

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**SPIKEVAX™ Bivalent  
(Original / Omicron BA.4/5)**

Elasomeran / davesomeran mRNA vaccine

[COVID-19 mRNA vaccine, Bivalent (Original/Omicron B.1.1.529 (BA.4/5) Variant)]

Dispersion for intramuscular injection

Multidose Vial, 0.10 mg / mL

Active Immunizing Agent

SPIKEVAX Bivalent Original / Omicron BA.4/5 (elasomeran/davesomeran) vaccine indicated for:

Active immunization against coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 18 years of age and older, has been issued marketing authorization with Terms and Conditions that need to be met by the Market Authorization Holder to ascertain the continued quality, safety and effectiveness of the vaccine.

Patients should be advised of the nature of the authorization. For further information for SPIKEVAX Bivalent Original / Omicron BA.4/5 (elasomeran/davesomeran mRNA vaccine) please refer to Health Canada's [COVID-19 vaccines and treatments portal](#).

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## RECENT MAJOR LABEL CHANGES

N/A

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

SPIKEVAX Bivalent (elasomeran/davesomeran) Original/Omicron BA.4/5 mRNA vaccine is indicated as a booster dose for active immunization against coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 18 years of age and older.

The safety and effectiveness of a booster dose of SPIKEVAX Bivalent (elasomeran/davesomeran) Original/Omicron BA.4/5 mRNA vaccine for individuals 18 years of age and older is inferred from studies of a booster dose of SPIKEVAX Bivalent (Original/Omicron BA.1).

The National Advisory Committee on Immunization (NACI) provides additional guidance on the use of the COVID-19 vaccines in Canada. Please refer to the COVID-19 vaccine: Canadian Immunization Guide and current vaccine statements.

#### **1.1 Pediatrics**

The safety and efficacy of SPIKEVAX Bivalent Original/Omicron BA.4/5 in individuals under 18 years of age has not yet been established (see [ADVERSE REACTIONS](#), and [CLINICAL TRIALS](#) sections).

#### **1.2 Geriatrics**

Clinical studies of SPIKEVAX Bivalent (Original/Omicron BA.1) that included participants 65 years of age and older and their data contribute to the overall assessment of safety and effectiveness of SPIKEVAX Bivalent Original / Omicron BA.4/5 (elasomeran / davesomeran) mRNA COVID-19 vaccine (see [ADVERSE REACTIONS](#) and [CLINICAL TRIALS](#) sections).

### **2 CONTRAINDICATIONS**

SPIKEVAX Bivalent Original/Omicron BA.4/5 is contraindicated in individuals who are hypersensitive to the active ingredient or to any ingredients in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

### **3 SERIOUS WARNINGS AND PRECAUTIONS**

At the time of authorization, there are no known serious warnings or precautions associated with this product.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

SPIKEVAX Bivalent Original/Omicron BA.4/5 is a dispersion for intramuscular injection that should be administered by a trained healthcare worker.

*Individuals ≥ 18 Years of Age:* The SPIKEVAX Bivalent Original/Omicron BA.4/5 booster is one dose of 50 mcg.

Age Range	Vaccination	Presentation	Vial Cap Colour	Label Border Colour	Dose	Dose Volume
18 years of age or older	SPIKEVAX Bivalent Original / Omicron BA.4/5 Booster Dose	0.10 mg/mL	Royal Blue	Grey	50 mcg	0.5 mL

### 4.2 Recommended Dose and Dosage Adjustment

#### Booster Dose

A booster dose of 50 mcg may be administered intramuscularly at least 4 months after completion of a primary series and/or a previous booster dose in individuals 18 years of age or older.

### 4.3 Reconstitution

SPIKEVAX Bivalent Original/Omicron BA.4/5 must not be reconstituted, mixed with other medicinal products, or diluted. No dilution is required prior to administration.

### 4.4 Administration

**Use aseptic technique for preparation and administration.**

#### Preparation

SPIKEVAX Bivalent Original/Omicron BA.4/5 multidose vials are supplied as a frozen dispersion that does not contain preservative. Each vial must be thawed prior to administration.

Vaccination	Presentation	Volume in vial	Number of 0.5 mL doses
SPIKEVAX Bivalent Original/Omicron BA.4/5 Booster Dose	0.10 mg /mL	2.5 mL	5

Thaw each vial before use.

<b>Presentation</b>	<b>Vial Cap Colour</b>	<b>Thaw time under refrigeration between 2° to 8°C (36° to 46°F)</b>	<b>Thaw time at room temperature between 15° to 25°C (59° to 77°F)</b>
0.10 mg/mL	Royal blue	<ul style="list-style-type: none"> <li>• 2 hours</li> </ul> <i>After thawing, let vial stand at room temperature for 15 minutes before administering.</i>	<ul style="list-style-type: none"> <li>• 45 minutes</li> </ul>

Do not re-freeze vials after thawing.

Swirl the vial gently after thawing and between each withdrawal. Do not shake.

### **Administration**

SPIKEVAX Bivalent Original/Omicron BA.4/5 is a white to off-white dispersion. It may contain white or translucent product-related particulates. Visually inspect SPIKEVAX Bivalent Original/Omicron BA.4/5 vials for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

Administer SPIKEVAX Bivalent Original/Omicron BA.4/5 intramuscularly (IM) only. The preferred site is the deltoid muscle of the upper arm. A needle length of  $\geq 1$  inch should be used as needles  $< 1$  inch may be of insufficient length to penetrate muscle tissue in some adults.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. Withdraw each dose of vaccine from the vial using a new sterile needle and syringe (preferentially a low dead-volume syringe and/or needle) for each injection. Pierce the stopper preferably at a different site each time.

**After Vial Puncture:** The dose in the syringe should be used as soon as feasible and no later than 24 hours after the vial was first entered (needle-punctured).

SPIKEVAX Bivalent Original/Omicron BA.4/5 is preservative free. Once the vial has been entered, it should be discarded after 24 hours. Do not refreeze. Thawed vials and filled syringes can be handled in room light conditions. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

## **5 OVERDOSAGE**

In the case of a suspected vaccine overdose, monitoring of vital functions and symptomatic treatment are recommended. Contact your regional poison control centre.

## **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Dispersion, (0.10 mg /mL)  Elasomeran (mRNA) encoding the pre-fusion stabilized Spike glycoprotein of 2019 novel Coronavirus (SARS-CoV-2), and davesomeran (mRNA) encoding the pre-fusion stabilized conformation variant (K981P and V982P) of the SARS-CoV-2 Spike glycoprotein (Omicronvariant B.1.1.529 [BA.4/5])  Multidose vial (2.5 mL)	<ul style="list-style-type: none"> <li>• Acetic acid</li> <li>• Cholesterol</li> <li>• DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)</li> <li>• Lipid SM-102</li> <li>• PEG2000-DMG (1,2-dimyristoyl-rac-glycerol, methoxy-polyethyleneglycol)</li> <li>• Sodium acetate trihydrate</li> <li>• Sucrose</li> <li>• Trometamol</li> <li>• Trometamol hydrochloride</li> <li>• Water for injection</li> </ul>

SPIKEVAX Bivalent Original/Omicron BA.4/5 is provided as a white to off-white, sterile, preservative-free, frozen dispersion for intramuscular injection. SPIKEVAX Bivalent contains lipid nanoparticle (LNP), comprised of two messenger ribonucleic acids (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus and the pre-fusion stabilized S glycoprotein of the omicron variant (K981P and V982P), and four lipids, formulated with the non-medicinal ingredients listed in [Table 1](#). SPIKEVAX Bivalent Original/Omicron BA.4/5 does not contain any preservatives, antibiotics, adjuvants, or human- or animal-derived materials.

SPIKEVAX Bivalent Original / Omicron BA.4/5 is supplied in a multi-dose 10R type I glass vial with a 20 mm Fluro Tec-coated chlorobutyl elastomer stopper, 20 mm flip-off aluminum seal. The vial stopper does not contain natural rubber latex. Vials are packaged in a secondary carton containing a total of ten (10) SPIKEVAX Bivalent Original / Omicron BA.4/5 vials per carton. The 0.10 mg/mL multi-dose vial is supplied with a royal blue flip-off plastic cap and has a vial label with a grey border.

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

## 7 WARNINGS AND PRECAUTIONS

As with any vaccine, vaccination with SPIKEVAX Bivalent Original / Omicron BA.4/5 may not protect all recipients.

### Hypersensitivity and Anaphylaxis

Anaphylaxis has been reported in individuals who have received SPIKEVAX (elasomeran). As with all vaccines, appropriate medical treatment, training for immunizers and supervision after immunization should always be readily available in case of a rare anaphylactic event following the administration of this vaccine.

Vaccine recipients should be kept under observation for at least 15 minutes after immunization; 30 minutes is a preferred interval when there is a specific concern about a possible vaccine reaction.

Subsequent doses of the vaccine should not be given to those who have experienced anaphylaxis to an earlier dose of SPIKEVAX.

## **Cardiovascular**

### Myocarditis and Pericarditis

Very rare cases of myocarditis and/or pericarditis following vaccination with SPIKEVAX have been reported during post-authorization use. These cases occurred more commonly after the second dose and in adolescents and young adults. Typically, the onset of symptoms has been within a few days following receipt of SPIKEVAX. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking. The decision to administer SPIKEVAX to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances.

Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis if individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early diagnosis and treatment. Cardiology consultation for management and follow up should be considered.

### **Acute Illness**

Consideration should be given to postponing immunization in persons with severe febrile illness or severe acute infection. Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.

### **Hematologic-Bleeding**

As with other intramuscular injections, SPIKEVAX Bivalent Original / Omicron BA.4/5 should be given with caution in individuals with bleeding disorders, such as haemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of haematoma following the injection, and when the potential benefit clearly outweighs the risk of administration.

### **Immune**

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

### **Syncope**

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.



## 7.1 Special Populations

### 7.1.1 Pregnant Women

The safety and efficacy of SPIKEVAX Bivalent Original/Omicron BA.4/5 in pregnant women have not yet been established.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPIKEVAX Bivalent Original/Omicron BA.4/5 during pregnancy. Women who are vaccinated with SPIKEVAX Bivalent Original/Omicron BA.4/5 during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

### 7.1.2 Breast-feeding

It is unknown if SPIKEVAX Bivalent Original/Omicron BA.4/5 is excreted in human milk. A risk to the newborns/infants cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19.

### 7.1.3 Pediatrics

The safety and efficacy of SPIKEVAX Bivalent Original/Omicron BA.4/5 in children under 18 years of age have not yet been established.

### 7.1.4 Geriatrics

Clinical studies of SPIKEVAX Bivalent (Original/Omicron BA.1) that included participants 65 years of age and older and their data contribute to the overall assessment of safety and effectiveness of SPIKEVAX Bivalent (Original / Omicron BA.4/5 (elasomeran / davesomeran) mRNA COVID-19 vaccine (see [ADVERSE REACTIONS](#) and [CLINICAL TRIALS](#) sections).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The safety of a booster dose of SPIKEVAX Bivalent Original/Omicron BA.4/5 (elasomeran/davesomeran) mRNA vaccine for individuals 18 years of age and older is inferred from studies of a booster dose of SPIKEVAX Bivalent (Original/Omicron BA.1).

The safety profile of SPIKEVAX Bivalent (Original/Omicron BA.1) in participants  $\geq 18$  years of age presented below is based on data generated from an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the SPIKEVAX Bivalent (Original/Omicron BA.1) 50 mcg booster dose (mRNA-1273.214, as 25 mcg elasomeran and 25 mcg imelasomeran), and 377 participants received the SPIKEVAX original 50 mcg booster dose (mRNA-1273).

Overall, the frequency of solicited adverse reactions after the SPIKEVAX Bivalent 50 mcg booster dose

was similar to that observed following the SPIKEVAX (elasomeran) original 50 mcg booster dose. The most frequently reported adverse reactions after the SPIKEVAX Bivalent 50 mcg booster dose were pain (77.3%), fatigue (54.9%), headache (43.9%), myalgia (39.6%), arthralgia (31.1%) and axillary swelling or tenderness (17.4%). The median duration of local and systemic adverse reactions was 2 days. The most common adverse reactions after the SPIKEVAX original 50 µg booster dose was fatigue (51.4%), headache (41.1%), myalgia (38.6%), and arthralgia (31.7%). The median duration of local and systemic adverse reactions was 2 days.

Overall, after both the SPIKEVAX Bivalent 50 mcg booster dose and the SPIKEVAX original 50 mcg booster dose there was a higher reported rate of solicited adverse reactions in younger age groups. The incidence of pain, erythema, swelling/induration, lymphadenopathy (axillary swelling/tenderness), fatigue, headache, myalgia, arthralgia, and nausea/vomiting was higher in adults 18 to 64 years of age than in those 65 years of age and above (see [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#) respectively).

## 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse vaccine reactions in real-world use.

### SPIKEVAX Bivalent (Original/Omicron BA.1) Booster Dose

#### Solicited Adverse Reactions

The safety, reactogenicity, and immunogenicity of a booster dose of SPIKEVAX Bivalent (Original/Omicron BA.1) are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the SPIKEVAX Bivalent 50 mcg booster dose (mRNA-1273.214, as 25 mcg elasomeran and 25 mcg imelasomeran), and 377 participants received the SPIKEVAX original 50 mcg booster dose (mRNA-1273). Participants were followed for a median duration of 43 days and 57 days for the SPIKEVAX Bivalent 50 mcg booster dose and SPIKEVAX 50 mcg booster dose, respectively.

Solicited adverse reaction data were collected from Day 1 to Day 7 and reported by participants in an electronic diary (e-Diary) after each dose and on electronic case report forms. The reactogenicity observed for both local and systemic adverse reactions was similar for both groups with 380 (87%) of subjects in the mRNA-1273.214 group and 301 (85%) of subjects in the mRNA-1273 group experiencing any solicited adverse reactions (AR)s. The frequency of grade 3 adverse reactions was 8.0% in both groups. There were no grade 4 solicited ARs in either group. Reported solicited local and systemic adverse reactions are presented in [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#) respectively.

**Table 2 – Summary of Participants with Solicited Local Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.214, mRNA-1273 Participants 18 to 64 (Solicited Safety Set\*)**

Solicited local AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=263 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N=211 n (%)
<b>Pain</b>		
Any grade	231 (87.8)	175 (82.9)
Grade 3 <sup>a</sup>	2 (0.8)	4 (1.9)
<b>Erythema</b>		
Any grade	20 (7.6)	10 (4.7)
Grade 3 <sup>b</sup>	7 (2.7)	1 (0.5)
<b>Swelling/Induration</b>		
Any grade	22 (8.4)	15 (7.1)
Grade 3 <sup>b</sup>	4 (1.5)	2 (0.9)
<b>Axillary swelling/ Tenderness</b>		
Any grade	56 (21.3)	39 (18.5)
Grade 3 <sup>c</sup>	0 (0)	4 (1.9)

\*Solicited Safety Set: All participants who received a dose and contributed any solicited Adverse Reaction data.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Pain - Grade 3: any use of Rx pain reliever/prevents daily activity

<sup>b</sup> Erythema and Swelling/Induration - Grade 3: >100mm/>10cm

<sup>c</sup> Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity

**Table 3 – Summary of Participants with Solicited Local Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.214, mRNA-1273 Participants 65 Years of Age and Older (Solicited Safety Set\*)**

Solicited local AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=174 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N=140 n (%)
<b>Pain</b>		
Any grade	107 (61.5)	94 (67.1)
Grade 3 or 4 <sup>a</sup>	2 (1.1)	0 (0)
<b>Erythema</b>		
Any grade	10 (5.7)	3 (2.1)
Grade 3 <sup>b</sup>	2 (1.1)	1 (0.7)
<b>Swelling/Induration</b>		

Solicited local AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=174 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N=140 n (%)
Any grade	8 (4.6)	8 (5.7)
Grade 3 <sup>b</sup>	1 (0.6)	3 (2.1)
<b>Axillary swelling/ Tenderness</b>		
Any grade	20 (11.5)	15 (10.7)
Grade 3 <sup>c</sup>	1 (0.6)	0 (0)

\*Solicited Safety Set: All participants who received a dose and contributed any solicited Adverse Reaction data.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Pain - Grade 3: any use of Rx pain reliever/prevents daily activity

<sup>b</sup> Erythema and Swelling/Induration - Grade 3: >100mm/>10cm

<sup>c</sup> Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity

**Table 4 – Summary of Participants with Solicited Systemic Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.214, mRNA-1273 Participants 18 to 64 (Solicited Safety Set\*)**

Solicited Systemic AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=263 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N=263 n (%)
<b>Fatigue</b>		
Any grade	154 (58.6)	115 (54.5)
Grade 3 <sup>a</sup>	10 (3.8)	7 (3.3)
<b>Headache</b>		
Any grade	129 (49.0)	100 (47.4)
Grade 3 <sup>b</sup>	4 (1.5)	1 (0.5)
<b>Myalgia</b>		
Any grade	113 (43.0)	90 (42.7)
Grade 3 <sup>a</sup>	9 (3.4)	8 (3.8)
<b>Arthralgia</b>		
Any grade	87 (33.1)	69 (32.7)
Grade 3 <sup>a</sup>	3 (1.1)	2 (0.9)
<b>Chills</b>		
Any grade	64 (24.3)	54 (25.6)
Grade 3 <sup>c</sup>	1 (0.4)	0 (0.0)
<b>Nausea/vomiting</b>		
Any grade	35 (13.3)	27 (12.8)
Grade 3 <sup>d</sup>	0 (0.0)	0 (0.0)
<b>Fever</b>		
Any grade	10 (3.8)	10 (4.7)

Solicited Systemic AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=263 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N=263 n (%)
Grade 3 <sup>e</sup>	1 (0.4)	0 (0)
Use of antipyretic or pain medication	104 (39.5)	67 (31.8)

\*Solicited Safety Set: All participants who received a dose and contributed any solicited Adverse Reaction data.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>b</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>c</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>d</sup> Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

<sup>e</sup> Grade 3 fever: Defined as  $\geq 39.0 - \leq 40.0^{\circ}\text{C}$  /  $\geq 102.1 - \leq 104.0^{\circ}\text{F}$ .

