RESPONSE TO FDA COMMENTS ON CLINICAL RECEIVED ON 17 SEPTEMBER 2021

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

Our review of your August 24, 2021 submission (STN 125752/0) is ongoing. We have the following requests for additional information:

Please respond to the following requests by September 27, 2021:

ITEM 1:

With regards to the SMQ analyses (Tables 65-110 in CBER Requested Tables) submitted under Amendment 3 to the BLA, please submit the same SMQ analyses using Part B data.

Sponsor Response

The Sponsor respectfully requests the Agency to reconsider the request for this analysis. The majority of the data that is included in these SMQ analyses are based on acute reactions that occur following vaccination.

The data acquired in the blinded phase (Part A) of the study represents a large, randomized, and blinded database to establish the safety profile.

The relatively short follow-up time in Part B on recently crossed-over participants who were initially on Placebo in Part A; and the small amount of added follow-up time from Part A participants that remained in their originally randomized group, we believe adds little additional data to these SMQ analyses.

Of note, in Part B, SAE, MAAE, and AEs leading to discontinuation from dosing and/or study are being collected; solicited Adverse Reactions (ARs) and AEs that do not meet the above criteria are not collected. Additionally, we have included SAEs, MAAEs, and AEs leading to discontinuation in the P301 CSR Addendum that describes these events in Part B. There was no systematic collection or analysis of ARs.

We respectfully suggest that this analysis does not serve any additional analytical purpose.

ITEM 2:

Please provide the following additional SMQ analyses that are separate analyses for Part A and Part B (as separate documents). Please provide as separate tables SMQ analyses with broad and narrow terms combined and SMQ analyses with narrow terms only.

a. Ischemic heart disease

b. Cardiac arrhythmia
c. Cardiac failure

Sponsor Response

Please find below the requested SMQs based on the Part A blinded analysis using narrow terms, and using narrow and broad terms for the mRNA-1273 and Placebo groups respectively. We have not provided the same analysis for Part B for the same reasons as described in Item #1.

Table 1. Requested SMQ Analysis on mRNA-1273 in P301 Part A (Narrow Scope) - Subject Incidence of Unsolicited AEs Up to End of Part A – Safety Set

SMQ Subordinate SMQ Preferred Term	Placebo (N=15162) n(%)	mRNA-1273 (N=15184) n(%)
Ischaemic Heart Disease	**36 (0.24)**	**35 (0.23)**
Myocardial Infarction	16 (0.11)	17 (0.11)
Acute coronary syndrome	0	3 (0.02)
Acute myocardial infarction	6 (0.04)	4 (0.03)
Angina unstable	0	1 (0.01)
Coronary artery occlusion	0	2 (0.01)
Myocardial infarction	9 (0.06)	7 (0.05)
Troponin increased	1 (0.01)	1 (0.01)
Other Ischaemic Heart Disease	21 (0.14)	22 (0.14)
Angina pectoris	12 (0.08)	11 (0.07)
Angina unstable	0	1 (0.01)
Arteriosclerosis coronary artery	1 (0.01)	1 (0.01)
Coronary artery disease	9 (0.06)	10 (0.07)
Stress cardiomyopathy	1 (0.01)	1 (0.01)
Cardiac Arrhythmias	**70 (0.46)**	**60 (0.40)**
Arrhythmia Related Investigations, Signs and Symptoms	0	0
Cardiac Arrhythmia Terms (Incl Bradyarrhythmias and Tachyarrhythmias)	70 (0.46)	60 (0.40)
Arrhythmia	8 (0.05)	5 (0.03)
Atrial fibrillation	28 (0.18)	25 (0.16)
Atrial flutter	4 (0.03)	3 (0.02)
Atrial tachycardia	2 (0.01)	0
Atrioventricular block	0	1 (0.01)

