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3.2.P.2.2 Drug Product

The mRNA-1273 Drug Product is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-024414) that encodes for the pre-fusion stabilized Spike glycol protein of 2019-novel Coronavirus (SARS-CoV-2) and four lipids which act as protectants and carriers of the mRNA. The four lipids are: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol.

mRNA-1273 Drug Product is supplied as a preservative-free multiple-dose liquid ready-to-use solution at 0.20 mg/mL for intramuscular administration in 10R clear Type 1 borosilicate glass vials with rubber serum stopper and an aluminum seal with flip-off plastic cap.

3.2.P.2.2.1 Formulation Development

Formulation development activities for mRNA-1273 Drug Product leveraged historical knowledge from similar platform products to develop a suitable formulation for Intramuscular (IM) injection. The proprietary formulation was developed to ensure a stable product and compatibility with the mRNA-1273 Drug Product container closure system. The feasibility of developing a multiple-dose product was studied by examining the impact of common preservatives on the biophysical characteristics of the product.

3.2.P.2.2.1.1 LNP Composition Justification

Lipid nanoparticles (LNPs) are typically composed of four components, an ionizable lipid, a phospholipid such as DSPC, cholesterol, and a PEG-lipid. Each of the lipids serves a specific function. Early evaluations of LNPs as a delivery system for mRNA vaccines used MC3 as an ionizable lipid to deliver mRNA vaccines. Vaccines using this lipid generated potent immune responses in rodents, non-human primate (NHP), and humans. However, the lack of lipid biodegradability was identified as a potential liability for tolerability. The working hypothesis was that lipid remaining at the injection site for an extended period was not critical to generating an immune response but a potential liability for tolerability.

ModernaTX, Inc. screened LNPs specifically for IM delivery of vaccines as reported in Hassett et al. (2019). Using model reporter mRNA in rodent and NHP studies showed that among the lipids studied, a number of proprietary biodegradable lipids showed superior protein expression and immunogenicity compared to the then current standard non-degradable ionizable lipid (MC3) when injected by the IM route. Biodegradability of the lipids was assessed by measuring lipid levels after IM administration using liquid chromatography-tandem mass spectroscopy in select tissues. IM delivery of the LNPs made using SM-102 showed rapid clearance in mice.

SM-102 was selected as the most potent lipid out of a panel of 30 ionizable lipids that were screened for expression and vaccine potency via the IM route of administration in rodents. SM-102 was also selected as the lead ionizable lipid due to improved tolerability over the five lipid leads that were advanced into NHPs.

The mRNA-1273 LNP comprises four lipids: SM-102, DSPC, cholesterol, and PEG-lipid. The molar lipid ratio of 50:38.5:10:1.5 (ionizable lipid:cholesterol:DSPC:PEG-lipid) has been used in the literature for systemic delivery of LNPs. Further verification of the lipid composition was conducted using one of ModernaTX, Inc.'s vaccine constructs. It was observed that slight variations in the percentage of SM-102, DSPC, or PEG-lipid can be made without a detectable difference in immunogenicity. Minor adjustments were made to the literature composition to harmonize with the platform composition, which resulted in a molar lipid ratio of [redacted]

3.2.P.2.2.1.2 Commercial and Clinical Formulations

The early clinical formulation (Phase 1 and Phase 2) utilized a target concentration of 0.5 mg/mL mRNA in the LNP composition as described above. A range of doses were tested in the clinic in Phase 1 and Phase 2. These doses were prepared by clinical dilution of the 0.5 mg/mL product. After selection of the final dose, a target concentration of 0.20 mg/mL mRNA was developed for Phase 3 and commercial product as a ready-to-use solution.

Dilution of the mRNA-1273 LNP to varying target concentrations during development resulted in minor differences in sodium acetate content. While the distribution of Tris in the Dilution Buffer (Tris base and Tris HCl) varied between the formulations, the total buffer strength (20 mM) and pH (7.5) remained constant. Sucrose was unchanged between the two formulations. A tabular comparison of the differences in formulation composition is provided in Table 1.

