

## Table of Contents

Table of Contents .....	1
3.2.P.8.1 Stability Summary and Conclusion .....	2
3.2.P.8.1.1 Stability Summary .....	2
3.2.P.8.1.2 Stability Study Protocols .....	3
3.2.P.8.1.2.1 Study Protocols to Support the Initial Use Period for mRNA-1273 LS Injection .....	3
3.2.P.8.1.2.2 Real-Time Stability Study Protocols for GMP mRNA-1273 LS Injection ....	4
3.2.P.8.1.2.3 Freeze/Thaw Stability Study Protocol for mRNA-1273 LS Injection .....	5
3.2.P.8.1.2.4 Clinical In-use Stability Study Protocol for mRNA-1273 LS Injection.....	6
3.2.P.8.1.3 Stability Study Results .....	6
3.2.P.8.1.3.1 Stability Study Results to Support the Initial Use Period for mRNA-1273 Injection .....	6
3.2.P.8.1.3.2 Stability Study Results for GMP mRNA-1273 Injection .....	8
3.2.P.8.1.3.3 Freeze/Thaw Stability Study Results.....	10
3.2.P.8.1.3.4 Clinical In-Use Stability Study Results .....	11
3.2.P.8.1.4 Conclusions and Use Period Claim .....	12

## List of Tables

Table 1:	GMP mRNA-1273 LS Injection Stability Testing Overview .....	2
Table 2:	Development mRNA-1273 LS Injection Stability Testing Overview .....	3
Table 3:	Development mRNA-1273 LS Injection Stability Protocols for 0.10 mg/mL mRNA and 0.5 mg/mL mRNA .....	4
Table 4:	GMP mRNA-1273 LS Injection Stability Protocol .....	4
Table 5:	GMP mRNA-1273 LS Injection Matrix Stability Protocol .....	5
Table 6:	Preparation Configurations for the Clinical In-use Stability Studies.....	6

### 3.2.P.8.1 Stability Summary and Conclusion

#### 3.2.P.8.1.1 Stability Summary

mRNA-1273 LS Injection is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-024414) that encodes for the pre-fusion stabilized Spike 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 LS Injection has a total lipid content of (b) (4) mg/mL and contains a 20 mM trometamol (Tris), 87 mg/mL sucrose and (b) (4) sodium acetate buffer at a dosage strength of 0.20 mg/mL mRNA, pH 7.5. mRNA-1273 LS Injection is presented in 10R USP Type I borosilicate glass vials with (b) (4)

mRNA-1273 LS Injection is stored long-term (storage between -60°C to -90°C) and stored short-term (storage between 2°C to 8°C). One vial of mRNA-1273 LS Injection contains 6 doses for intramuscular injection (0.5 mL each). For SM-102 containing mRNA-based vaccines, the mRNA purity method by RP-HPLC and particle size by Dynamic Light Scattering methods have been demonstrated to be stability indicating.

A use period of (b) (4) is proposed for mRNA-1273 LS Injection stored long-term (storage between -60°C to -90°C) based on available stability data. A use period of (b) (4) is proposed for mRNA-1273 LS Injection stored short-term (storage between 2°C to 8°C) based on available stability data. A clinical in use period of up to 8 hours at ambient temperature or between 2°C to 8°C in a syringe is recommended for mRNA-1273 LS Injection.

An overview of GMP mRNA-1273 LS Injection stability studies is provided in [Table 1](#).

**Table 1: GMP mRNA-1273 LS Injection Stability Testing Overview**

Lot Number	Usage	Concentration Fill Volume	mRNA-1273 LNP Lot Number	Date of Manufacture	Stability Storage Condition
6007520001	Clinical Supplies and Stability	0.20 mg/mL 5.0 mL	5006820002	28 May 2020	<ul style="list-style-type: none"> <li>-60°C to -90°C (Intended Long-term)</li> <li>-20°C ± 5°C</li> <li>2°C to 8°C (Intended Short-term)</li> <li>25°C ± 2°C</li> </ul>
6007520002				02 Jun 2020	
6007520003				04 Jun 2020	
6007520004			5006820003	26 Jun 2020	<ul style="list-style-type: none"> <li>-60°C to -90°C (Intended Long-term)</li> <li>-60°C to -90°C followed by storage at 2°C to 8°C (Intended Short-term)</li> </ul>
6007520005			5006820003	01 Jul 2020	
6007520006			5006820003 and 5006820004	08 Jul 2020	