Atrioventricular block complete	1 (0.01)	0
Atrioventricular block second degree	1 (0.01)	0
Cardiac flutter	1 (0.01)	1 (0.01)
Electrocardiogram QT prolonged	0	2 (0.01)
Extrasystoles	1 (0.01)	0
Heart rate irregular	6 (0.04)	2 (0.01)
Paroxysmal arrhythmia	1 (0.01)	0
Sinus arrest	1 (0.01)	0
Sinus bradycardia	1 (0.01)	1 (0.01)
Sinus tachycardia	8 (0.05)	7 (0.05)
Supraventricular extrasystoles	1 (0.01)	1 (0.01)
Supraventricular tachycardia	0	4 (0.03)
Ventricular arrhythmia	1 (0.01)	0
Ventricular extrasystoles	6 (0.04)	10 (0.07)
Ventricular fibrillation	1 (0.01)	0
Ventricular tachycardia	1 (0.01)	2 (0.01)
Congenital and Neonatal Arrhythmias	0	0
Cardiac Failure	**15 (0.10)**	**13 (0.09)**
Acute left ventricular failure	2 (0.01)	2 (0.01)
Cardiac failure	4 (0.03)	4 (0.03)
Cardiac failure acute	1 (0.01)	1 (0.01)
Cardiac failure congestive	9 (0.06)	6 (0.04)
Pulmonary oedema	0	1 (0.01)

Source: t-adhoc-BLA-CBER-IR2-narrow

Table 2. Requested SMQ Analysis on mRNA-1273 in P301 Part A (Narrow and Broad Scope) - Subject Incidence of Unsolicited AEs Up to End of Part A – Safety Set

SMQ Subordinate SMQ Preferred Term	Placebo (N=15162) n(%)	100µg mRNA-1273 (N=15184) n(%)
Ischaemic Heart Disease	**36 (0.24)**	**36 (0.24)**
Myocardial Infarction	16 (0.11)	17 (0.11)
Acute coronary syndrome	0	3 (0.02)
Acute myocardial infarction	6 (0.04)	4 (0.03)
Angina unstable	0	1 (0.01)
Coronary artery occlusion	0	2 (0.01)
Myocardial infarction	9 (0.06)	7 (0.05)
Troponin increased	1 (0.01)	1 (0.01)
Other Ischaemic Heart Disease	21 (0.14)	23 (0.15)

SMQ Subordinate SMQ Preferred Term	Placebo (N=15162) n(%)	100µg mRNA-1273 (N=15184) n(%)
Angina pectoris	12 (0.08)	11 (0.07)
Angina unstable	0	1 (0.01)
Arteriosclerosis coronary artery	1 (0.01)	1 (0.01)
Coronary artery disease	9 (0.06)	10 (0.07)
Electrocardiogram T wave inversion	0	1 (0.01)
Myocardial ischaemia	1 (0.01)	0
Stress cardiomyopathy	0	1 (0.01)
Cardiac Arrhythmias	**165 (1.09)**	**148 (0.97)**
Arrhythmia Related Investigations, Signs and Symptoms	101 (0.67)	91 (0.60)
Bradycardia	23 (0.15)	15 (0.10)
Cardiac arrest	0	1 (0.01)
Cardio-respiratory arrest	1 (0.01)	2 (0.01)
Heart rate increased	3 (0.02)	5 (0.03)
Loss of consciousness	1 (0.01)	1 (0.01)
Palpitations	13 (0.09)	22 (0.14)
Syncope	40 (0.26)	25 (0.16)
Tachycardia	23 (0.15)	21 (0.14)
Cardiac Arrhythmia Terms (Incl Bradyarrhythmias and Tachyarrhythmias)	**70 (0.46)**	**60 (0.40)**
Arrhythmia	8 (0.05)	5 (0.03)
Atrial fibrillation	28 (0.18)	25 (0.16)
Atrial flutter	4 (0.03)	3 (0.02)
Atrial tachycardia	2 (0.01)	0
Atrioventricular block	0	1 (0.01)
Atrioventricular block complete	1 (0.01)	0
Atrioventricular block second degree	1 (0.01)	0
Cardiac flutter	1 (0.01)	1 (0.01)
Electrocardiogram QT prolonged	0	2 (0.01)
Extrasystoles	1 (0.01)	0
Heart rate irregular	6 (0.04)	2 (0.01)
Paroxysmal arrhythmia	1 (0.01)	0
Sinus arrest	1 (0.01)	0
Sinus bradycardia	1 (0.01)	1 (0.01)
Sinus tachycardia	8 (0.05)	7 (0.05)
Supraventricular extrasystoles	1 (0.01)	1 (0.01)
Supraventricular tachycardia	0	4 (0.03)
Ventricular arrhythmia	1 (0.01)	0
Ventricular extrasystoles	6 (0.04)	10 (0.07)
Ventricular fibrillation	1 (0.01)	0
Ventricular tachycardia	1 (0.01)	2 (0.01)
Congenital and Neonatal Arrhythmias	0	0
Cardiac Failure	**49 (0.32)**	**47 (0.31)**
Acute left ventricular failure	2 (0.01)	2 (0.01)
Brain natriuretic peptide increased	1 (0.01)	0
Cardiac failure	4 (0.03)	4 (0.03)
Cardiac failure acute	1 (0.01)	1 (0.01)