Table 1: Comparison of Clinical and Commercial Formulations

Component	Phase 1/Phase 2		Phase 3/Commercial	
	mg/mL	mM	mg/mL	mM
CX-024414 (mRNA)	[redacted]	N/A	[redacted]	N/A
SM-102		N/A		N/A
Cholesterol		N/A		N/A
DSPC		N/A		N/A
PEG-2000-DMG		N/A		N/A
Tris (base)		[redacted]		[redacted]
Tris-HCl				
Acetic Acid				
Sodium Acetate [a]				
Sucrose				
Water for Injection	q.s. to [redacted]		q.s. to [redacted]	

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; HCl = hydrochloride; NaOH = sodium hydroxide; PEG-2000-DMG =1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene; q.s. = quantum sufficit, N/A = Not applicable
a Sodium acetate is formed from buffer(s) manufactured with glacial acetic acid and 10 N NaOH (30% w/w).

3.2.P.2.2.1.3 Developmental Stability Studies

The suitability of the formulation composition has been studied in a number of developmental stabilities studies at the intended long-term storage conditions as well as shorter term accelerated studies to enable manufacturing of the drug product. The data available to date demonstrates that there is no change in mRNA purity and LNP biophysical qualities when stored at -70°C (-60°C to -90°C). mRNA chemical degradation is observed at -20°C (-15°C to -25°C), 5°C (2°C to 8°C), and 25°C (23°C to 27°C) in a temperature-dependent manner. The data are summarized in Section 3.2.P.8.3.

3.2.P.2.2.1.4 Microbiological Characteristics: Impact of Preservatives

In order to evaluate the ability to develop a preserved multiple-dose product, a study was initiated to understand the impact of common anti-microbial preservatives on the biophysical characteristics of the mRNA-1273 Drug Product. The preservatives commonly used in parenteral products (including vaccines) are expected to have a strong tendency to partition into the LNPs. This assessment is based on the mechanism by which these compounds function, which requires partitioning into membranes or cell walls of microbes.

[redacted]

[redacted]

Based on the above results, the use of a preservative in the mRNA-1273 Drug Product was not pursued. The ability to use the mRNA-1273 Drug Product as an unpreserved multiple-dose product was examined with the microbiological challenge hold time study reported in Section 3.2.P.2.5.3 Microbiological Growth Promotion Characteristics to Assess Suitability as an Unpreserved Multiple-dose Product.

3.2.P.2.2.1.5 Overfill

A Monte Carlo simulation was performed to define the mRNA-1273 Drug Product 10R vial overfill volume to support definition of a 10-dose presentation. The stacked variability from material losses (vial hold-up, syringe dead volume) as well as fill weight variability was included in the simulation. The simulation demonstrates that a 6.3 mL fill volume provides a reasonable probability to successfully withdraw 10 doses (85%) while maximizing mRNA material utilization, thus representing a 26% overfill.

3.2.P.2.2.1.6 Assessment of Risk for Vial Breakage

A series of studies were conducted to evaluate fill volumes and glass breakage. Since breakage is a probabilistic phenomenon, the possibility of observing a rare event depends on the number of vials studied. The results showed that for storage at -70°C and -40°C, the risk of vial breakage can be reduced by using a 5 mL fill volume. However, for the intended -20°C (-15°C to -25°C) long-term storage condition, a 6.3 mL fill volume is not considered a risk since the amorphous matrix does not undergo significant contraction at this temperature (Jiang et al. 2007).

It must be noted that prior to storage at the intended long-term storage at -20°C (-15°C to -25°C), an intermediate process step of -40°C hold (24 to 48 hours) is implemented to eliminate supercooling and ensure that freezing is complete. Thus, a 6.3 mL fill volume held at -40°C could be considered a small risk since the Tg' of the matrix is approximately -35°C. However, vial breakage under these conditions has never been observed to date.

3.2.P.2.2.2 Overages

No overages are applied for the production of mRNA-1273 Drug Product.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical properties of mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 Drug Product (DP) solutions are provided in Table 2. The mRNA-1273 LNP (0.60 – 1.00 mg/mL CX-024414 mRNA) and mRNA-1273 Drug Product (0.20 mg/mL CX-024414 mRNA) are presented.