

RESPONSE TO CBER COMMUNICATION REGARDING CLINICAL DATASETS
RECEIVED ON DECEMBER 03, 2020

The Sponsor acknowledges CBER's communication regarding Clinical datasets.

This document provides the Sponsor's responses to CBER's requests (in **Bold**).

Item 1:

The term of "Confirmed COVID" is missing from the CE and suppdm datasets. In adjudicated COVID-19 cases listed in the CE dataset there are 103 subjects included with 3 of the subjects not meeting the charter definition. Was this category supposed to be the confirmed COVID subjects?

Sponsor Response:

Adjudication results are in the CE domain with CECAT="ADJUDICATION". At the first interim analysis, (data snapshot 1 on 11-Nov-2010), a total of 103 subjects had adjudication results, and 100 of them were deemed COVID-19 cases, based on the adjudication committee assessments. These 100 confirmed COVID-19 cases can be identified in the CE domain with CECAT="ADJUDICATION" AND CEREASON=: "EVENT MEETS THE CHARTER DEFINITION OF" AND CECAT = "COVID-19".

There were 3 subjects (US3022233, US3272361, US3872253) who were adjudicated not meeting the charter definition.

COVIDCECAT="ADJUDICATION" AND CEREASON=: "NOT A CHARTER-DEFINED EVENT"

As for efficacy, the analysis population to be used is important and the Per-Protocol Set (ADSL.PPROTFL='Y') is the primary analysis population for efficacy, COVID-19 cases are not in suppdm.

Item 2:

There are 113 cases defined per SAP and 95 adjudicated cases starting at 14 days after the second dose. Please clarify whether the non-adjudicated cases have been adjudicated and determined not to fulfill the case definition, or have not yet been adjudicated. For the cases which have been adjudicated, please list the reason they were determined by the committee to not to fulfill the case definition. Please also provide this information for the 4 non-adjudicated severe

Sponsor Response:

In this study, COVID-19 per protocol definition requires at least 2 eligible systemic symptoms OR 1 eligible respiratory symptom, confirmed by positive RT-PCR (Protocol Section 8.1.1). Cases were defined by the positive RT-PCR and eligible symptoms. At IA1, there were 113 COVID-19 cases starting 14 days after the 2nd injection in the Per-Protocol Set.

This study also has an adjudication committee (AC) to adjudicate potential COVID-19 or severe COVID-19 cases. Potential COVID-19 cases with reported symptom(s), confirmed by positive RT-PCR (central or local), as collected in the clinical database or EDC (electronic data capture) that include data collected in eCRF, and RT-PCR results from central/testing labs. For IA1, adjudication committee assessments have been prioritized and performed for all potential COVID-19 and severe COVID-19 cases starting 14 days after the 2nd injection. Adjudication committee assessments for cases with onset day prior to 14 days after the 2nd injection were not available at IA1. All potential COVID-19 cases starting 14 days after the 2nd injection were sent to adjudication committee as of the efficacy data cutoff date of 07-Nov-2020 for this interim analysis. All these potential cases have been adjudicated. There were 95 COVID-19 cases starting 14 days after the 2nd injection based on adjudication committee assessments in the Per-Protocol.

Below is a concordance table of cases based on Adjudication Committee and based on protocol definition (positive RT-PCR and eligible symptoms) in the PP Set.

		Adjudication Committee (AC)				Total
		Adjudicated Cases	Adjudicated cases prior to 14 days after dose 2	not adjudicated, with late onset date (04-Nov)	not adjudicated, other reasons	
Derived based on Protocol definition	Derived Case	94	2	13	4	113
	Not a Derived case	1				
	Total	95				

Out of the 95 cases based on AC,

- 94 were also cases based on protocol definition.
- 1 was not a case as derived based on protocol definition: subject US3032009 only have one eligible systemic symptom (chills), thus not a case per protocol-definition. Other symptoms reported by the subjects included Body Aches, Nasal Congestion, and Running Nose. These symptoms are not listed in the eligible systemic symptoms in Protocol

section 8.1.1. This case was adjudicated, and was deemed a case by the AC, please also refer to response to Q3 below.