**Table 5 – Summary of Participants with Solicited Systemic Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.214, mRNA-1273 Participants 65 Years of Age and Older (Solicited Safety Set)**

Solicited Systemic AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=174 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N= 140 n (%)
<b>Fatigue</b>		
Any grade	86 (49.4)	65 (46.8)
Grade 3 <sup>a</sup>	5 (2.9)	4 (2.9)
<b>Headache</b>		
Any grade	63 (36.2)	44 (31.7)
Grade 3 <sup>b</sup>	1 (0.6)	1 (0.7)
<b>Myalgia</b>		
Any grade	60 (34.5)	45 (32.4)
Grade 3 <sup>a</sup>	1 (0.6)	5 (3.6)
<b>Arthralgia</b>		
Any grade	49 (28.2)	42 (30.2)
Grade 3 <sup>a</sup>	1 (0.6)	1 (0.7)
<b>Chills</b>		
Any grade	40 (23.0)	20 (14.4)
Grade 3 <sup>c</sup>	0 (0.0)	1 (0.7)
<b>Nausea/vomiting</b>		
Any grade	10 (5.7)	8 (5.8)
Grade 3 <sup>d</sup>	1 (0.6)	0 (0.0)
<b>Fever</b>		
Any grade	9 (5.2)	2 (1.4)
Grade 3 <sup>e</sup>	0 (0.0)	0 (0.0)
Use of antipyretic or pain medication	46	40

Solicited Systemic AR	2nd Booster Dose	
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group (mRNA-1273.214) 50 mcg N=174 n (%)	SPIKEVAX Group (mRNA-1273) 50 mcg N= 140 n (%)
	(26.4)	(28.6)

\*Solicited Safety Set: All participants who received a dose and contributed any solicited Adverse Reaction data.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>b</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>c</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>d</sup> Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

<sup>e</sup> Grade 3 fever: Defined as  $\geq 39.0 - \leq 40.0^{\circ}\text{C}$  /  $\geq 102.1 - \leq 104.0^{\circ}\text{F}$ .

**Table 6 – Summary of Participants with Solicited Adverse Reactions Within 7 Days After the Injection by Grade and Pre-booster SARS-CoV-2 Status – 2nd Booster Dose: mRNA-1273.214; mRNA-1273 (Solicited Safety Set)**

Solicited Adverse Reaction Category Grade*	2nd Booster Dose			
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group mRNA-1273.214 50 µg		SPIKEVAX Group mRNA-1273 50 µg	
	Pre-booster SARS-CoV-2 Status		Pre-booster SARS-CoV-2 Status	
	Negative (N=340) n (%)	Positive (N=96) n (%)	Negative (N=250) n (%)	Positive (N=92) n (%)
<b>Solicited adverse reactions - N1</b>	340	96	250	92
Any grade solicited adverse reactions	299 (87.9)	80 (83.3)	217 (86.8)	77 (83.7)
95% CI	84.0, 91.2	74.4, 90.2	82.0, 90.7	74.5, 90.6
Grade 3	29 (8.5)	6 (6.3)	24 (9.6)	4 (4.3)
<b>Solicited local adverse reactions - N1</b>	340	96	250	92
Any grade solicited local adverse reactions	272 (80.0)	74 (77.1)	200 (80.0)	73 (79.3)
95% CI	75.3, 84.1	67.4, 85.0	74.5, 84.8	69.6, 87.1
Grade 3	14 (4.1)	1 (1.0)	9 (3.6)	3 (3.3)
<b>Pain - N1</b>	340	96	250	92
Any grade	265 (77.9)	72 (75.0)	193 (77.2)	71 (77.2)
Grade 3	4 (1.2)	0	3 (1.2)	1 (1.1)
<b>Erythema (redness)<sup>a</sup> - N1</b>	340	96	250	92
Any grade	27 (7.9)	3 (3.1)	10 (4.0)	3 (3.3)
Grade 3	8 (2.4)	1 (1.0)	1 (0.4)	1 (1.1)
<b>Swelling (hardness)- N1</b>	340	96	250	92
Any grade	26 (7.6)	4 (4.2)	19 (7.6)	4 (4.3)
Grade 3	5 (1.5)	0	5 (2.0)	0
<b>Axillary swelling or tenderness - N1</b>	340	96	250	92
Any grade	58 (17.1)	18 (18.8)	35 (14.0)	18 (19.6)
Grade 3	1 (0.3)	0	3 (1.2)	1 (1.1)

Solicited Adverse Reaction Category Grade*	2nd Booster Dose			
	SPIKEVAX Bivalent (Original/Omicron BA.1) Group mRNA-1273.214 50 µg		SPIKEVAX Group mRNA-1273 50 µg	
	Pre-booster SARS-CoV-2 Status		Pre-booster SARS-CoV-2 Status	
	Negative (N=340) n (%)	Positive (N=96) n (%)	Negative (N=250) n (%)	Positive (N=92) n (%)
<b>Solicited systemic adverse reactions - N1</b>	340	96	250	92
Any grade solicited systemic adverse reactions	244 (71.8)	63 (65.6)	171 (68.4)	57 (62.0)
95% CI	66.7, 76.5	55.2, 75.0	62.2, 74.1	51.2, 71.9
Grade 3	19 (5.6)	5 (5.2)	15 (6.0)	1 (1.1)
<b>Fever<sup>b</sup> - N1</b>	339	96	250	92
Any grade	16 (4.7)	3 (3.1)	10 (4.0)	2 (2.2)
Grade 3	1 (0.3)	0	0	0
<b>Headache - N1</b>	340	96	250	92
Any grade	154 (45.3)	38 (39.6)	106 (42.4)	37 (40.2)
Grade 3	5 (1.5)	0	2 (0.8)	0
<b>Fatigue - N1</b>	340	96	250	92
Any grade	194 (57.1)	46 (47.9)	134 (53.6)	42 (45.7)
Grade 3	11 (3.2)	4 (4.2)	10 (4.0)	1 (1.1)
<b>Myalgia - N1</b>	340	96	250	92
Any grade	137 (40.3)	36 (37.5)	93 (37.2)	40 (43.5)
Grade 3	10 (2.9)	0	13 (5.2)	0
<b>Arthralgia - N1</b>	340	96	250	92
Any grade	110 (32.4)	26 (27.1)	80 (32.0)	29 (31.5)
Grade 3	4 (1.2)	0	3 (1.2)	0
<b>Nausea/vomiting - N1</b>	340	96	250	92
Any grade	36 (10.6)	9 (9.4)	25 (10.0)	10 (10.9)
Grade 3	0	1 (1.0)	0	0
<b>Chills - N1</b>	340	96	250	92
Any grade	86 (25.3)	18 (18.8)	58 (23.2)	15 (16.3)
Grade 3	1 (0.3)	0	1 (0.4)	0

Abbreviations: CI = confidence interval; SARS-CoV-2 = severe acute respiratory infection coronavirus-2.

\*No Grade 4 Solicited Adverse Reactions were observed.

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method.

<sup>a</sup> Toxicity grade for erythema (redness) is defined as: Grade 1 = 25 – 50 mm; Grade 2 = 51 – 100 mm; Grade 3 = greater than 100 mm.

<sup>b</sup> Toxicity grade for fever is defined as: Grade 1 = 38 – 38.4°C; Grade 2 = 38.5 – 38.9°C; Grade 3 = 39 – 40°C.

Overall, there were no safety concerns or differences identified in solicited adverse reactions based on pre-booster SARS-CoV-2 status. The frequency of solicited local ARs was similar among participants with a positive pre-booster SARS-CoV-2 status (74/96 [77.1%]) and participants with a negative pre-booster SARS-CoV-2 status (272/340 [80.0%])

## Unsolicited Adverse Events

There were no important clinical differences between unsolicited events that occurred within 28 days for participants who received the SPIKEVAX Bivalent (Original/Omicron BA.1, mRNA-1273.214) 50 mcg booster dose when compared to participants who received the SPIKEVAX original (mRNA-1273) 50 mcg booster dose. There were 81/437 participants (18.5%) in the SPIKEVAX Bivalent group that reported unsolicited events, regardless of relationship to the vaccine, compared to 78/377 participants (20.7%) in the SPIKEVAX original group.

In both groups the majority of unsolicited events were consistent with reactogenicity events. The most commonly reported unsolicited events within 28 days after the SPIKEVAX Bivalent 50 mcg booster dose, regardless of causality were fatigue (11/437 [2.5%]); headache and arthralgia (7/437 [1.6%] each). The most commonly reported unsolicited events within 28 days after the SPIKEVAX original 50 mcg booster dose, regardless of causality were fatigue (12/377 [3.2%]), upper respiratory tract infection (9/377 [2.4%]), and coronavirus infection (i.e., coronaviruses other than SARS-CoV-2) (8/377 [2.1%]). There were no deaths reported in any of the two groups in the study.

Serious adverse events (SAE) were reported in 0.5% (2/437) of subjects who received the SPIKEVAX Bivalent 50 mcg booster dose; and 0.3% (1/377) of subjects who received the SPIKEVAX original 50 mcg booster dose, within 28 days after vaccination. Up to the data cut-off date (27 Apr 2022), one additional SAE occurred in the SPIKEVAX Bivalent 50 mcg booster dose group.

