Analysis Data Reviewer's Guide

ModernaTX, Inc.

Study mRNA-1273-P201

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)

1.4 Source Data Used for Analysis Dataset Creation

In addition to the clinical database for Primary Analysis Day 57, the source data include lookup file that was used to record per protocol information and wrong dose information. The lookup table spreadsheet was converted to a SAS transport file dose_err.xpt and included in misc (miscellaneous) folder.

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-Finding 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 3

Main Rationale for the Amendment:

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.

Summary of Major Changes in Protocol Amendment 3:

Section # and Name	**Description of Change**	**Brief Rationale**
Title page, Signature page, and header	Updated the protocol version and date	Reflect the new version and date of the protocol
Synopsis, Section 3.1 Study Design	Deleted repeated text about Safety Monitoring Committee review before expansion in Cohort 2.	Editorial removal of redundant text.
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7.1 Primary Study Analysis	Added information about potential participant populations to be included in the primary analysis of safety and immunogenicity after completion of Day 57 procedures.	Clarification that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit.
Synopsis, Section 4.6.2 Safety Analyses	Revisions to clarify that separate summaries of Grade 3 or higher solicited ARs are not planned.	Clarification of planned safety analyses.
Section 3.5.2 Use of Electronic Diaries, Section 7.1 Appendix 1: Schedule of Events (Table 7)	Added clarification about site follow-up of relevant safety events from eDiary entries (includes revisions to Footnote 12).	Clarification that follow-up by telephone of relevant safety events from eDiary entries is not the same as scheduled safety follow-up telephone calls.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The acceptable window around the Day 29 visit has been clarified as + 7 days with no negative visit window.	Correction to reflect the minimum interval between vaccine administrations of 28 days.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The footnotes and footnote numbering have been updated to accommodate the footnotes that were added with Amendment 2.	Editorial clarification.

Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 4 has been revised to clarify that study days for safety follow-up are relative to Day 1 vaccine administration.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 5 has been revised to explain how to handle potential visit window overlap related to Visit 8.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 10 has been revised to clarify the timing of nasopharyngeal swab samples on vaccination days.	Editorial clarification.

Abbreviations: AE = adverse event; AR = adverse reaction; MAAE = medically attended adverse event; SAE = serious adverse event.

