RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 28 SEPTEMBER 2021

The Sponsor acknowledges FDA comments on CLINICAL topics (in **Bold)**

Clinical: efficacy data; CMC: manufacturing processes

Our review of your August 16, 2021 submission (STN 125752/1) is ongoing.

The following are Non-Priority items requested for additional clinical information regarding efficacy data. A response is requested by October 5, 2021:

ITEM 1:

For the 13 COVID-19 cases (at the time of March 26 data cut) which *did meet the protocol COVID-19 definition but which were not assessed* to meet the primary endpoint case definition by the adjudication committee, please provide a summary for why each case was not considered a primary endpoint case by the adjudication committee.

Sponsor Response

In this study, the concordance of COVID-19 cases based on the adjudication committee (AC) assessments compare to cases based on RT-PCR results and reported eligible symptoms derived per protocol definition is very high. Table 1-1 summarize the concordance of COVID-19 cases starting 14 days after Dose 2 in the Per-Protocol Set.

Table 1-1 Concordance of COVID-19 cases starting 14 days after Dose 2 – Per-Protocol Set

	COVID-19 based on RT-PCR and reported symptoms per protocol definition starting 14 days after Dose 2					
COVID-19 based on Adjudication Committee assessment starting 14 days after Dose 2	Placebo (N=14164) n (%)		mRNA-1273 (N=14287) n (%)		Total (N=28451) n (%)	
	Yes	No	Yes	No	Yes	No
Yes	739	5	54	1	793	6
No	12		1		13	

Source: Table 14.2.1.1.1.3.1

There were 13 cases based on positive RT-PCR results and eligible symptoms per protocol definition (please see response to Item 2 for details), but were not adjudicated COVID-19 cases. Out of the 13 cases per-protocol definition, 4 were not yet adjudicated pending additional information needed (US3022111 and US3052315 at the time only had positive RT-PCR results at local labs not the central testing lab and were pending additional information on the local labs);

and 7 were not sent to AC yet. These 11 potential cases will be sent to AC for adjudication. In addition, there were 2 potential cases (US3762251 and US3932120) adjudicated not to be a case; We looked into the details of adjudication, in both situations, there was comment on inadequate symptoms. The table below lists all 13.

SUBJID	Treatment group randomized to	Comment
US3022111	Placebo	Sent to AC, not yet adjudicated
US3052281	Placebo	Was not yet sent to AC
US3052315	Placebo	Sent to AC, not yet adjudicated
US3222577	Placebo	Sent to AC, not yet adjudicated
US3302310	Placebo	Sent to AC, not yet adjudicated
US3362090	Placebo	Was not yet sent to AC
US3422172	mRNA-1273	Was not yet sent to AC
US3572199	Placebo	Was not yet sent to AC
US3762251	Placebo	Adjudicated not to be a case. Comment by adjudicator: "PCR + ON 12/31, BUT ONLY A HEADACHE, WHICH ALONE DID NOT QUALIFY FOR COVID". In the final DBL, headache and body ache were reported (2 eligible systemic symptoms)
US3832011	Placebo	Was not yet sent to AC
US3832151	Placebo	Was not yet sent to AC
US3932120	Placebo	Adjudicated not to be a case. Comment by adjudicator: "SUBJECT HAS A POSITIVE COVID TEST ON 12/2. HOWEVER, NO SYMPTOMS ARE PROVIDED". In the final DBL, cough was reported (1 eligible respiratory symptom)
US3972022	Placebo	Was not yet sent to AC

ITEM 2:

For the 6 COVID-19 cases (at the time of the March 26 data cut) which *did not meet the protocol COVID-19 definition but which were assessed* to meet the primary endpoint case definition by the adjudication committee, please provide a summary for why each case did not meet the protocol definition and why the adjudication committee assessed each as meeting the primary endpoint.

Sponsor Response

COVID-19, per protocol definition, requires positive RT-PCR and eligible symptoms, and the positive RT-PCR result and eligible symptoms are required to be within 14 days of each other (Section 6.3.1.1 of SAP version 2.0; P301 CSR Appendix 16.1.9). The eligible symptoms are either

- at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR

- at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia;

as explained in Section 8.1.1 of the protocol.

There were 6 adjudicated COVID-19 cases starting 14 days after Dose 2 in the PP Set, which did not meet the protocol definition of COVID-19 based on positive RT-PCR and eligible symptoms. The adjudication committee, in review of the totality of the blinded clinical data at the time for each of these cases, determined that each of these individuals did in fact constitute a COVID-19 case. The detailed summary for each of these 6 cases are provided below:

SUBJID	Treatment group randomized to	Adjudicated Date of COVID-19	Comment
US3352245	Placebo	8-Nov-20	reported symptoms within 14 days of positive RT-PCR: fatigue, nasal congestion and sore throat. Only 1 eligible systemic symptom: sore throat
US3392112	mRNA-1273	9-Nov-20	No eligible symptoms within 14 days of positive RT-PCR (9-Nov-20). Symptoms were reported 17-Oct-20 through 21-Oct-20 and included body aches, Myalgia, and sore throat
US3562076	Placebo	18-Dec-20	reported symptoms within 14 days of positive RT-PCR: fatigue, myalgia and nasal congestion. Only 1 eligible systemic symptom: myalgia
US3722006	Placebo	16-Nov-20	reported symptoms within 14 days of positive RT-PCR: new loss of smell and new loss of taste, considered as eligible systemic symptom
US3812280	Placebo	19-Nov-20	No positive RT-PCR result in database, reported eligible symptoms included chills, cough, difficulty breathing, headache, myalgia
US3822244	Placebo	23-Nov-20	reported symptoms within 14 days of positive RT-PCR: fatigue, new loss of smell and new loss of taste, considered as only having 1 eligible systemic symptom