## **SPIKEVAX Primary Series (Original)**

### **Participants 18 Years of Age and Older**

#### Solicited Adverse Reactions

The safety profile presented below is based on data generated in an ongoing Phase 3, placebo-controlled clinical study of SPIKEVAX (elasomeran) in subjects  $\geq 18$  years of age in which pre-specified cohorts of subjects who were either  $\geq 65$  years of age or 18 to 64 years of age with comorbid medical conditions were included. At the time of the analysis, the safety analysis set included a total of 30,351 subjects who received at least one dose of SPIKEVAX (n=15,181) or placebo (n=15,170). Subjects were followed for a median of 92 days from first injection and 63 days from second injection.

Solicited adverse reaction data were collected from Day 1 to Day 7 and reported by participants in an electronic diary (e-Diary) after each dose and on electronic case report forms. Reported solicited local and systemic adverse reactions are presented in [Table 7](#), [Table 8](#), [Table 9](#) and [Table 10](#) respectively.



**Table 7 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade-Participants 18 to 64 Years of Age (Safety Analysis Set\*)**

Solicited local AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=11,406 n (%)	Placebo Group N=11,407 n (%)	SPIKEVAX Group 100 mcg N=10,985 n (%)	Placebo Group N=10,918 n (%)
<b>Pain</b>				
Any grade	9,908 (86.9)	2,177 (19.1)	9,873 (89.9)	2,040 (18.7)
Grade 3 or 4 <sup>a</sup>	366 (3.2)	23 (0.2)	506 (4.6)	22 (0.2)
<b>Erythema</b>				
Any grade	344 (3.0)	47 (0.4)	982 (8.9)	43 (0.4)
Grade 3 or 4 <sup>b</sup>	34 (0.3)	11 (<0.1)	210 (1.9)	12 (0.1)
<b>Swelling/Induration</b>				
Any grade	767 (6.7)	34 (0.3)	1,389 (12.6)	36 (0.3)
Grade 3 or 4 <sup>b</sup>	62 (0.5)	3 (<0.1)	182 (1.7)	4 (<0.1)
<b>Axillary swelling/ Tenderness</b>				
Any grade	1,322 (11.6)	567 (5.0)	1,775 (16.2)	470 (4.3)
Grade 3 or 4 <sup>c</sup>	37 (0.3)	13 (0.1)	46 (0.4)	11 (0.1)

\*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Pain - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

<sup>b</sup> Erythema and Swelling/Induration - Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

<sup>c</sup> Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

**Table 8 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 65 Years of Age and Older (Safety Analysis Set\*)**

Solicited local AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=3,762 n (%)	Placebo Group N=3,748 n (%)	SPIKEVAX Group 100 mcg N=3,692 n (%)	Placebo Group N=3,648 n (%)
<b>Pain</b>				
Any grade	2,782 (74.0)	481 (12.8)	3,070 (83.2)	437 (12.0)
Grade 3 or 4 <sup>a</sup>	50 (1.3)	32 (0.9)	98 (2.7)	18 (0.5)
<b>Erythema</b>				
Any grade	86 (2.3)	20 (0.5)	275 (7.5)	13 (0.4)
Grade 3 or 4 <sup>b</sup>	8 (0.2)	2 (<0.1)	77 (2.1)	3 (<0.1)
<b>Swelling/Induration</b>				
Any grade	165	18	400	13

Solicited local AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=3,762 n (%)	Placebo Group N=3,748 n (%)	SPIKEVAX Group 100 mcg N=3,692 n (%)	Placebo Group N=3,648 n (%)
	(4.4)	(0.5)	(10.8)	(0.4)
Grade 3 or 4 <sup>b</sup>	20 (0.5)	3 (<0.1)	72 (2.0)	7 (0.2)
<b>Axillary swelling/ Tenderness</b>				
Any grade	231 (6.1)	155 (4.1)	315 (8.5)	97 (2.7)
Grade 3 or 4 <sup>c</sup>	12 (0.3)	14 (0.4)	21 (0.6)	8 (0.2)

\*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Pain - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

<sup>b</sup> Erythema and Swelling/Induration - Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

<sup>c</sup> Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

**Table 9 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 18 to 64 Years of Age (Safety Analysis Set\*)**

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=11,406 n (%)	Placebo Group N=11,407 n (%)	SPIKEVAX Group 100 mcg N=10,985 n (%)	Placebo Group N=10,918 n (%)
<b>Fatigue</b>				
Any grade	4,384 (38.4)	3,282 (28.8)	7,430 (67.6)	2,687 (24.6)
Grade 3 <sup>a</sup>	120 (1.1)	83 (0.7)	1,174 (10.7)	86 (0.8)
Grade 4 <sup>b</sup>	1 (<0.1)	0 (0)	0 (0)	0 (0)
<b>Headache</b>				
Any grade	4,030 (35.3)	3,304 (29.0)	6,898 (62.8)	2,760 (25.3)
Grade 3 <sup>c</sup>	219 (1.9)	162 (1.4)	553 (5.0)	129 (1.2)
<b>Myalgia</b>				
Any grade	2,699 (23.7)	1,628 (14.3)	6,769 (61.6)	1,411 (12.9)
Grade 3 <sup>a</sup>	73 (0.6)	38 (0.3)	1,113 (10.1)	42 (0.4)
<b>Arthralgia</b>				
Any grade	1,893 (16.6)	1,327 (11.6)	4,993 (45.5)	1,172 (10.7)

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=11,406 n (%)	Placebo Group N=11,407 n (%)	SPIKEVAX Group 100 mcg N=10,985 n (%)	Placebo Group N=10,918 n (%)
Grade 3 <sup>a</sup>	47 (0.4)	29 (0.3)	647 (5.9)	37 (0.3)
Grade 4 <sup>b</sup>	1 (<0.1)	0 (0)	0 (0)	0 (0)
<b>Chills</b>				
Any grade	1,051 (9.2)	730 (6.4)	5,341 (48.6)	658 (6.0)
Grade 3 <sup>d</sup>	17 (0.1)	8 (<0.1)	164 (1.5)	15 (0.1)
<b>Nausea/vomiting</b>				
Any grade	1,068 (9.4)	908 (8.0)	2,348 (21.4)	801 (7.3)
Grade 3 <sup>e</sup>	6 (<0.1)	8 (<0.1)	10 (<0.1)	8 (<0.1)
<b>Fever</b>				
Any grade	105 (0.9)	37 (0.3)	1,908 (17.4)	39 (0.4)
Grade 3 <sup>f</sup>	10 (<0.1)	1 (<0.1)	184 (1.7)	2 (<0.1)
Grade 4 <sup>g</sup>	4 (<0.1)	4 (<0.1)	12 (0.1)	2 (<0.1)
<b>Use of antipyretic or pain medication</b>	2,656 (23.3)	1,523 (13.4)	6,292 (57.3)	1,248 (11.4)

\*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>b</sup> Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.

<sup>c</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>d</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>e</sup> Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

<sup>f</sup> Grade 3 fever: Defined as ≥39.0 – ≤40.0°C / ≥102.1 – ≤104.0°F.

<sup>g</sup> Grade 4 fever: Defined as >40.0°C / >104.0°F.

**Table 10 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 65 Years of Age and Older (Safety Analysis Set\*)**

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=3,762 n (%)	Placebo Group N=3,748 n (%)	SPIKEVAX Group 100 mcg N=3,692 n (%)	Placebo Group N=3,648 n (%)
<b>Fatigue</b>				
Any grade	1,251 (33.3)	851 (22.7)	2,152 (58.3)	716 (19.6)
Grade 3 <sup>a</sup>	30 (0.8)	22 (0.6)	254 (6.9)	20 (0.5)

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group 100 mcg N=3,762 n (%)	Placebo Group N=3,748 n (%)	SPIKEVAX Group 100 mcg N=3,692 n (%)	Placebo Group N=3,648 n (%)
<b>Headache</b>				
Any grade	921 (24.5)	723 (19.3)	1,704 (46.2)	650 (17.8)
Grade 3 <sup>b</sup>	52 (1.4)	34 (0.9)	106 (2.9)	33 (0.9)
<b>Myalgia</b>				
Any grade	742 (19.7)	443 (11.8)	1,739 (47.1)	398 (10.9)
Grade 3 <sup>a</sup>	17 (0.5)	9 (0.2)	205 (5.6)	10 (0.3)
<b>Arthralgia</b>				
Any grade	618 (16.4)	456 (12.2)	1,291 (35.0)	397 (10.9)
Grade 3 <sup>a</sup>	13 (0.3)	8 (0.2)	123 (3.3)	7 (0.2)
<b>Chills</b>				
Any grade	202 (5.4)	148 (4.0)	1,141 (30.9)	151 (4.1)
Grade 3 <sup>c</sup>	7 (0.2)	6 (0.2)	27 (0.7)	2 ( $<0.1$ )
<b>Nausea/vomiting</b>				
Any grade	194 (5.2)	166 (4.4)	437 (11.8)	133 (3.6)
Grade 3 <sup>d</sup>	4 (0.1)	4 (0.1)	10 (0.3)	3 ( $<0.1$ )
Grade 4 <sup>e</sup>	0 (0)	0 (0)	1 ( $<0.1$ )	0 (0)
<b>Fever</b>				
Any grade	10 (0.3)	7 (0.2)	370 (10.0)	4 (0.1)
Grade 3 <sup>f</sup>	1 ( $<0.1$ )	1 ( $<0.1$ )	18 (0.5)	0 (0)
Grade 4 <sup>g</sup>	0 (0)	2 ( $<0.1$ )	1 ( $<0.1$ )	1 ( $<0.1$ )
<b>Use of antipyretic or pain medication</b>	673 (17.9)	477 (12.7)	1546 (41.9)	329 (9.0)

\*Safety Analyses Set: all randomized participants who received  $\geq 1$  vaccine or control dose.

n= # of participants with specified reaction, percentages are based on n/N

N= number of exposed subjects who submitted any data for the event.