2.2 Protocol Design in Relation to ADaM Concepts

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

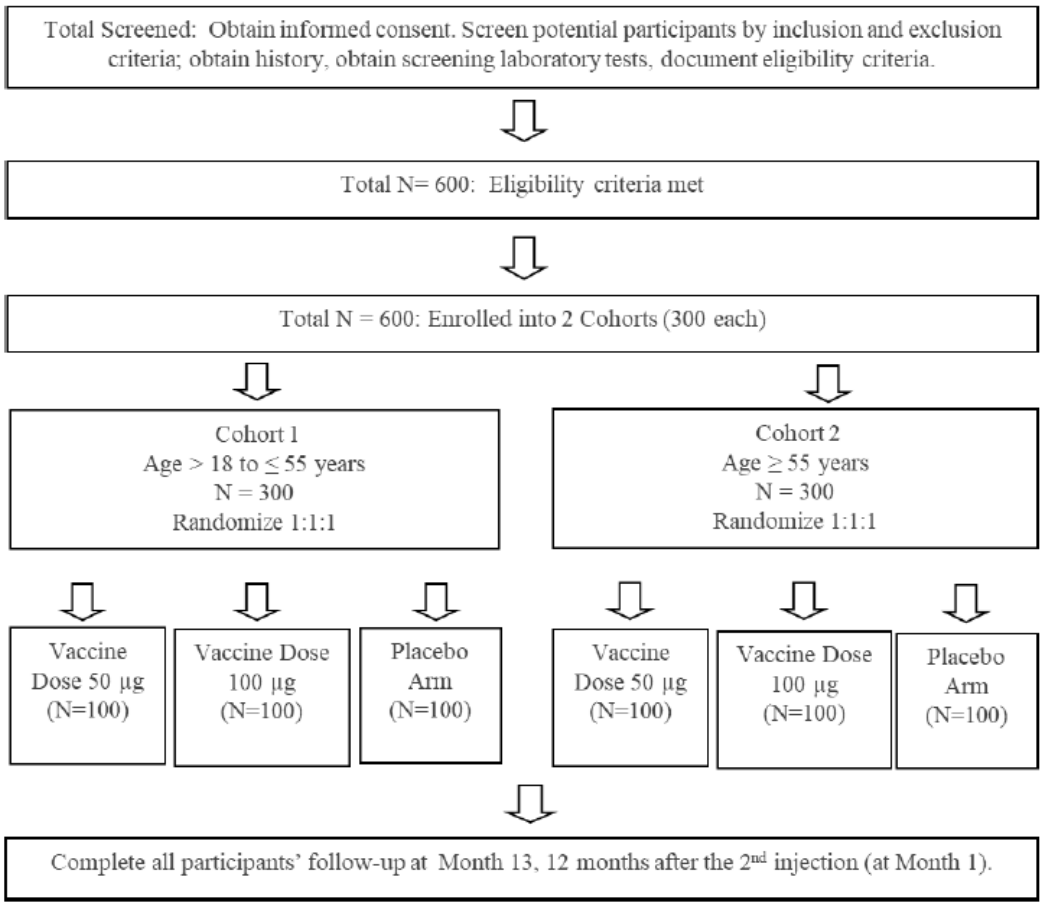
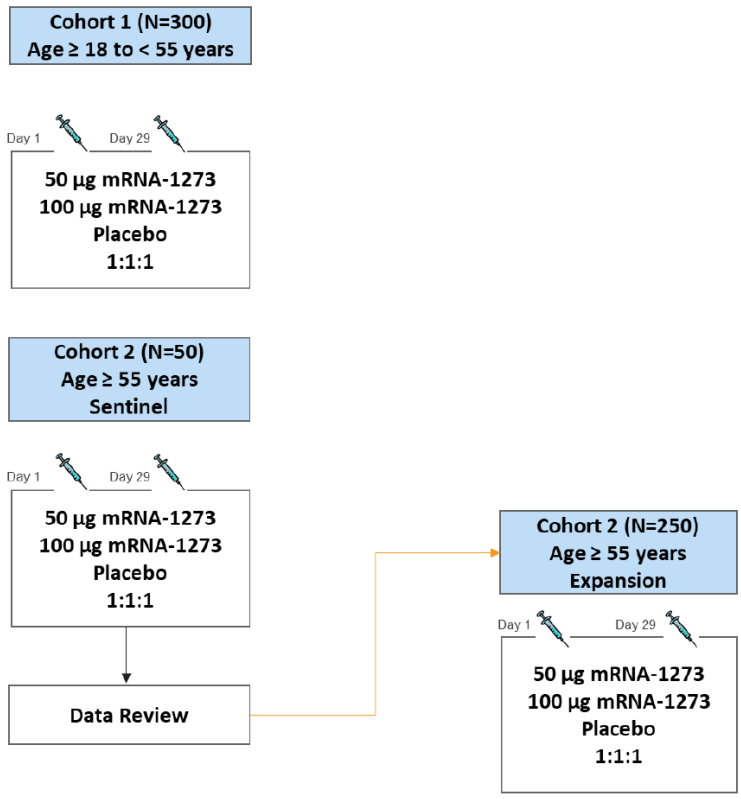


Figure 2: Sentinel and Expansion Cohort Schema



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
COMPLFL	Completers Population Flag
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
PPND29FL	Per Protocol nAb Day 29 Flag
PPND57FL	Per Protocol nAb Day 57 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
COV19BL	Baseline COVID Infection
COV19FL	COVID Infection Flag
SENTLFL	Sentinel Participant Flag
D29W7DFL	Day 29 Out of 7-Day Window Flag

Variable Name	Variable Description
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.