SMQ Subordinate SMQ Preferred Term	Placebo (N=15162) n(%)	100µg mRNA-1273 (N=15184) n(%)
Cardiac failure congestive	9 (0.06)	6 (0.04)
Cardiomegaly	2 (0.01)	0
Diastolic dysfunction	1 (0.01)	0
Lower respiratory tract congestion	1 (0.01)	0
Oedema	1 (0.01)	0
Oedema peripheral	17 (0.11)	14 (0.09)
Peripheral swelling	14 (0.09)	19 (0.13)
Pulmonary congestion	0	1 (0.01)
Pulmonary oedema	0	1 (0.01)

Source: t-adhoc-BLA-CBER-IR2-broad

ITEM 3:

The following comment is provided as a clarification and applies to all requested SMQ tables.
For each SMQ, please provide a table for each study part (Part A, Part B as separate documents) with the relevant study groups in each (Part A: mRNA- 1273, Placebo; Part B: mRNA-1273, Placebo, Placebo-mRNA1273). Please provide a separate table for broad (including narrow events) and narrow SMQ searches. For each table provide the following information:
- # of events reported for each term for each group
- 'n' participants and percentage (%) who reported each term for each group

Sponsor Response

Thank you for providing sample table shells.

ITEM 4:

In the ADAE dataset, there are at least 378 records that have an AESTDTC value with a time code of "T00:00" and ASTDTM values with time codes of '12:00:00 AM'. It is likely that these times are derived due to a lack of a time input. The 49 of these records that occur on study day 1 are all found to be not treatment emergent (TRTEMFL = ""), however that is unclear because of the derived time issue. Can you please provide additional clarification on these 49 records and if they occurred after the first dose of treatment on study day 1.

Sponsor Response

The Sponsor would like to thank the reviewers' thorough review. "T00:00" in the time portion are indeed 'collected data' based on the raw data (raw.AE), and thus present as is in the SDTM AE domain variable AESTDTC and ADAE.ASTDTM (date/time) variable. TRTEMFL is derived using ASTDTM (date/time) compared with TR01SDTM; if the time portion is not available, only

the date portion is used to derive TRTEMFL. For the 49 records that occur on study day 1 with "T00:00" in time portion, as "T00:00" is "collected" data not imputation for missing data, the start date and time are deemed as earlier than the dosing time, and thus TRTEMFL were set to "".

The Sponsor will update the logic, and set TRTEMFL="Y" in future submissions when ASTDTM with time "T00:00" that occur on the same date of the date of first dose.