Material for the development of mRNA-1273 Lipid Nanoparticle (LNP) (Lot AMPDP-200022) was prepared using a manufacturing process which is representative of the GMP mRNA-1273 LNP process as described in [Section 3.2.S.2.2 {mRNA-1273 LNP}](#). Two separate lots of mRNA-1273 LS Injection were prepared with Lot AMPDP-200022 using 87 mg/mL sucrose and 20 mM Tris, pH 7.5 as the formulation buffer, as specified in [Section 3.2.P.3.3](#). One development lot was prepared with a total RNA content of (b) (4) mRNA (b) (4). The other development lot was prepared with a total RNA content of (b) (4) mRNA (b) (4) (b) (4). At the time of manufacture of the development lots, the final total mRNA content for the GMP mRNA-1273 LS Injection had not been finalized. Therefore, these two different total RNA contents were filled in order to appropriately bracket any proposed total RNA content (final total RNA content was established as (b) (4)). Therefore, the stability of mRNA-1273 LS Injection at dosage strength of 0.10 mg/mL (b) (4) and 0.5 mg/mL (b) (4) is a suitable bracket to establish the initial long-term (storage between -60°C to -90°C) and short-term (storage between 2°C to 8°C) use periods for mRNA-1273 LS Injection at the intended clinical dose concentration of 0.20 mg/mL mRNA.

An overview of development mRNA-1273 LS Injection stability studies is provided in [Table 2](#).

**Table 2: Development mRNA-1273 LS Injection Stability Testing Overview**

Lot Number	Usage	Concentration Fill Volume	mRNA-1273 LNP Lot Number	Date of Manufacture	Stability Storage Condition
(b) (4)	Initial Use Period	0.10 mg/mL 0.6 mL	AMPDP-200022	01 Apr 2020	<ul style="list-style-type: none"> <li>-60°C to -90°C (Intended Long-term)</li> <li>-20°C ± 5°C</li> <li>2°C to 8°C (Intended Short-term)</li> </ul>
	Initial Use Period	0.5 mg/mL 0.6 mL	AMPDP-200022	01 Apr 2020	<ul style="list-style-type: none"> <li>-60°C to -90°C (Intended Long-term)</li> <li>-20°C ± 5°C</li> <li>2°C to 8°C (Intended Short-term)</li> </ul>

### 3.2.P.8.1.2 Stability Study Protocols

#### 3.2.P.8.1.2.1 Study Protocols to Support the Initial Use Period for mRNA-1273 LS Injection

Development mRNA-1273 LS Injection stability samples used to establish initial use period are tested according to the protocol described in [Table 3](#). Samples stored at the intended condition are evaluated against the specification provided in the stability tables. Samples stored at accelerated storage conditions used the specification at the intended condition as a reference point to characterize stability trends at the accelerated conditions.

**Table 3: Development mRNA-1273 LS Injection Stability Protocols for 0.10 mg/mL mRNA and 0.5 mg/mL mRNA**

Condition	Time Interval (Months)												
	0	1	2	3	4	5	6	9	12	18	24	36	48
-60°C to -90°C	ABCD	A	N/A	AB	N/A	N/A	A	A	AB	A	AB	AB	AB
-20°C ± 5°C		N/A	A	AB	N/A	N/A	AB	AB	AB	N/A	AB	N/A	AB
2°C to 8°C		A	AB	AB	A	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

A = Appearance, %purity, particle size, polydispersity, %RNA encapsulation

B = RNA content, lipid content, lipid impurities, lipid identity, pH, cell-free translation

C = Bacterial endotoxin, bioburden, particulate matter

D = Osmolality, identity

N/A = Not required per the stability protocol

### 3.2.P.8.1.2.2 Real-Time Stability Study Protocols for GMP mRNA-1273 LS Injection

GMP mRNA-1273 LS Injection stability samples (Lot 6007520001, Lot 6007520002, Lot 6007520003 and Lot 6007520004) are tested according to the protocols described in [Table 4](#). Samples stored at the intended condition are evaluated against the specification provided in the stability tables. Samples stored at accelerated storage conditions used the specification at the intended condition as a reference point to characterize stability trends at the accelerated conditions.