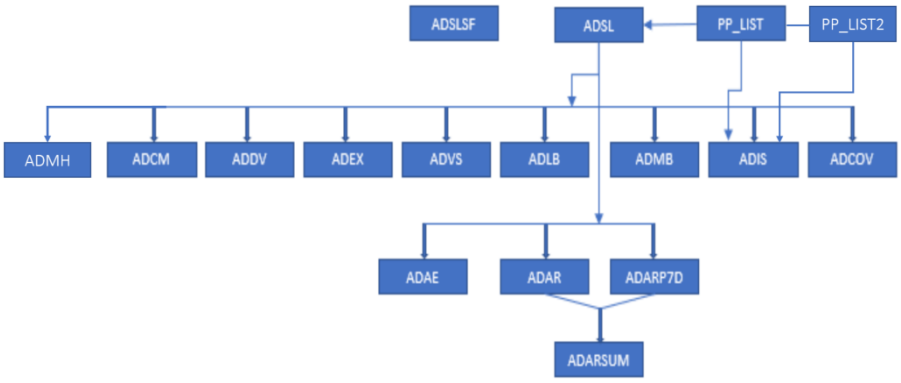
4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

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

4.2 Data Dependencies

PP_LIST was created first as an intermediate dataset. 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 dataset 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 D57 Primary 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 for one subject

Subject Identifier for the Study	Visit Timepoint	Visit Timepoint (N)	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	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	1	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y		
US2011004	Day 29	5	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y		
US2011004	Day 43	7	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y		
US2011004	Day 57	8	N	Not Detected	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y		
US2011004	Day 209	9	Y	Not Detected	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	N	N	There was no immunogenicity result at corresponding visit	There was no immunogenicity result at corresponding visit
US2011004	Day 394	10	Y	Not Detected	Y	Y	Y	N	N	N	N	N	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 for one subject

Subject Identifier for the Study	Visit Timepoint	Visit Timepoint (N)	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	Reason exclusion from nAb PP	MNET LLOQ ULOQ	MN50 LLOQ ULOQ
US2011004	Baseline	1	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y		40 - 1280	91.1 - 2031.87
US2011004	Day 29	5	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y		40 - 1280	91.1 - 2031.87
US2011004	Day 43	7	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y		40 - 1280	91.1 - 2031.87
US2011004	Day 57	8	N	Not Detected	Y	Y	Y	N	Y	Y	Y	N	Y		40 - 1280	91.1 - 2031.87
US2011004	Day 209	9	Y	Not Detected	Y	Y	Y	N	N	N	Y	N	N	There was no immunogenicity result at corresponding visit		
US2011004	Day 394	10	Y	Not Detected	Y	Y	Y	N	N	N	Y	N	N	There was no immunogenicity result at corresponding visit		

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, a primary interim analysis of safety and immunogenicity data will be triggered after all participants have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (data are as clean as possible).

For the primary 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 characteristics	PK/PD	Primary Objective	Structure
ADSL - Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			X			One record per subject
ADAR - Solicited AR Analysis Dataset	BASIC DATA STRUCTURE		X			X	One record per subject, per parameter, per analysis timepoint

Dataset – Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADARP7D - Solicited AR post D7 Analysis Dataset	BASIC DATA STRUCTURE		X			X	One record per subject, per parameter, per analysis timepoint
ADARSUM - Solicited AR Summary Analysis Dataset	BASIC DATA STRUCTURE		X			X	One record per subject, per summary parameter, per analysis timepoint
ADCOV - COVID-19 Analysis Dataset	BASIC DATA STRUCTURE		X				One record per subject, per category, per test, per assessment
ADIS - Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE	X				X	One record per subject, per parameter category, per parameter, per assessment
ADLB - Laboratory Analysis Dataset	BASIC DATA STRUCTURE		X			X	One record per subject per parameter per assessment