Out of the 113 cases based on protocol definition,

- 94 were cases based on AC,
- 2 subjects (US3312605 and US3752344) were adjudicated a case prior to 14 days after 2nd injection,
- 13 subjects with late onset date (on or after 04-Nov) that were not adjudicated, these subjects were likely to have supporting data entered in the clinical database after 07-Nov. The list of these 13 subjects are provided in [Table 1](#) of Appendix
- 4 subjects were not adjudicated:
 - Subject US3592197 had positive RT-PCR pre-dose 2 (scheduled RT-PCR) on 14-Sept and was not sent for adjudication. This subject reported cough, headache, running nose, shortness of breath on 14-Oct, and RT-PCR test on 14-Oct was positive, thus was a case based on positive RT-PCR and eligible symptoms (pre-dose 2 scheduled RT-PCR result is not considered in determining whether a case per protocol definition).
 - Subject US3412291 and US3302310 still require verification of RT-PCR data .
 - Subject US3852070 was sent to AC after IA1.

At IA1, there were 11 severe COVID-19 cases starting 14 days after 2nd injection based on adjudication committee assessments in PP Set; 15 severe COVID-19 cases starting 14 days after 2nd injection based on positive RT-PCR, and symptoms in PP Set. The 15 severe COVID-19 cases include the 11 severe COVID-19 cases based on adjudication. The 4 subjects who were not an adjudicated severe COVID-19 cases are listed below, all on Placebo group:

- Subject US3272361 was sent for adjudication on 23-Oct for COVID-19, and on 30-Oct for severe COVID-19. This subject was not considered a case for either COVID-19 and severe COVID-19 by the adjudication committee due to the fact that COVID-19 criteria were not met 14 days after 2nd dose.
- Subject US3412291 was sent for adjudication on 11-Nov, at the time, positive RT-PCR on 21-Oct was entered in eCRF page; results from testing lab based on Nasal Swab showed negative followed by negative results based on 3 Saliva samples taken on 3 separate days following 21-Oct. The eCRF data entry was later changed by the site to “no” on 18-Nov. This subject is not a COVID-19 case at data snapshot 2 (25-Nov) because of no positive RT-PCR results

- Subjects US3742123 and US3872223 had COVID-19 symptoms prior to 14 days after 2nd injection, and were not prioritized to be adjudicated. Subject US3742123 had O2 Saturation of 93%, and Subject US3872223 had O2 Saturation of 92%.

Below is a quick reference to find these cases in the ADEFF, ADTTE and ADTTEA datasets:

95 cases based on adjudication assessments in the PP Set: (ADEFF.PARAMCD=' COVIDA' or ADTTEA.PARAMCD='TTCVD1') and PPROTFL='Y'

113 cases based on RT-PCR and eligible symptoms in the PP Set: (ADEFF.PARAMCD=' COVID' or ADTTE.PARAMCD='TTCVD1') and PPROTFL='Y'

Item 3:

One subject (mRNA-1273-P301-US303-2009) was defined as a case per adjudication committee but does not appear to meet the per-protocol definition of a case. Please clarify.

Sponsor Response:

Subject US3032009 was sent to Adjudication Committee to be adjudicated as this subject had positive RT-PCR and symptoms. This subject was determined to be a case by the adjudication committee.

However, this subject only had 1 eligible systemic symptoms based on the derived definition, and thus is not a COVID-19 case as derived based on protocol definition which requires at least 2 eligible systemic symptoms OR 1 eligible respiratory symptom, confirmed by positive RT-PCR. The eligible symptoms are listed in Section 8.1.1 of the protocol (copied below). The only eligible systemic symptom reported by the subject was Chills. Other symptoms reported by the subjects included Body Aches, Nasal Congestion, and Running Nose, which are not listed as eligible systemic symptoms in Section 8.1.1.

This subject is the ONLY case that was a COVID-19 case based on adjudication committee assessments but NOT a COVID-19 case based on protocol definition using RT-PCR and eligible symptoms.

8.1.1. Efficacy Assessments Related to COVID-19 and SARS-CoV-2 Infection

Each study participant will have an NP swab sample collected for SARS-CoV-2 testing by RT-PCR on Day 1 and Day 29, prior to receiving a dose of the IP as specified in the SoE (Table 14).

COVID-19:

To be considered as a case of COVID-19 for the evaluation of the Primary Efficacy Endpoint, the following case definition must be met:

- The participant must have experienced at least TWO of the following systemic symptoms: Fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Item 4:

One subject (mRNA-1273-P301-US384-2040) was defined as a COVID-19 case on 11/3, and subsequently had oxygen saturation $\leq 93\%$ on 11/8 based on the CE domain. This subject appears to fulfill the protocol definition of severe COVID-19, but does not appear to be included in the analysis of severe cases. Please comment.

Sponsor Response:

At IA1, Subject US3842040 was a COVID-19 case based on adjudication committee assessments. The efficacy data cutoff date for IA1 was 07-Nov-2020. This subject started reporting severe symptoms, e.g. O2 saturation of 92% on 08-Nov. Therefore, this subject was not adjudicated for severe COVID-19. This subject was also a case based on protocol-definition.