<sup>a</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>b</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>c</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>d</sup> Grade 3 Nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

<sup>e</sup> Grade 4 Nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.

<sup>f</sup> Grade 3 fever: Defined as  $\geq 39.0 - \leq 40.0^{\circ}\text{C}$  /  $\geq 102.1 - \leq 104.0^{\circ}\text{F}$ .

<sup>g</sup> Grade 4 fever: Defined as  $>40.0^{\circ}\text{C}$  /  $>104.0^{\circ}\text{F}$ .

## Unsolicited Adverse Events

### Serious Adverse Events

Serious adverse events were reported in 0.6% of participants who received SPIKEVAX and 0.6% of participants who received a placebo, from the first dose until 28 days following the last vaccination. Serious adverse events were reported in 1% of participants who received SPIKEVAX and 1% of participants who received a placebo, from the first dose until the last observation (cut-off date November 25, 2020). In these analyses, 87.9% of study participants had at least 28 days of follow-up after dose 2, and the median follow-up time for all participants was 9 weeks after dose 2.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

Three serious adverse events were likely related to SPIKEVAX: two cases of facial swelling occurring within 7 days of receiving Dose 2, in female patients aged 46 and 51; one case of nausea and vomiting with headaches and fever occurring within 7 days after Dose 2 and requiring in-hospital treatment in a 61-year-old female, with past medical history of headaches with nausea and vomiting requiring hospitalization. One case of Bell's palsy, which occurred 32 days following receipt of vaccine, was classified as a serious adverse event. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine.

No deaths related to the vaccine were reported in the study.

### Non-Serious Adverse Events

In the COVE Phase 3 study, unsolicited adverse events occurring within 28 days after each vaccination were reported by 23.9% of subjects who received SPIKEVAX, and 21.6% of subjects who received the placebo. These adverse events were predominantly solicited adverse reactions occurring outside of the conventional 7-day monitoring period after the injection (injection site pain, fatigue, headaches, myalgia, etc.).

Unsolicited adverse events that occurred in  $\geq 1\%$  of study participants who received SPIKEVAX and at a rate at least 1.5-fold higher rate than placebo, were lymphadenopathy related events (1.1% of versus 0.6%) and delayed injection site reactions reported  $>7$  days after vaccination (1.2% versus 0.4%). All of the lymphadenopathy events are similar to the axillary swelling/tenderness in the injected arm reported as solicited adverse reactions. Delayed injection site reactions included one or more of the following: erythema, pain and swelling, and are likely related to vaccination. Hypersensitivity events were reported in 1.5% of the SPIKEVAX group compared to 1.1% of the placebo group, but this imbalance was mostly due to injection site rash and injection site erythema/swelling occurring more frequently in the SPIKEVAX group.

There were three reports of Bell's palsy in the SPIKEVAX group (one of which was a serious adverse event), which occurred 22, 29, and 32 days after the second dose of vaccine, and one in the placebo group which occurred 17 days after the first dose of saline. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious

adverse events (including neurologic, musculoskeletal or inflammatory events) that would suggest a causal relationship to SPIKEVAX.

### **SPIKEVAX Booster Dose (Original)**

Study P201 Part B is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of SPIKEVAX (elasomeran) in participants 18 years of age and older (NCT04405076). In an open-label phase of this study, 171 participants received a single booster dose (50 mcg) at least 6 months after receiving the second dose (100 mcg) of the SPIKEVAX primary series. At the time of analysis, participants were followed-up for safety for one month after receiving the booster.

The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series. The most common solicited local adverse reactions (ARs) were pain at injection site (84%) and axillary swelling or tenderness (20%). The most common solicited systemic ARs were fatigue (59%), headache (55%), myalgia (49%), arthralgia (41%), and chills (35%). The local and systemic ARs were transient, and most resolved by Day 4. The frequency and severity of solicited ARs was numerically comparable between age cohorts (18 to <55; ≥55 years of age). The most common unsolicited AEs were headache (2.3%) and fatigue (2.3%); these were also solicited AEs that extended beyond Day 7. All unsolicited AEs were mild or moderate in severity. Of the 171 participants who received a booster dose of SPIKEVAX, there were no serious adverse events reported from the booster dose through 29 days after the booster dose.

### **8.3 Less Common Clinical Trial Adverse Reactions**

The following events were reported in the ongoing Phase 3, placebo-controlled clinical study of SPIKEVAX (elasomeran) in participants ≥ 18 years of age:

Nervous System Disorders: Acute peripheral facial paralysis†

Skin and Subcutaneous Tissue Disorders: Rash.

General Disorders and Administration Site Conditions: Injection site pruritus, injection site rash, injection site swelling, injection site erythema, injection site urticaria, facial swelling.<sup>§</sup>

† Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the SPIKEVAX group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.

§ There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported on Day 1 and Day 3, respectively, relative to day of vaccination.

### **8.4 Post-Market Adverse Reactions**

The following adverse reactions have been identified during post-authorization use of SPIKEVAX (elasomeran).

Immune System Disorders: Anaphylaxis, hypersensitivity (including urticaria).

Cardiac Disorders: Myocarditis and/or pericarditis (see WARNINGS AND PRECAUTIONS).

Skin and Subcutaneous Tissue Disorders: Erythema multiforme.

Nervous System Disorders: facial paralysis / Bell's palsy, hypoaesthesia / paraesthesia, dizziness.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

## 9 DRUG INTERACTIONS

No interaction studies have been performed.

Do not mix SPIKEVAX Bivalent Original/Omicron BA.4/5 with other vaccines/products in the same syringe.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

SPIKEVAX Bivalent Original/Omicron BA.4/5 encodes for the pre-fusion stabilized Spike (S) protein of SARS-CoV-2 original variant and Omicron variant (B.1.1.529 [BA.4/5]). After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequences into cells for expression of the SARS-CoV-2 S antigen. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The proteins undergo post-translational modification and trafficking resulting in properly folded, fully functional Spike proteins that are inserted into the cellular membrane of the expressing cell(s). The Spike proteins are membrane bound, mimicking the presentation of natural infection. The vaccine induces both neutralizing antibody and cellular immune responses (T-cell and B-cell) to the Spike (S) antigen, which may contribute to protection against COVID-19 disease.

## 11 STORAGE, STABILITY AND DISPOSAL

### Storage Prior to Use

#### As Displayed on the Vial Labels and Cartons

The SPIKEVAX Bivalent Original/Omicron BA.4/5 multidose vials are stored frozen between -50° to -15°C (-58° to 5°F). Store in the original carton to protect from light.

#### Additional Storage Information Not Displayed on the Vial Labels and Cartons

- Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use.
- Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 24 hours.
- Do not refreeze once thawed.

### Transportation of Thawed Vials in Liquid State at 2° to 8°C (36° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Precautions should be taken (packaging/dunnage) to minimize vibration of vials when transporting at this temperature. Once thawed and transported in liquid state at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

### Thawing Vials Prior To Use

The SPIKEVAX Bivalent Original/Omicron BA.4/5) multidose vial contains a frozen dispersion that does not contain a preservative and must be thawed prior to administration. Remove the required number of vial(s) from storage and thaw each vial before use.

<b>Presentation</b>	<b>Vial Cap Colour</b>	<b>Thaw time under refrigeration between 2° to 8°C (36° to 46°F)</b>	<b>Thaw time at room temperature between 15° to 25°C (59° to 77°F)</b>
0.10 mg/mL	Royal blue	<ul style="list-style-type: none"><li>• 2 hours</li></ul> <i>After thawing, let vial stand at room temperature for 15 minutes before administering.</i>	<ul style="list-style-type: none"><li>• 45 minutes</li></ul>

After thawing, do not refreeze.

### **Storage After Use (Punctured Vials)**

SPIKEVAX Bivalent Original/Omicron BA.4/5 is preservative-free. Once the vial has been entered (needle-punctured), it can be stored at room temperature or refrigerated, but must be discarded after 24 hours. Do not refreeze.

## **12 SPECIAL HANDLING INSTRUCTIONS**

SPIKEVAX Bivalent Original/Omicron BA.4/5 must not be mixed with other medicinal products or diluted. Any unused vaccine or waste material should be disposed of in accordance with local requirements.



## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Elasmomoran / davesomoran (mRNA vaccine)

Chemical name: mRNA-1273 LS (Large Scale) Lipid Nanoparticle (LNP) and mRNA-1273.045 LS LNP

#### Product Characteristics

SPIKEVAX Bivalent Original/Omicron BA.4/5 is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains elasmomoran (mRNA CX-024414) that encodes for the pre-fusion stabilized Spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2) and imelasmomoran (mRNA CX-034476) that encodes for the pre-fusion stabilized Spike glycoprotein of the SARS-CoV-2 omicron variant (K981P and V982P), and four lipids which act as protectants and carriers of the mRNA.

SPIKEVAX Bivalent Original/Omicron BA.4/5 is supplied as a multidose liquid ready-to-use dispersion of 0.10 mg/mL for intramuscular administration. SPIKEVAX Bivalent Original/Omicron BA.4/5 is in a 10R clear Type 1 glass vial with a rubber serum stopper and an aluminum seal with flip-off plastic cap.

### 14 CLINICAL TRIALS

#### 14.1 Trial Design and Study Demographics

The effectiveness of a booster dose of SPIKEVAX Bivalent Original/Omicron BA.4/5 (elasmomoran/davesomoran) mRNA vaccine for individuals 18 years of age and older is inferred from studies of a booster dose of SPIKEVAX Bivalent (Original/Omicron BA.1).

**Table 11 – Summary of SPIKEVAX and SPIKEVAX Bivalent Clinical Trials**

Study #	Study Drug	Study Design	Dosage, route of administration and duration	Study subjects <sup>a</sup> (n)
P301	SPIKEVAX	Randomized, placebo-controlled study in adults 18 years of age and older	100 mg, IM, 2 doses 29 days apart	14,134
P201 Part B	SPIKEVAX	Open-label study arm assessing immunogenicity in participants 18 years of age and older	50 mcg booster dose, IM, at least 6 months following primary series	171
P205 Part G	SPIKEVAX Bivalent (Original/Omicron BA.1)	Open-label Phase 2/3 assessing immunogenicity and safety in participants 18 years of age and older	50 mcg second booster dose, IM	437

<sup>a</sup> Total vaccinated subjects; does not include placebo population

#### 14.1.1 SPIKEVAX Bivalent (Original / Omicron BA.1) Booster (Participants ≥ 18 Years of Age)

The safety, reactogenicity, and immunogenicity of the SPIKEVAX Bivalent (Original / Omicron BA.1) booster dose are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (Study P205). In this study 437 participants received the SPIKEVAX Bivalent 50 mcg booster dose and 377 participants received the SPIKEVAX original 50 mcg booster dose. Overall, of the SPIKEVAX Bivalent group 59.0% were female, 41.0% were male, 89.2% were White, and 10.8% were Hispanic or Latino. The median age was 60 years (range: 20 to 88 years) and 39.8% of participants were ≥ 65 years of age. Demographic and baseline characteristics were similar between the SPIKEVAX Bivalent 50 mcg and SPIKEVAX 50 mcg groups.

In Study P205 SPIKEVAX Bivalent was administered as a second booster dose. The median time between a first booster dose and the second booster dose with SPIKEVAX Bivalent was 136 days (range: 88 to 408 days). At baseline, 22.0% of subjects receiving SPIKEVAX Bivalent as a second booster dose had evidence of prior SARS-CoV-2 infection.

#### 14.1.2 SPIKEVAX - Participants 18 Years of Age and Older

The safety and efficacy of SPIKEVAX (elasomeran) were evaluated in Study P301, a Phase 3 randomized, placebo-controlled, multicentre study in participants 18 years of age and older (COVE Study). A total of 30,351 (15,181 in the SPIKEVAX group and N=15,170 in the placebo group) participants were randomized equally to receive 2 doses of SPIKEVAX or placebo separated by 28 days. Randomization was stratified by age and risk of severe COVID-19 as follows: ≥ 65 years old, < 65 years old and at increased risk for the complications of COVID-19, and < 65 years old and not at increased risk for the complications of COVID-19.

Pregnant or breastfeeding women and individuals with known history of SARS-CoV-2 infection, immunosuppressive or immunodeficient state, asplenia or recurrent severe infections were excluded from the study. The primary efficacy was symptomatic\* COVID-19 infection confirmed by Polymerase Chain Reaction (PCR) and by a clinical adjudication committee. The population for the analysis of the primary efficacy endpoint included participants who did not have evidence of prior infection with SARS-CoV-2 through 14 days after the second dose. Participants are planned to be followed for up to 24 months for assessments of safety and efficacy against COVID-19 disease.

\* Symptomatic COVID-19 case definition: At least two of the following systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

**Table 12 – Demographic Characteristics – Subjects ≥ 18 Years of Age Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy Population (Data Accrued Through November 21, 2020)**

	<b>SPIKEVAX Group</b> (N=14,134) n (%)	<b>Placebo Group</b> (N=14,073) n (%)	<b>Total</b> (N=28,207) n (%)
<b>Sex</b>			
Female	6,768 (47.9)	6,611 (47.0)	13,379 (47.4)
Male	7,366 (52.1)	7,462 (53.0)	14,828 (52.6)
<b>Age (years)</b>			
Mean (SD)	51.6 (15.44)	51.6 (15.54)	51.6 (15.49)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
<b>Age – Subgroups (years)</b>			
18 to <65	10,551 (74.6)	10,521 (74.8)	21,072 (74.7)
65 and older	3,583 (25.4)	3,552 (25.2)	7,135 (25.3)
<b>Race</b>			
American Indian or Alaska Native	108 (0.8)	111 (0.8)	219 (0.8)
Asian	620 (4.4)	689 (4.9)	1,309 (4.6)
Black or African American	1,385 (9.8)	1,349 (9.6)	2,734 (9.7)
Native Hawaiian or Other Pacific Islander	35 (0.2)	31 (0.2)	66 (0.2)
White	11,253 (79.6)	11,174 (79.4)	22,427 (79.5)
Other	299 (2.1)	295 (2.1)	594 (2.1)
<b>Ethnicity</b>			
Hispanic or Latino	2,789 (19.7)	2,780 (19.8)	5,569 (19.7)
Not Hispanic or Latino	11,212 (79.3)	11,165 (79.3)	22,377 (79.3)
<b>Race and Ethnicity</b>			
Non-Hispanic White	9,023 (63.8)	8,916 (63.4)	17,939 (63.6)
Communities of color	5,088 (36.0)	5,132 (36.5)	10,220 (36.2)
<b>Occupational Risk*</b>	11,586 (82.0)	11,590 (82.4)	23,176 (82.2)
<b>Healthcare worker</b>	3,593 (25.4)	3,581 (25.4)	7,174 (25.4)
<b>High Risk Condition**</b>			
One high risk condition present	2,616 (18.5)	2,591 (18.4)	5,207 (18.5)
Two or more high risk conditions present	590 (4.2)	576 (4.1)	1,166 (4.1)
No high risk condition	10,928 (77.3)	10,906 (77.5)	21,834 (77.4)
<b>Age and Health Risk for Severe COVID-19***</b>			
18 to <65 years and not at risk	8,189 (57.9)	8,200 (58.3)	16,389 (58.1)
18 to <65 years and at risk	2,367 (16.7)	2,324 (16.5)	4,691 (16.6)
≥ 65 years	3,578 (25.3)	3,549 (25.2)	7,127 (25.3)

\* Occupational risk includes: Healthcare Workers; Emergency Response; Retail/Restaurant Operations; Manufacturing and Production; Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel Personal care and in-home services; Hospitality and Tourism Workers, Pastoral; Social or Public Health Workers; and Educators and Students.

\*\* High risk for severe COVID-19 is defined as patients who meet at least one of the following criteria (protocol-defined):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)

- Severe obesity (body mass index  $\geq 40$  kg/m<sup>2</sup>)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human immunodeficiency virus (HIV) infection

\*\*\* Age and health risk for severe COVID-19 is used as stratification factor for randomization.

### 14.1.3 SPIKEVAX Booster Dose (Participants $\geq 18$ Years of Age)

A booster dose of SPIKEVAX (elasomeran) was evaluated in Study P201 Part B, an open-label part assessing immunogenicity following administration of a 50 ug booster dose in participants 18 years of age and older (N=171) who had received a SPIKEVAX primary series in Study P201 Part A. Participants were predominantly female (60.8%), had a mean age of approximately 52 years and were predominantly white (95.9%).

## 14.2 Study Results

### 14.2.1 SPIKEVAX Bivalent (Original / Omicron BA.1) Booster Dose Immunogenicity in Participants $\geq 18$ Years of Age

The safety, reactogenicity, and immunogenicity of the SPIKEVAX Bivalent (Original/Omicron BA.1) booster dose are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (Study P205). For the purpose of this clinical indication, data from Part G and Part F of the study are considered. Part G consisted of participants that were administered SPIKEVAX Bivalent vaccine as a second booster dose (50 mcg, mRNA-1273.214 [25 mcg elasomeran and 25 mcg imelasomeran]). The comparator group is from Part F, where study participants received SPIKEVAX original (50 mcg, mRNA-1273) as a second booster dose.

Immunobridging analyses compared the neutralizing antibody titers (ID<sub>50</sub>) 29 days following the second booster dose (P205 Part G; N=334) to the corresponding titers 29 days following the second booster dose (P205 Part F; N=260) against the Omicron BA.1 subvariant.

In this study, the primary analysis was based on the immunogenicity set, which included participants with no evidence of SARS-CoV-2 infection at baseline (pre-second booster dose).