**Table 4: GMP mRNA-1273 LS Injection Stability Protocol**

Condition	Months (unless noted)												
	0	24 hr	72 hr	1	2	2.5	3	4	6	9	12	18	24
-60°C to -90°C	ABCDE	N/A	N/A	ABC	AB	N/A	ABC	N/A	ABC	ABC	ABCD	ABC	ABCD
-20°C ± 5°C		N/A	N/A	ABC	AB	N/A	ABC	N/A	ABC	ABC	ABC	N/A	N/A
2°C to 8°C		N/A	N/A	ABC	B	B	ABC	B	ABCD	N/A	N/A	N/A	N/A
23°C to 27°C		ABC	ABC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

A = %RNA encapsulation

B = Appearance, %purity, particle size, polydispersity

C = In-vitro Translation (Potency), pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, sterility, container content

E = Identity, lipid identity, osmolality

N/A = not required per stability protocol

GMP mRNA-1273 LS Injection stability samples (Lot 6007520005 and Lot 6007520006) are tested according to the protocols described in [Table 5](#). Samples stored at the intended condition are evaluated against the specification provided in the stability tables. Samples stored at accelerated storage conditions used the specification at the intended condition as a reference point to characterize stability trends at the accelerated conditions. This protocol has been established to monitor stability for samples stored between -60°C to -90°C followed by storage at 2°C to 8°C at specified intervals for up to three (3) months.

**Table 5: GMP mRNA-1273 LS Injection Matrix Stability Protocol**

Condition	Months						
	0	1	2	2.5	3	6	9
-60°C to -90°C	ABCDE	ABC <sup>(1)</sup>	ABC	N/A	ABC <sup>(2)</sup>	ABC	ABCD <sup>(3)</sup>
-60°C to -90°C followed by 2°C to 8°C (inverted)	N/A	B	B	B	ABCD	N/A	N/A

A = Appearance (after thaw from -60°C to -90°C), %RNA encapsulation

B = Appearance (after 2°C to 8°C storage), %purity, particle size, polydispersity

C = In-vitro Translation (Potency), pH, total RNA content, lipid content and lipid impurities

D = Bacterial endotoxins, particulate matter, sterility, container content

E = Identity, lipid identity, osmolality

N/A = not required per stability protocol

- 1) After thaw from -60°C to -90°C at T = 1 month, stability testing at 2°C to 8°C (inverted) is conducted at T = 1 month, at T = 2 month, at T = 2.5 month and T = 3 month.
- 2) After thaw from -60°C to -90°C at T = 3 month, stability testing at 2°C to 8°C (inverted) is conducted at T = 1 month, at T = 2 month, at T = 2.5 month and T = 3 month.
- 3) After thaw from -60°C to -90°C at T = 9 month, stability testing at 2°C to 8°C (inverted) is conducted at T = 1 month, at T = 2 month, at T = 2.5 month and T = 3 month.

### 3.2.P.8.1.2.3 Freeze/Thaw Stability Study Protocol for mRNA-1273 LS Injection

Stability studies in support of mRNA-1273 LS Injection freeze-thaw cycling were performed using representative mRNA-1273 LS Injection. Two separate lots of mRNA-1273 LS Injection were formulated from Lot AMPDP-200022. One development lot was prepared with a total RNA content of (b) (4) mRNA (DHM-47522). The other development lot was prepared with a total RNA content of (b) (4) mRNA (DHM-47518). Similarly, as the studies to establish the initial use period, mRNA-1273 LS Injection lots at dosage strength of 0.10 mg/mL mRNA (DHM-47522) and 0.5 mg/mL mRNA (DHM-47518) were utilized to bracket for freeze-thaw cycling studies. (b) (4)

