RESPONSE TO FDA COMMENTS ON CMC RECEIVED ON 23 SEPTEMBER 2021

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

CMC: Analytical method procedure and validation

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following request for additional information regarding your assay for product-related impurities:

ITEM 1:

According to your pre-BLA briefing document submitted on May 19, 2021, the Ion Pair Reversed Phase High Performance Liquid Chromatography (IP-RP-HPLC) method (SOP-0996) for analysis of mRNA purity in the CX-024414 mRNA Drug Substance (DS), mRNA-1273 LNP DS, and mRNA-1273 Drug Product (DP) was modified to improve (b) (4) (b) (4) **However, the updated method (SOP-1142) and its validation have not been submitted to the BLA. Please provide the updated SOP-1142 and full validation of the method or confirm your intent to use the original method as described in SOP-0996.**

Sponsor Response

The intent is to use SOP-1142 for analysis of mRNA purity in the CX-024414, mRNA-1273 LNP and mRNA-1273 DP. The SOP (SOP-1142), the method validation (QC-MVR-0025) and the bridging study report (QC-OTH-0801) are provided as attachments.

An improved reversed-phase ion-pair (RP-IP) HPLC method (SOP-1142) was developed for the analysis of mRNA purity by (b) (4)
(b) (4)

The validation of Method SOP-1142 is complete (QC-MVR-0025). The validation demonstrated the suitability for testing of CX-024414 mRNA, mRNA-1273 LNP and mRNA-1273 DP samples.

In addition to the method validation, the bridging of SOP-1142 and SOP-0996 for mRNA-1273 was performed by testing stability samples from Phase 3 clinical lots of the intended storage and scale B lots. Release and shelf life acceptance criteria for mRNA purity was confirmed with the completion of bridging. The bridging study report, QC-OTH-0801, details the bridging dataset for SOP-1142 and SOP-0996. The Justification of Specifications are being updated accordingly in 3.2.S.4.5 Justification of Specification {CX-024414}, 3.2.S.4.5 Justification of Specification {mRNA-1273 LNP} and 3.2.P.5.6 Justification of Specifications and confirms the release and shelf life acceptance criteria. The three Justification of Specification sections will be submitted to BLA 125752 on October 15, 2021.

The intent is to continue testing the purity of the mRNA-1273 Drug Product, CX-024414 mRNA and mRNA-1273 LNP in accordance with SOP-0996 until the BLA is approved. Once the BLA is approved, the transition of the purity testing of the mRNA-1273 Drug Product, CX-024414 mRNA and mRNA-1273 LNP from SOP-0996 to SOP-1142 will independently occur within (b) (4) (b) (4) for the initiation of manufacturing. The Sponsor will provide a formal notification to the BLA when the transition has been completed concerning lot impact.

ITEM 2:

If you intend to use the original method (SOP-0996) for Drug Substances (DS) and Drug Product (DP) release testing, please provide (b) (4) (b) (4) **that were used in the validation study.**

Sponsor Response

Not Applicable per response to ITEM 1.