Dataset – Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADMB - Microbiology Analysis Dataset	BASIC DATA STRUCTURE	X					One record per subject, per parameter, per analysis timepoint
ADVS - Vital Signs Analysis Dataset	BASIC DATA STRUCTURE		X			X	One record per subject per parameter per assessment
ADSLSF - Screen Fail Subj-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			X			One record per screen failed subject
ADAE - Adverse Event Analysis Dataset	OCCURRENCE DATA STRUCTURE		X			X	One record per subject per adverse event
ADCM - Concomitant Medication Analysis Dataset	OCCURRENCE DATA STRUCTURE			X			One record per subject per medication per medication start date
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

Dataset – Dataset Label	Class	Effi-cacy	Safety	Baseline or other subject charac-teristics	PK/ PD	Pri-mary Objec-tive	Structure
ADMH - Medical History Analysis Dataset	OCCUR-RENCE DATA STRUC-TURE		X	X			One record per subject per medical history

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.

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 contains analysis data if symptom occurs after 7 days. Per CDISC TAUG-VAX 1.1, flat model was utilized which included a record for each subject, each symptom, and each day by vaccine reference. PARAM represented each symptom reported by either subject via e-Diary or investigator via CRF.

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, $j \neq k$

PARAMCD	PARAM
L10MN50	LOG10(MN50)
L10MNET	LOG10(MN Endpoint Titer)
LV58IGGN	LOG10(VAC58 Nucleocapsid IgG Antibody)
LV58IGGS	LOG10(VAC58 Spike IgG Antibody)

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	ADAE	301 (100.00%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADAR	108849 (98.95%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADARP7D	150 (100.00%)	This is due to study is still ongoing

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0019	COMPLFL subject-population flag value is null	Error	ADAR-SUM	22050 (98.92%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADCM	1701 (98.84%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADCOV	10292 (99.08%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADDV	271 (96.10%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADEX	1179 (98.58%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADIS	18648 (99.32%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADLB	36442 (99.05%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADMB	37332 (99.22%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADMH	2406 (98.45%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADSL	590 (98.33%)	This is due to study is still ongoing
AD0019	COMPLFL subject-population flag value is null	Error	ADVS	38058 (99.01%)	This is due to study is still ongoing

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0223	Calculation issue: CHG != AVAL - BASE	Error	ADIS	1 (< 0.1%)	This is due to decimal issue, No rounding rule is used for ADIS.CHG, but Pinnacle 21 checking is based 8 decimal
AD0253	Record key from SDTM AE is not traceable to ADaM ADAE (not enough ADAE recs)	Error	AE	84 (21.82%)	This is due to REMOVEFL='Y' for solicited adverse reaction records being mapped to CE domain.
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADAR	755 (0.69%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADAR-SUM	144 (0.65%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADCM	7 (0.41%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADCOV	64 (0.62%)	RACE = "MULTIPLE" because patient checked more that 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	ADDV	2 (0.71%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADEX	8 (0.67%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADIS	128 (0.68%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADLB	130 (0.35%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADMB	252 (0.67%)	RACE = "MULTIPLE" because patient checked more that 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 that 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	ADSL	4 (0.67%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
CT2002	RACE value not found in 'Race' extensible codelist	Warning	ADVS	256 (0.67%)	RACE = "MULTIPLE" because patient checked more that one race. RACE = "OTHER" because data was captured from CRF
SD1229	AVAL value is null when PARAMCD == 'MNET' @or PARAMCD == 'MN50' @or PARAMCD == 'V58IGGES' @or PARAMCD == 'V58IGGEN'	Error	ADIS	4 (< 0.1%)	There was no immunogenicity result at corresponding visit and ISSTRESC =’NR’
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	3 (100.00%)	‘SPECIFIED IN SAP’ is not in Analysis Reason extensible codelist
DD0100	Extended value for AnalysisPurpose	Warning	DEFINE	3 (100.00%)	‘PRIMARY OUTCOME MEASURE’ is not in Analysis Purpose extensible codelist

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 2020-11-10.