At data snapshot 2 occurred on 25-Nov-2020, this subject was a COVID-19 case and a severe COVID-19 case based on adjudication committee assessments; as well as a COVID-19 and severe COVID-19 case based on RT-PCR and symptoms.

Item 5:

We have identified 46 events in the MH dataset that have start dates after the RFSTDTC. Are these dates correct and if so should they have been reported in the AE dataset?

Sponsor Response:

These terms were actively being cleaned at the time of this data snapshot. These issues were continuing to be resolved at Data Snapshot 2 (DS2) which occurred on 25-Nov-2020. At DS2, there continue to be 19 MH terms in which the start date is after RFSTDTC. All of these remaining terms have been actively queried to determine if they should remain in the MH SDTM domain or move to the AE SDTM domain.

Item 6:

Please provide the AEDECOD for the 560 events where it is missing.

Sponsor Response:

These events were actively being cleaned at the time of this data snapshot. This issue is resolved in data snapshot 2 which occurred on 25-Nov-2020. At DS2, the number of null AEDECOD is 17, all due to null AE terms.

Item 7:

Please explain why 1565 (4.9%) of subjects in SDTM DM are not included in ADSL and correct if needed.

Sponsor Response:

There were a total of 1791 subjects without dose in DM domain.

- 68 were randomized but not treated; these subjects are included in ADSL with RANDFL='Y' and FASFL='N'
- 158 subjects were not screen fails but not randomized; these subjects are included in ADSL with RANDFL='N'

Thus, the total number of subjects in SDTM DM are not included in ADSL is: $1791 - 68 - 158 = 1565$

Dataset / domain	condition	N	Description
DM		1791	Screen failure + without dose
ADSL	RANDFL='Y' and FASFL='N'	68	randomized but not treated
ADSL	RANDFL='N'	158	Not screen fail but not randomized

Item 8:

Please clarify, the Safety Set analysis population includes 15165 placebo recipients, and 15184 vaccine recipients, which when combined = 30349. However, the total (Table 4 in Clinical Overview, Source-Table 14.1.2.3) was reported as 30350. Please comment if you can confirm that subject # mRNA- 1273-P301-US357-2365 had received placebo dose #1, based on review of source documents.

Sponsor Response:

The numbers on Placebo, mRNA-1273, and total in the Safety Set are correct. At IA1, there is one subject, US3572365, had dosing information as recorded in eCRF, but the drug kit information was not registered in IRT system. ADSL.TRT01A is missing. Thus, for subject US3572365: ADSL.SAFFL='Y', ADSL.FASFL='Y', ADSL.TRT01A=.

Therefore, the total number in the Safety Set = 30350 while the number on placebo and mRNA-1273 add up to 30349. This issue is resolved in data snapshot 2 occurred on 25-Nov-2020, this subject received Placebo and is included under Placebo (TRT01A='Placebo') in the Safety Set.

Item 9:

In general for tomorrow's meeting, please plan to walk us through each of the flags used in the data to include/exclude subjects in your analyses. For example please provide the criteria to include/exclude subjects in the following analyses sets: safety population, full analyses population, solicited safety set, solicited safety set-dose 1, solicited safety set-dose 2, and per protocol data set. Please explain where data are not provided in the images below where there is 'null' value listed, but subjects have been flagged as either Y or N.

Sponsor Response:

Please see below for a summary of analysis populations, population flags, and treatment group variables to be used:

Analysis Population	Population Flag to be used	Treatment group to be used	Comments
Randomized Set	RANDFL	TRT01P	Subjects are included in the group to which they were randomized, 'intent-to-treat'
Full Analysis Set (FAS)	FASFL	TRT01P	
Modified Intent-to-Treat (mITT)	MITTFL	TRT01P	
Per-Protocol (PP) Set	PPROTFL	TRT01P	
Safety Set	SAFFL	TRT01A	Subjects are included in the group which they actually received 'as treated'.
Solicited Safety Set	SARAFL	TRT01A	

First Injection Solicited Safety Set	SAR1FL	TRT01A	If a subject received at least one dose of mRNA-1273, the subject would be included under 'mRNA-1273'
Second Injection Solicited Safety Set	SAR2FL	TRT01A	

SAFFL: The Safety Set (SAFFL='Y') consists of all randomized participants who received at least one dose of IP.