The estimated Day 29 neutralising antibody GMTs against Omicron were 2479.9 (95%CI: 2264.5, 2715.8) and 1421.2 (95%CI: 1283.0, 1574.4) in the SPIKEVAX Bivalent (Part G) and SPIKEVAX original (Part F) second booster groups, respectively, and the GMR was 1.75 (97.5% CI: 1.49, 2.04). The Omicron SRRs were 100% (95%CI: 98.9, 100) and 99.2% (95%CI: 97.2, 99.9), 29 days in the mRNA-1273.214 and mRNA-1273 groups, respectively, and the SRR difference was 1.5% (97.5%CI: -1.1, 4.0). The findings are summarized in [Table 13](#).

**Table 13 – Ancestral SARS-CoV-2 (D614G) and Omicron Neutralizing Antibody Titres (ID<sub>50</sub>) - SPIKEVAX Bivalent (mRNA-1273.214) 50 µg and SPIKEVAX (mRNA-1273) 50 µg Administered as Second Booster Doses**

	Omicron variant		Ancestral SARS-CoV-2	
	P205 Part G	P205 Part F	P205 Part G	P205 Part F
	SPIKEVAX Bivalent (Original/Omicron BA.1) mRNA-1273.214 50 µg (N=334)	SPIKEVAX mRNA-1273 50 µg (N=260)	SPIKEVAX Bivalent (Original/Omicron BA.1) mRNA-1273.214 50 µg (N=334)	SPIKEVAX mRNA-1273 50 µg (N=260)
<b>Antibody: PsVNA nAb ID<sub>50</sub> titres</b>				
<b>Pre-booster, n</b>	334	260	334	260
Observed GMT (95% CI) <sup>a</sup>	298.13 (258.75, 343.49)	332.02 (282.05, 390.85)	1266.74 (1120.19, 1432.47)	1521.00 (1352.77, 1710.15)
<b>Day 29, n</b>	334	260	334	260
Observed GMT (95% CI) <sup>a</sup>	2372.42 (2070.63, 2718.20)	1473.46 (1270.85, 1708.38)	5977.26 (5321.90, 6713.32)	5649.33 (5056.85, 6311.23)
Observed GMFR (95% CI) <sup>a</sup>	7.96 (7.18, 8.82)	4.44 (3.97, 4.96)	4.72 (4.36, 5.11)	3.71 (3.42, 4.03)
GLSM [estimated GMT] (95% CI) <sup>b</sup>	2479.89 (2264.47, 2715.80)	1421.24 (1282.98, 1574.41)	6422.32 (5990.12, 6885.71)	5286.63 (4887.07, 5718.86)
<b>GMR (97.5% CI)<sup>b</sup></b>	<b>1.75</b> <b>(1.49, 2.04)</b>		<b>1.22</b> <b>(1.08, 1.37)</b>	
<b>Seroresponse, N1</b>	333	258	334	260
Seroresponse rate, n (%) <sup>c</sup>	333 (100)	256 (99.2)	334 (100)	260 (100)
95% CI <sup>d</sup>	(98.9, 100.0)	(97.2, 99.9)	(98.9, 100.0)	(98.6, 100.0)
<b>Difference in seroresponse rates (97.5%)<sup>e</sup></b>	<b>1.5</b> <b>(-1.1, 4.0)</b>		<b>0</b>	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold-rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID<sub>50</sub> = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome-2; n = number of participants with non-missing data at the corresponding timepoint; N1 = number of participants with non-missing data at pre-vaccination baseline and the corresponding timepoint.

<sup>a</sup> 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

<sup>b</sup> Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titres, and age groups.

<sup>c</sup> Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibody titer information, seroresponse is defined as >= 4\*LLOQ for participants with negative SARS-CoV-2 status at their pre-dose 1 of the primary series, and these titers are imputed as <LLOQ at pre-dose 1 of primary series. For participants without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

<sup>d</sup> 95% CI is calculated using the Clopper-Pearson method.

<sup>e</sup> 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate of the CI cannot be calculated when the seroresponse rate in both groups is 100%, absolute difference is reported.

#### 14.2.1.1 *SPIKEVAX Bivalent (Original/Omicron BA.1) Observed Neutralising Antibody Titres for Omicron Subvariant BA.4/5*

In an exploratory analysis, additional analytical testing of SPIKEVAX Bivalent (Original/Omicron BA.1) was conducted to assess neutralizing antibody response against the dominant circulating SARS-CoV-2 Omicron subvariants BA.4/5 in July 2022.

For all participants regardless of prior SARs-CoV-2 infection the estimated Day 29 neutralising antibody GMTs against Omicron BA. 4/5 were 985.38 (95%CI: 914.77, 1061.434) and 588.36 (95%CI: 544.08, 636.24) in the SPIKEVAX Bivalent (Part G) and SPIKEVAX original (Part F) second booster groups, respectively, and the GMR was 1.68 (95%CI: 1.52, 1.84).

For participants without prior SARs-CoV-2 infection, the estimated Day 29 neutralising antibody GMTs against Omicron BA. 4/5 were 776.45 (95%CI: 719.49, 837.92) and 458.28 (95%CI: 420.62, 499.32) in the SPIKEVAX Bivalent (Part G) and SPIKEVAX original (Part F) second booster groups, respectively, and the GMR was 1.69 (95%CI: 1.51, 1.90).

For participants with prior SARs-CoV-2 infection, the estimated Day 29 neutralising antibody GMTs against Omicron BA. 4/5 were 2246.25 (95%CI: 1975.52, 2554.09) and 1406.89 (95%CI: 1227.88, 1612.01) in the SPIKEVAX Bivalent (Part G) and SPIKEVAX original (Part F) second booster groups, respectively, and the GMR was 1.60 (95%CI: 1.34, 1.91).

#### 14.2.2 SPIKEVAX Efficacy in Participants $\geq$ 18 Years of Age (Based on Cut-off Date of November 21, 2020)

The analysis of the primary efficacy endpoint in the COVE Study (P301) included 28,207 participants 18 years of age and older (14,134 in the SPIKEVAX group and 14,073 in the placebo group). At the time of the final primary efficacy analysis, participants had been followed for symptomatic COVID-19 disease for a median of 2 months after the second dose, corresponding to 3304.9 person years for the SPIKEVAX group and 3273.7 person years in the placebo group.

There were 11 confirmed COVID-19 cases identified in the SPIKEVAX group and 185 in placebo group, respectively, for the primary efficacy analysis. Compared to placebo, efficacy of SPIKEVAX in participants with first COVID-19 occurrence from 14 days after Dose 2 was 94.1% (two-sided 95% confidence interval of 89.3% to 96.8%). In participants 65 years of age and older, efficacy of SPIKEVAX was 86.4% (two-sided 95% confidence interval of 61.4% to 95.5%). At the time of primary efficacy analysis, there was a total of 30 severe COVID-19 cases reported in the placebo group starting 14 days after Dose 2, per adjudication committee assessment. No cases of severe COVID-19 were reported in the SPIKEVAX group.

#### 14.2.3 SPIKEVAX Immunogenicity in Participants $\geq$ 18 Years of Age – After Booster Dose

Effectiveness of the single booster dose of 50 mcg of SPIKEVAX in adults 18 years of age and older who received a 2-dose primary series with 100 mcg SPIKEVAX at least 6 months prior to booster was inferred by comparing the antibody titers from Study P201 Part B to the pivotal adult Study P301.

Study P201 Part B was an open-label study assessing immunogenicity responses following administration of a 50 mcg booster of SPIKEVAX to participants primed with 100 mcg doses of SPIKEVAX.

Participants with negative baseline SARS-CoV-2 status were randomly selected from Study P301 participants in the SPIKEVAX group to form an Immunogenicity Subset in Study P301, which was used as the comparator arm for the Study P201 Part B immunobridging analysis.

Immunobridging analyses compared the neutralizing antibody titers (ID50) 28 days following the booster dose (201 Part B; N=149) to the corresponding titers 28 days after completion of the primary series in a random subset of participants 18 years of age and older from the Phase 3 efficacy study (P301; N=1055).

In participants who were primed with a 2-dose series of 100 mcg of SPIKEVAX, single booster dose of 50 mcg of SPIKEVAX demonstrated a geometric mean fold rise of 12.99 (95% CI: 11.04, 15.29) from pre-booster values of neutralizing antibodies as compared to 28 days after the booster dose. The geometric mean ratio (comparing the antibody levels on Day 29 in Study P201 Part B vs. the antibody levels on Day 57 after the priming series in Study P301) was 1.76 (95% CI: 1.50, 2.06), successfully meeting the pre-specified non-inferiority criterion of 0.67 corresponding to non-inferiority margin of 1.5. The analysis is summarized in [Table 14](#).