7.1 ADaM Programs

Program Name	Output	Macro Used
A10ADSL	ADSL.SAS7BDAT	_adsl_vars_
A20ADAE	ADAE.SAS7BDAT	madam, revsupp, adam_dataset_update
A20ADAR	ADAR.SAS7BDAT	madam, revsupp, revco, iso2sas, adam_dataset_update
A20ADARP7D	ADARP7D.SAS7BDAT	madam, revsupp, iso2sas, adam_dataset_update
A20ADCM	ADCM.SAS7BDAT	madam, revsupp, adam_dataset_update
A20ADCOV	ADCOV.SAS7BDAT	madam, revsupp, adam_dataset_update
A20ADDV	ADDV.SAS7BDAT	revsupp, adam_dataset_update
A20ADEX	ADEX.SAS7BDAT	madam, adam_dataset_update
A20ADIS	ADIS.SAS7BDAT	_adis_vars_, madam, adam_dataset_update
A20ADLB	ADLB.SAS7BDAT	madam, revsupp, iso2sas, adam_dataset_update
A20ADMB	ADMB.SAS7BDAT	madam, revsupp, iso2sas, adam_dataset_update
A20ADMH	ADMH.SAS7BDAT	madam, revsupp, adam_dataset_update
A20ADSLSF	ADSLSF.SAS7BDAT	madam, revsupp, adam_dataset_update
A20ADVS	ADVS.SAS7BDAT	madam, revsupp, adam_dataset_update

Program Name	Output	Macro Used
A30ADARSUM	ADARSUM.SAS7BDAT	madam, revsupp, adam_dataset_update
PP_LISTING	PP_Listing.dat/xls	_adsl_vars, _adis_vars_, revsupp
PP_LISTING2	PP_Listing2.dat/xls	_adsl_vars, _adis_vars_, revsupp

7.2 Analysis Output Programs

Program Name	Purpose
t1402010101	Summary of Binding Antibody Levels Per-Protocol Set for Binding Antibody
t1403010101	Summary of Solicited Adverse Reactions within 7 Days After First Injection by Grade First Injection Solicited Safety Set
t1403010102	Summary of Solicited Adverse Reactions within 7 Days After First Injection by Grade First Injection Solicited Safety Set
modmrna1273p201_IA_defaults	SAS program to be included in t1402010101, t1403010101 and t1403010102
tmimmsummbind	SAS program to be included in t1402010101
tmsolae	SAS program to be included in t1403010101 and t1403010102

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
adam_dataset_update	Set attributes on ADaM Datasets from spec

Program Name	Purpose
get_tf	To create Title and Footnote statements or a TF data set from an ASCII metadata file for RTF output.
iso2sas	Macro to convert Date in ISO 8601 format to DATE9 format.
ma_bign	outputs a dataset called BIGN containing population counts categorized according to SUBGROUPS and TREATMENTS; creates macro variables identified as BIGN(subgroup) treatment; creates a new format by adding the N=xxx to the label of an existing format; creates macro variables identified as COLHEAD(_subgroup) treatment which are also the labels of the formats described above
ma_count_categorical	outputs a dataset as specified in parameter &OUT_DATA containing counts categorized according to SUBGROUPS and TREATMENTS and CATEGORICAL VARIABLE.
ma_count_one_row	outputs a dataset as specified in parameter &OUT_DATA containing counts categorized according to SUBGROUPS and TREATMENTS.
ma_n_pcnt	produce percentages of n/N where N is obtained from the denominator dataset (default name of denominator dataset is "BIGN")
ma_summ_stats	outputs a dataset as specified in parameter &OUT DATA containing summary statistics based on VARS and SUMM_STATS_ADDITIONAL parameters grouped by BY VARS, SUBGROUPS, and TREATMENTS groups
ma_summ_stats_display	outputs a dataset as specified in parameter &OUT_DATA containing summary statistics specified in &STAT LABEL FMT, statistics order variable STAT ROW specified in &STAT LABEL FMT with NOTSTORTED option, grouped by SUBGROUPS, BY VARS
ma summ stats precision	calculate precision
ma summ stats rules	produce a rules data set that controls the display of summary statistics
md byvar check	extract and verify the BYVARS information from input macro parameter
md clean and reset	set the MPRINT options value to whatever is passed
md_default_check	check macro variable exist