The freeze-thaw cycling was repeated up to five times. Samples were tested for appearance, %purity, %RNA encapsulation, particle size and polydispersity after samples were subjected to one freeze-thaw cycle (b) (4) three freeze-thaw cycles (b) (4) and five freeze-thaw cycles (b) (4)

### 3.2.P.8.1.2.4 Clinical In-use Stability Study Protocol for mRNA-1273 LS Injection

Clinical in-use stability studies were performed to mimic the handling of mRNA-1273 LS Injection at the clinical sites, using representative materials, representative test articles and the appropriate dose preparation procedure for clinical use. Two lots of mRNA-1273 LS Injection (representative multi-dose vials with 6.5 mL fill volume) were used for the study, as described in Table 6 and manufactured under cGMP conditions, were used for bracketing the intended clinical dose concentrations to demonstrate compatibility of administration materials (b) (4)

with mRNA-1273 LS Injection. Similarly, as the studies to establish the initial use period, mRNA-1273 LS Injection lots at dosage strength of 0.10 mg/mL mRNA (Lot 6006820001) and 0.5 mg/mL mRNA (Lot 6006920001) were utilized to bracket the clinical in-use studies. mRNA-1273 LS Injection was not diluted for this study.

**Table 6: Preparation Configurations for the Clinical In-use Stability Studies**

Lot No.	Dose, µg	Dose Concentration (mg/mL)	Dose volume (mL)
6006820001	(b) (4)	0.10	0.5
6006920001		0.5	0.5

### 3.2.P.8.1.3 Stability Study Results

#### 3.2.P.8.1.3.1 Stability Study Results to Support the Initial Use Period for mRNA-1273 Injection

Stability testing results for development mRNA-1273 LS Injection Lot (b) (4) (0.10 mg/mL) are provided in Table 1, Section 3.2.P.8.3, Table 2, Section 3.2.P.8.3 and Table 3, Section 3.2.P.8.3.

(b) (4)

(b) (4)



Stability testing results for development mRNA-1273 LS Injection Lot (b) (4) (0.5 mg/mL) are provided in [Table 4, Section 3.2.P.8.3](#), [Table 5, Section 3.2.P.8.3](#) and [Table 6, Section 3.2.P.8.3](#).

(b) (4)



### 3.2.P.8.1.3.2 Stability Study Results for GMP mRNA-1273 Injection

Stability data for GMP mRNA-1273 LS Injection is presented in the following section. Stability testing for Lot 6007520001, Lot 6007520002 and Lot 6007520003 has been conducted at T = 1 month. There is no stability data available for Lot 6007520004, Lot 6007520005 and Lot 6007520006.

Stability testing results for GMP mRNA-1273 LS Injection Lot 6007520001 (0.20 mg/mL) are provided in [Table 7, Section 3.2.P.8.3](#), [Table 8, Section 3.2.P.8.3](#), [Table 9, Section 3.2.P.8.3](#) and [Table 10, Section 3.2.P.8.3](#).

(b) (4)





Stability testing results for GMP mRNA-1273 LS Injection Lot 6007520002 (0.20 mg/mL) are provided in [Table 11, Section 3.2.P.8.3](#), [Table 12, Section 3.2.P.8.3](#), [Table 13, Section 3.2.P.8.3](#) and [Table 14, Section 3.2.P.8.3](#).

(b) (4)



Stability testing results for GMP mRNA-1273 LS Injection Lot 6007520003 (0.20 mg/mL) are provided in [Table 15, Section 3.2.P.8.3](#), [Table 16, Section 3.2.P.8.3](#), [Table 17, Section 3.2.P.8.3](#) and [Table 18, Section 3.2.P.8.3](#).

(b) (4)




(b) (4)



### 3.2.P.8.1.3.3 Freeze/Thaw Stability Study Results

Freeze-thaw stability studies were performed using representative mRNA-1273 LS Injection lots at 0.10 mg/mL mRNA (Lot DHM-47522) and 0.5 mg/mL mRNA (Lot DHM-47518). mRNA-1273 LS Injection samples were subjected to a series of five freezing and thawing cycles and assessed for appearance, % RNA encapsulation, mRNA purity by RP-HPLC, mean particle size and polydispersity index.

