1. NAME OF THE MEDICINAL PRODUCT

Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection
COVID-19 mRNA Vaccine 250 micrograms/2.5 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Table 1. Spikevax 2023-2024 Formula (XBB.1.5) qualitative and quantitative composition

Strength	**Container**	**Dose(s)**	**Composition per dose**
Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms/2.5 mL	Multidose 2.5 mL vial (blue flip-off cap)	5 doses of 0.5 mL each or 10 doses of 0.25 mL each	One dose (0.5 mL) contains 50 micrograms of andusomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles). One dose (0.25 mL) contains 25 micrograms of andusomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles).

Andusomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection
White to off white suspension (pH: 7.0 – 8.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spikevax 2023-2024 Formula (XBB.1.5) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older (see sections 4.2 and 5.1).

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Table 2. Spikevax 2023-2024 Formula (XBB.1.5) posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS CoV-2 infection	Two doses of 0.25 mL each, given intramuscularly	Administer the second dose 28 days after the first dose (see sections 4.4 and 5.1). If a child has received one prior dose of any Spikevax vaccine, one dose of Spikevax 2023-2024 Formula (XBB.1.5) should be administered to complete the two-dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly	Spikevax 2023-2024 Formula (XBB.1.5) should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.
Children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly	
Individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	
Individuals 65 years of age and older	One dose of 0.5 mL, given intramuscularly	One additional dose may be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Table 3. Spikevax 2023-2024 Formula (XBB.1.5) posology for immunocompromised individuals

Age(s)	Dose	Additional recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly	A third dose in severely immunocompromised may be given at least 28 days after the second dose.
Immunocompromised children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly	Additional age-appropriate dose(s) may be administered in severely immunocompromised at least 2 months following the most recent dose of a COVID-19 vaccine at the discretion of the healthcare provider, taking into consideration the
Immunocompromised children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly	

Age(s)	Dose	Additional recommendations
Immunocompromised individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	individual's clinical circumstances.

Paediatric population
The safety and efficacy of Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection COVID-19 mRNA Vaccine 250 micrograms/2.5 mL in children less than 6 months of age have not yet been established. No data are available.

Elderly
No dose adjustment is required in elderly individuals ≥65 years of age.

Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported in individuals who have received Spikevax (original). Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. Subsequent doses of Spikevax 2023-2024 Formula (XBB.1.5) should not be given to those who have experienced anaphylaxis to a prior dose of Spikevax (original).

Myocarditis and pericarditis

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax.

These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often in younger males, and more often after the second dose compared to the first dose (see section 4.8).

Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Capillary leak syndrome flare-ups

A few cases of capillary leak syndrome (CLS) flare-ups have been reported in the first days after vaccination with Spikevax (original). Healthcare professionals should be aware of signs and symptoms of CLS to promptly recognise and treat the condition. In individuals with a medical history of CLS, planning of vaccination should be made in collaboration with appropriate medical experts.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical studies.

Limitations of vaccine effectiveness

As with all vaccines, vaccination with Spikevax 2023-2024 Formula (XBB.1.5) may not protect all vaccine recipients.

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Spikevax 2023-2024 Formula (XBB.1.5) with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of andusomeran during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with Spikevax (original) during the second and third trimester has not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Since differences between products are confined to the spike protein sequence, and there are no clinically meaningful differences in reactogenicity, andusomeran can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of andusomeran during breastfeeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to the vaccine is negligible. Observational data from women who were breastfeeding after vaccination with Spikevax (original) have not shown a risk for adverse effects in breastfed newborns/infants. Andusomeran can be used during breastfeeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Andusomeran has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Adults
The safety of Spikevax (original) was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 30 351 participants 18 years of age and older who received at least one dose of Spikevax (original) (n=15 185) or placebo (n=15 166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22 831 (75.2%) of participants were 18 to 64 years of age and 7 520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Adolescents 12 through 17 years of age
Safety data for Spikevax (original) in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study with multiple parts conducted in the United States. The first portion of the study involved 3 726 participants 12 through 17 years of age who received at least one dose of Spikevax (original) (n=2 486) or placebo (n=1 240) (NCT04649151). Demographic characteristics were similar among participants who received Spikevax (original) and those who received placebo.