Program Name	Purpose
md_workinfo	captures current options value of MPRINT and places it in global macro variable MPRINTTOGGLE; if DEBUG parameter is to Y, MPRINT options will be turned on; creates list of data sets and data views found within a provided LIBREF and places the lists into respective global macro variables
gmt_gmr_ci	create Inferential Statistical Analysis Macro
ml_create_meta	build metadata to be used by the listing macros ML_Process_Meta and ML_Report.
ml_create_meta_reset	remove a macro variable, named ML_Create_Meta_First_Call, from the SAS symbol table
ml_report	set-up how proc report will be generated
mr_add_by_rec	create a row for each variable entered in BYVARS containing a description of the BYVARS variable and an ordering number; If no ordering variable is passed, one will be created based upon SORTVARS ordering and it will be named ORDER1 ; upon demand will created indent variable needed for MR_PACK functionality
mr_odsclose	close ODS options for use in TLF programming
mr_odsout	set ODS options for TLF programming
mr_pack	run packtext against a variable in a nested counting data set; create concatenated versions of upper level variables that can be used later in reporting as (continued) lines; create a label for text column in the proc report
mr_pagebreak_table	macro to assist in breaking RTF pages for non-nested tables
mu_align	embeds RTF code in variable value for variables entered in COLUMNS parm to produce decimal aligned values in proc xxxx; will work with values that do not contain decimals; If numeric variables are included, they will be converted to character using best format and then have RTF code inserted.
mu_check_data_and_var_exist	check to see if specified data sets and variables exist. It will also create global macro variables to indicate whether the dataset / variable exists or not.
mu_check_req_parameters	check if the parent macro has required parameters that are null. If a particular parameter is null, this macro will issue an alert and abort.

Program Name	Purpose
mu_checkrc	check result code of previous macro and abort the program if it is greater then INRC
mu_create_format	create a format using two variables, the short value, and the long value. It is designed to save programmers from having to type the entire format.
mu_get_sort_order	get the sort order from a data set.
mu_help_debug	determine if there are _default_ values for HELP and DEBUG that have been assigned elsewhere. If there are, and the the local parameters of HELP and DEBUG from where the macro this is called are blank, then the local macro will inherit the _default_ values
mu_lines_per_page	calculates number of lines to fit per page
mu_nobs	return a macro variable in the form IN_DATA_NOBS containing the number of observations in IN_DATA
mu_rtf_template	create RTF template
mu_setall	set a list of data sets together to create a new data set
mu_transpose	outputs a dataset from the transpose procedure transposing the user specified variables into observations.
mu_var_attributes	provide the attributes of supplied variables
mu_wordscan	scans a character string and returns: an array of GLOBAL macro variables consisting of the individual elements of the string as defined by a user supplied delimiter.; optionally, a GLOBAL macro variable containing the number of elements in the string as defined by a user supplied delimiter
mw_format_footnote_reference	analyze a string variable and translate footnote references per MW guidance
mw_sentence_case	resulting data set post sentence casing
revco	merges CO back onto the specified domain dataset and removes merged records from CO

Program Name	Purpose
revsupp	merges SUPPQUAL back onto the original datasets
mgm_ci	macro to calculate 95% CI based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise
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.