For Lot DHM-47522 (0.10 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws at room temperature, (b) (4)



These data are presented in [Table 19, Section 3.2.P.8.3](#).

For Lot DHM-47522 (0.10 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws between 2°C to 8°C, (b) (4)

These data are presented in [Table 20, Section 3.2.P.8.3](#).

For Lot DHM-47518 (0.5 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws at room temperature, (b) (4)

These data are presented in [Table 21, Section 3.2.P.8.3](#).

For Lot DHM-47518 (0.5 mg/mL mRNA), for five cycles of storage between -60°C to -90°C and thaws between 2°C to 8°C, (b) (4)

These data are presented in [Table 22, Section 3.2.P.8.3](#).

These studies support five freeze/thaw cycles for bracketing dosage strengths of 0.10 mg/mL to 0.5 mg/mL mRNA for mRNA-1273 LS Injection.

#### 3.2.P.8.1.3.4 Clinical In-Use Stability Study Results

Clinical in-use stability studies for mRNA-1273 LS Injection were conducted using Lot 6006820001 and Lot 6006920001 and materials of contact planned for clinical dosing (b) (4) to determine material compatibility and in-use stability. mRNA-1273 LS Injection under evaluation is a multi-dose vial. The study was designed to enable direct removal of product solution from vial and holding in syringes. The product solution was held in the vial at room temperature for either 1 hour or 7 hours after thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 7 hours upon completion of a 1 hour thaw at room temperature. The syringes were then held for 0, 8, and 24 hours at room temperature and refrigerated conditions, and assayed for RNA content by AEX-HPLC, % purity by RP-HPLC, lipid content by UPLC-CAD, % RNA encapsulation, and mean particle size and polydispersity by DLS. Attributes of mRNA-1273 LS Injection stayed within specification when held in a vial for 6 hours at room temperature, followed by storage in a syringe for 8 hours, at either 0.5 mg/mL or 0.10 mg/mL. Clinical in-use stability was demonstrated for bracketing dosage strengths of 0.10 mg/mL to 0.5 mg/mL

mRNA for up to 6 hours in the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C. These data are provided in [Table 23](#), [Section 3.2.P.8.3](#) to [Table 28](#), [Section 3.2.P.8.3](#).

#### **3.2.P.8.1.4 Conclusions and Use Period Claim**

Based on the one month of stability data for GMP mRNA-1273 LS Injection lots (Lot 6007520001, Lot 6007520002 and Lot 6007520003) and three (3) month of bracketing dosage stability data for development mRNA-1273 LS Injection, Lot (b) (4) (0.10 mg/mL) and (b) (4) (0.5 mg/mL), an initial use period of six (6) months at the long-term storage condition (storage between -60°C to -90°C) is proposed for mRNA-1273 LS Injection.

Based on the one month of stability data for GMP mRNA-1273 LS Injection lots (Lot 6007520001, Lot 6007520002 and Lot 6007520003) and three (3) months of bracketing dosage stability data for development mRNA-1273 LS Injection, Lot (b) (4) (0.10 mg/mL) and (b) (4) (0.5 mg/mL), an initial use period of (b) (4) at the short-term storage condition (storage between 2°C to 8°C) is proposed for mRNA-1273 LS Injection.

Based on the bracketing clinical in-use dosage stability data for mRNA-1273 LS Injection, Lot 6006820001 (0.10 mg/mL) and Lot 6006920001 (0.5 mg/mL), clinical in-use stability for mRNA-1273 LS Injection was demonstrated when held up to 8 hours in the dosing syringe, at either ambient temperature or at 5°C.

#### **Extension of Use Period**

As long-term and short-term stability data for mRNA-1273 LS Injection is obtained, the use period may be extended using an extension interval not to exceed two times the available stability data, and the use period cannot exceed the duration of the stability protocols.