAS Server platform using V9.4. The internal reference date used to create dates in ADaM datasets is 2021-06-11.

7.1 ADaM Programs

Program Name	Output	Macro Used
A10ADSL	ADSL.SAS7BDAT	_adsl_vars_ madam
A20ADAE	ADAE.SAS7BDAT	madam
A20ADAR	ADAR.SAS7BDAT	madam
A20ADARP7D	ADARP7D.SAS7BDAT	madam
A20ADCM	ADCM.SAS7BDAT	madam

Program Name	Output	Macro Used
A20ADCOV	ADCOV.SAS7BDAT	madam
A20ADDV	ADDV.SAS7BDAT	madam
A20ADEX	ADEX.SAS7BDAT	madam
A20ADIS	ADIS.SAS7BDAT	_adis_vars_, madam
A20ADLB	ADLB.SAS7BDAT	madam
A20ADMB	ADMB.SAS7BDAT	madam
A20ADMH	ADMH.SAS7BDAT	madam
A20ADSLSF	ADSLSF.SAS7BDAT	madam
A20ADVS	ADVS.SAS7BDAT	madam
A30ADARSUM	ADARSUM.SAS7BDAT	madam

7.2 Analysis Output Programs

Program Name	Purpose
t140201011201	Summary of Binding Antibody Levels Specific to SARS-CoV-2 Spike Protein by ELISA Per-Protocol Set for SARS-CoV-2-specific bAb
t140202010102	Summary of Neutralizing Antibody Titers Per-Protocol Set for SARS-CoV-2-specific nAb from All Lots
t1403010702	Summary of Unsolicited TEAE from Day 1 to End of Part A Safety Set

7.3 Macro Programs

Program Name	Purpose
madam	Contains a list of macros for ADaM development: %mergeadsl: macro to merge with adsl by subject and keep records in both datasets %calcdy: macro to calculate study day based on a given reference date %trta: macro to derive actual treatment variable at record level
_adsl_vars_	Create common code for analysis dataset adsl
_adis_vars_	Create common code for analysis dataset adis
mclopper	Create Inferential Statistical Analysis Macro
mgm_ci	Create Inferential Statistical Analysis Macro (95%)
mmwintext	Post process of dataset using mw_sentence_case and mw_footnote
modmrna1273p201_IA_ae_defaults	ARTz AE default
modmrna1273p201_IA_defaults	ARTz default
tmaeunsteae	Production of unsolicited AE count tables
tmimmsummneut	Create macro tmimmsummneut
mclopper	macro to calculate 95% CI using the Clopper-Pearson method

8. Appendix

Appendix A: Dosing Error Collection Data Lookup Table

STUDYID	SUBJID	VISIT	RAND_TO	ACTUAL_DOSE_RECEIVED	COMMENTS
mRNA-1273-P201	US2051003	Day 1	mRNA-1273 100ug	mRNA-1273: >100-125 ug	The Site withdrew more than 0.6 mL from the IP Vial #2. This solution is then to be diluted with 0.9 mL Saline to prepare the dosing solution. So likely the final diluted concentration was higher than 0.2 mg/mL and thus the dose was greater than 100 mcg.
mRNA-1273-P201	US2061024	Day 1	mRNA-1273 100ug	Placebo	Dose was Switched at time of adminitration by the Unblinded Administrator due to lapse in following the verification process
mRNA-1273-P201	US2061024	Day 29	mRNA-1273 100ug	Placebo	Subject Admistered same dose adminstered on Day 1
mRNA-1273-P201	US2061025	Day 1	Placebo	mRNA-1273 100 ug	Dose was Switched at time of adminitration by the Unblinded Administrator due to lapse in following the verification process
mRNA-1273-P201	US2061025	Day 29	Placebo	mRNA-1273 100 ug	Subject Admistered same dose adminstered on Day 2

Appendix B: Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 1 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.

- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 1 Visit Window

Visit	Target Study Day	Visit Window in Study Day
Labs and Nasal Swabs for SARS-CoV-2		
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43] Pre-second-dose
Day 57 (Month 2)	57	≥44
Vital Signs		
Day 8	8	[2, 11]
Day 15	15	[12, 22]
Day 29 (Month 1)	29 (Date of Second Injection)	[23, 32] Pre-second-dose
Day 36	36	[33, 39]
Day 43	43	[40, 50]
Day 57 (Month 2)	57	[51, 133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Immunogenicity		
Day 15	15	[2, 22]
Day 29 (Month 1)	29 (Date of Second Injection)	[23, 36] Pre-second-dose
Day 43	43	[37, 50]
Day 57 (Month 2)	57	[51,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302

Appendix C: Imputation

Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:

   - If only DAY is missing, use the first day of the month, unless:

     The CM end date is after the date of first injection or is missing AND the start month and year of the CM coincide with the start month and year of the first injection. In this case, use the date of first injection.

   - If DAY and Month are both missing, use the first day of the year, unless:

The CM end date is after the date of first injection or is missing AND the start year of the CM coincide with the start year of the first injection. In this case, use the date of first injection

- If DAY, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.

2. Missing or partial medication stop date:

- If only DAY is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).

- If DAY and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).

- If DAY, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

3. Missing or partial AE start date:

- If only DAY is missing, use the first day of the month, unless:

The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.

- If DAY and Month are both missing, use the first day of the year, unless:

The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection

- If DAY, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment emergent.

4. Missing or partial AE end dates will not be imputed.