**Table 14 – Neutralizing Antibody Geometric Mean Titers (ID50) Against a Pseudovirus Expressing the SARS-CoV-2 Spike Protein at 28 Days After a Booster Dose in Study P201 Part B vs 28 Days After Completion of the Primary Series in Study P301, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set**

Study P201 Part B Booster Dose N <sup>a</sup> =149 GMT <sup>b</sup> (95% CI)	Study P301 Primary Series N <sup>a</sup> =1053 GMT <sup>b</sup> (95% CI)	GMT Ratio (Study P201 Part B/ Study P301)	Met Success Criteria <sup>c</sup>
1802 (1548, 2099)	1027 (968, 1089)	1.76 (1.50, 2.06)	Lower limit of 95% CI ≥0.67 Criterion: Yes Point Estimate ≥1.0 Criterion: Yes

\* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study P201 Part B Day 1) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study P201 Part B Day 1), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study P201 Part B and Day 57 for Study P301).

<sup>a</sup> Number of subjects with non-missing data at the corresponding timepoint.

<sup>b</sup> The statistical analysis plan pre-specified an analysis of covariance model for estimating the geometric mean titer that adjusts for differences in age groups (<65 years, ≥65 years).

<sup>c</sup> Immunobridging is declared if the lower limit of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GLSM ratio is ≥1.0.

Note: Antibody values < the lower limit of quantitation (LLOQ) are replaced by 0.5 × LLOQ. Values > the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.

GLSM = Geometric least squares mean

GMR = Geometric mean ratio

## 15 MICROBIOLOGY

No microbiological information is required for this vaccine product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** Intramuscular administration of SPIKEVAX (or other Moderna mRNA investigational vaccines) at doses ranging from 9 to 150 mcg/dose administered once every 2 weeks for up to 6 weeks

resulted in transient injection site erythema and edema, body temperature increases, and a generalized systemic inflammatory response. Transient hepatocyte vacuolation and/or Kupffer cell hypertrophy, often observed without liver enzyme elevations, was observed and considered secondary to the systemic inflammatory response. In general, all changes resolved within 2 weeks.

**Carcinogenicity:** SPIKEVAX has not been evaluated for carcinogenicity in animals, as carcinogenicity studies were not considered relevant to this vaccine.

**Genotoxicity:** SM-102, a proprietary lipid component of SPIKEVAX, SPIKEVAX Bivalent, and SPIKEVAX Bivalent Original/Omicron BA.4/5 is not genotoxic in the bacterial mutagenicity and the human peripheral blood lymphocytes chromosome aberration assays. Two intravenous in vivo micronucleus assays were conducted with mRNA therapies using the same lipid nanoparticle (LNP) formulation as SPIKEVAX Bivalent (Original/Omicron BA.1). Equivocal results observed at high systemic concentrations were likely driven by micronuclei formation secondary to elevated body temperature induced by a LNP-driven systemic inflammatory response. The genotoxic risk to humans is considered to be low due to minimal systemic exposure following intramuscular administration, limited duration of exposure, and the negative in vitro results.

**Reproductive and Developmental Toxicology:** In a pre- and post-natal developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 mcg) and other ingredients included in a single human dose of SPIKEVAX was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, fetal development or postnatal development were reported in the study.



## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

#### **SPIKEVAX Bivalent™ Original / Omicron BA.4/5**

[COVID-19 mRNA vaccine, Bivalent (Original/Omicron B.1.1.529 (BA.4-BA.5) Variant)]

#### **Elasomeran / davesomeran mRNA vaccine, Dispersion for Intramuscular Injection**

Read this carefully before you start taking **SPIKEVAX Bivalent Original/Omicron BA.4/5**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SPIKEVAX Bivalent Original/Omicron BA.4/5**.

#### **What is SPIKEVAX Bivalent Original/Omicron BA.4/5 used for?**

SPIKEVAX Bivalent Original/Omicron BA.4/5 is a vaccine used to prevent the coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus. It can be given to people aged 18 years and older.

The safety and effectiveness of a booster dose of SPIKEVAX Bivalent (elasomeran/davesomeran) Original/Omicron BA.4/5 mRNA vaccine for individuals 18 years of age and older is inferred from studies of a booster dose of SPIKEVAX Bivalent (Original/Omicron BA.1).

#### **How does SPIKEVAX Bivalent work?**

SPIKEVAX Bivalent Original/Omicron BA.4/5 works by causing the body to produce its own protection (antibodies) against the SARS-CoV-2 virus that causes the COVID-19 infection. SPIKEVAX Bivalent Original/Omicron BA.4/5 uses a molecule called messenger ribonucleic acid (mRNA, the genetic code for a piece of the virus) to deliver the set of instructions that cells in your body can use to make antibodies to help fight the virus that causes COVID-19. The vaccine is given by injection with a needle in the upper arm.

You cannot get COVID-19 from this vaccine.

As with any vaccine, SPIKEVAX Bivalent Original/Omicron BA.4/5 may not fully protect all those who receive it. Even after you have had the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

Individuals may not be optimally protected until after receiving the second dose of the vaccine.

#### **What are the ingredients in SPIKEVAX Bivalent Original/Omicron BA.4/5?**

Medicinal ingredients: Elasomeran and davesomeran (mRNA)

Non-medicinal ingredients:

- acetic acid
- cholesterol
- DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)
- PEG2000-DMG (1,2-dimyristoyl-rac-glycerol, methoxy-polyethyleneglycol)
- lipid SM-102

- sodium acetate trihydrate
- sucrose
- trometamol
- trometamol hydrochloride
- water for injection

**SPIKEVAX Bivalent Original/Omicron BA.4/5 comes in the following dosage forms:**

White to off-white dispersion for injection provided in a multidose vial. For individuals 18 years of age the SPIKEVAX Bivalent Original/Omicron BA.4/5 dose is 50 micrograms.

**Do not receive SPIKEVAX Bivalent Original/Omicron BA.4/5 if:**

- you are allergic to the active substance or any of the other ingredients of this vaccine (see What are the ingredients in SPIKEVAX Bivalent Original/Omicron BA.4/5?)
- you have had an allergic reaction to a previous dose of SPIKEVAX
- you currently have symptoms that could be due to COVID-19. Talk with your healthcare professional about your symptoms and getting a COVID-19 test. Your healthcare professional will advise you when you are able to receive the vaccine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SPIKEVAX Bivalent Original/Omicron BA.4/5. Talk about any health conditions or problems you may have, including if you:**

- have any allergies
- have had previous problems following administration of SPIKEVAX such as an allergic reaction or breathing problems
- have a weakened immune system due to a medical condition or are on a medicine that affects your immune system
- have a bleeding problem, bruise easily or use a blood thinning medication
- have a high fever or severe infection
- have any serious illness
- have previously had episodes of myocarditis (inflammation of the heart muscle) and/or pericarditis (inflammation of the lining outside the heart)
- are pregnant, think you may be pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

There is limited information on the use of SPIKEVAX Bivalent Original/Omicron BA.4/5 with other vaccines. Tell your healthcare professional if you have recently received any other vaccine.

**How is SPIKEVAX Bivalent Original/Omicron BA.4/5 given:**

- Your doctor, pharmacist or nurse will inject the vaccine into a muscle (intramuscular injection) in your upper arm
- During and after each injection of the vaccine, your doctor, pharmacist or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

**Usual dose:**

A booster dose of 50 mcg may be administered intramuscularly at least 4 months after completion of a primary series and/or a previous booster dose in individuals 18 years of age or older.

**Overdose:**

In the event of suspected overdose with SPIKEVAX Bivalent Original/Omicron BA.4/5, contact your regional poison control centre.

**Missed Dose:**

If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice.

**What are possible side effects from using SPIKEVAX Bivalent Original/Omicron BA.4/5?**

Like all vaccines, SPIKEVAX Bivalent Original/Omicron BA.4/5 can cause side effects.

The following are common or very common side effects of SPIKEVAX Bivalent Original/Omicron BA.4/5. Most of these side effects are mild and do not last long. Tell your doctor if you have side effects that bother you:

- pain at the injection site
- tiredness
- headache
- muscle ache and stiffness
- chills
- fever
- swelling or redness at the injection site
- nausea and/or vomiting
- enlarged lymph nodes
- hypoaesthesia (decreased sense of touch or sensation, numbness) or paraesthesia (tingling, itching or pricking sensation)
- dizziness

Non-severe allergic reactions (such as rash, itching, hives or swelling of the face), severe allergic reactions, erythema multiforme (red round patches on the skin) and facial paralysis / Bell's palsy have been reported with the administration of SPIKEVAX.

These are not all the possible side effects you may have when taking SPIKEVAX Bivalent Original/Omicron BA.4-BA.5. If you experience any side effects not listed here, tell your healthcare professional.

Should you develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention right away. Symptoms of an allergic reaction include:

- hives (bumps on the skin that are often very itchy)
- swelling of the face, tongue or throat
- difficulty breathing

If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### **Reporting Suspected Side Effects for Vaccines**

**For the general public:** Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and ModernaTX, Inc. cannot provide medical advice.

**For healthcare professionals:** If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (<https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html>) and send it to your local Health Unit.

#### **Storage:**

Your doctor or pharmacist is responsible storing, supplying and administering SPIKEVAX Bivalent Original/Omicron BA.4/5, as well as disposing of any unused product correctly.

Keep out of reach and sight of children.

#### **If you want more information about SPIKEVAX Bivalent Original/Omicron BA.4/5:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <https://www.modernacovid19global.com/ca/>, or by calling 1-866-MODERNA (1-866-663-3762).

This leaflet was prepared by ModernaTX, Inc.

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