- Line 1: SAFFL='N', 227 subjects did not receive any dose, TRT01A (actual treatment) value is unknown.
- Line 2: SAFFL='Y', 1 subject received a dose which is recorded in eCRF, but the drug kit number was not registered in IRT system. This is the subject discussed in response to Q8 (US3572365). For this subject, TRT01A value is unknown, although the subject was dosed. This issue has been resolved for DS2

	SAFFL	TRT01A	N Rows
1	N		227
2	Y		1
3	Y	mRNA-1273	15184
4	Y	Placebo	15165

FASFL: The Full Analysis Set (FAS, FASFL='Y') consists of all randomized participants who received at least one dose of IP. Subjects are included in the vaccine group to which they were randomized (TRT01P)

- Lines 1- 4: subjects did not receive any dose
- Lines 1 and 3: 105+53=158 not randomized
- Lines 2 and 4: 29 in mRNA and 40 in placebo: randomized but not dosed (FASFL='N')

	FASFL	ARM	N Rows
1	N		105
2	N	mRNA-1273	29
3	N	Not Assigned	53
4	N	Placebo	40
5	Y	mRNA-1273	15180
6	Y	Placebo	15170

SARAFL: The Solicited Safety Set consists of randomized participants who received at least one dose of IP and contributed any solicited AR data, i.e. have at least one post-baseline solicited safety (eDiary) assessment.

- Line 1: 227 subjects did not receive any dose
- Line 4: 1 subject received at least one dose but for which drug received, it is unknown (subject US3572365 as discussed in response to Q8).
- Lines 2-3: subjects received at least one dose, but did not submit any solicited AR data following an injection.

	SARAFL	TRT01A	N Rows
1	N		227
2	N	mRNA-1273	8
3	N	Placebo	3
4	Y		1
5	Y	mRNA-1273	15176
6	Y	Placebo	15162

SAR1FL and SAR2FL

The First (Second) Injection Solicited Safety Set consists of all who have received the first (second) study injection and have contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days respectively.

- Line 1 and Line 4 same as above.
- Lines 2-3: subjects received 1st injection, but had no solicited AR data following 1st injection.

	SAR1FL	TRT01A	N Rows
1	N		227
2	N	mRNA-1273	17
3	N	Placebo	11
4	Y		1
5	Y	mRNA-1273	15167
6	Y	Placebo	15154

- Line 1: subjects did not receive 2nd injection.
- Lines 2-3: subjects received 2nd injection but had no solicited AR data following 2nd injection.

	SAR2FL	TRT01A	N Rows
1	N		228
2	N	mRNA-1273	1237
3	N	Placebo	1295
4	Y	mRNA-1273	13947
5	Y	Placebo	13870

PPROTFL: The Per-protocol Set consists of all participants with negative SARS-CoV-2 status (both NEG RT-PCR and NEG Elecsys serology [bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay)]) at baseline who received planned doses of IP per schedule and have no major protocol deviations (as determined and documented by Sponsor prior to database lock (DBL) and unblinding) which impact critical or key study data.

Please note subjects are included in the group to which the subjects are randomized in the Per-Protocol Set, thus TRT01P should be used for the Per-Protocol Set. Per-Protocol Set is the primary analysis population for efficacy analysis. TRT01A is the actual group a subject received, and is used for analysis of safety.

- Line 1: 227 subjects not dosed + 1 subject dosed with unknown treatment receive
- Lines 2-3: subjects dosed but not meeting the criteria for inclusion in PP set.
- (In efficacy analysis, TRT01P (planned treatment) from randomization is used).

	PPROTEFL	TRT01A	N Rows
1	N		228
2	N	mRNA-1273	1250
3	N	Placebo	1282
4	Y	mRNA-1273	13934
5	Y	Placebo	13883

Appendix:

Table 1. List of subjects who were not sent for adjudication for IA1 with onset date of COVID-19 on or after 04-Nov-2020

(ADTTE.PARAMCD='TTCVD1')

US3272144	TTCVD1	4-Nov-20
US3042153	TTCVD1	5-Nov-20
US3112049	TTCVD1	5-Nov-20
US3372237	TTCVD1	5-Nov-20
US3802034	TTCVD1	5-Nov-20
US3852090	TTCVD1	5-Nov-20
US3042115	TTCVD1	6-Nov-20
US3202047	TTCVD1	6-Nov-20
US3442069	TTCVD1	6-Nov-20
US3462180	TTCVD1	6-Nov-20
US3592117	TTCVD1	6-Nov-20
US3592189	TTCVD1	6-Nov-20
US3812168	TTCVD1	6-Nov-20