The most frequent adverse reactions in adolescents 12 to 17 years of age were injection site pain (97%), headache (78%), fatigue (75%), myalgia (54%), chills (49%), axillary swelling/tenderness (35%), arthralgia (35%), nausea/vomiting (29%), injection site swelling (28%), injection site erythema (26%), and fever (14%).

This study transitioned to an open-label Phase 2/3 study in which 1 346 participants 12 years through 17 years of age received a booster dose of Spikevax at least 5 months after the second dose of the primary series. No additional adverse reactions were identified in the open-label portion of the study.

Children 6 years through 11 years of age
Safety data for Spikevax (original) in children were collected in an ongoing Phase 2/3 two-part randomised, observer-blind clinical study conducted in the United States and Canada (NCT04796896). Part 1 is an open-label phase of the study for safety, dose selection, and immunogenicity and included 380 participants 6 years through 11 years of age who received at least 1 dose (0.25 mL) of Spikevax (original). Part 2 is the placebo-controlled phase for safety and included 4 016 participants 6 years through 11 years of age who received at least one dose (0.25 mL) of Spikevax (original) (n=3 012) or placebo (n=1 004). No participants in Part 1 participated in Part 2. Demographic characteristics were similar among participants who received Spikevax (original) and those who received placebo.

The most frequent adverse reactions in participants 6 years through 11 years of age following administration of the primary series (in Part 2) were injection site pain (98.4%), fatigue (73.1%), headache (62.1%), myalgia (35.3%), chills (34.6%), nausea/vomiting (29.3%), axillary swelling/tenderness (27.0%), fever (25.7%), injection site erythema (24.0%), injection site swelling (22.3%), and arthralgia (21.3%).

The study protocol was amended to include an open-label booster dose phase that included 1 294 participants 6 years through 11 years of age who received a booster dose of Spikevax at least 6 months after the second dose of the primary series. No additional adverse reactions were identified in the open-label portion of the study.

Children 6 months through 5 years of age
An ongoing Phase 2/3 randomised, placebo-controlled, observer-blind study to evaluate the safety, tolerability, reactogenicity, and efficacy of Spikevax was conducted in the United States and Canada. This study involved 10 390 participants 6 months through 11 years of age who received at least one dose of Spikevax (n=7 798) or placebo (n=2 592).

The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months. This paediatric study involved 6 388 participants 6 months through 5 years of age who received at least one dose of Spikevax (n=4 791) or placebo (n=1 597). Demographic characteristics were similar among participants who received Spikevax and those who received placebo.

In this clinical study, the adverse reactions in participants 6 months through 23 months of age following administration of the primary series were irritability/crying (81.5%), pain at the injection

site (56.2%), sleepiness (51.1%), loss of appetite (45.7%), fever (21.8%), swelling at the injection site (18.4%), erythema at the injection site (17.9%), and axillary swelling/tenderness (12.2%).

The adverse reactions in participants 24 through 36 months of age following administration of the primary series were pain at the injection site (76.8%), irritability/crying (71.0%), sleepiness (49.7%), loss of appetite (42.4%), fever (26.1%), erythema at the injection site (17.9%), swelling at the injection site (15.7%), and axillary swelling/tenderness (11.5%).

The adverse reactions in participants 37 months through 5 years of age following administration of the primary series were pain at the injection site (83.8%), fatigue (61.9%), headache (22.9%), myalgia (22.1%), fever (20.9%), chills (16.8%), nausea/vomiting (15.2%), axillary swelling/tenderness (14.3%), arthralgia (12.8%), erythema at the injection site (9.5%), and swelling at the injection site (8.2%).

Tabulated list of adverse reactions

The safety profile presented below is based on data generated in several placebo-controlled clinical studies:

- 30 351 adults ≥ 18 years of age
- 3 726 adolescents 12 through 17 years of age
- 4 002 children 6 years through 11 years of age
- 6 388 children aged 6 months through 5 years of age
- and post-marketing experience.

Adverse reactions reported are listed according to the following frequency convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (Table 4).

Table 4. Adverse reactions from Spikevax (original) clinical studies and post authorisation experience in children and individuals 6 months of age and older

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite†
Psychiatric disorders	Very common	Irritability/crying†
Nervous system disorders	Very common	Headache Sleepiness†
	Uncommon	Dizziness
	Rare	Acute peripheral facial paralysis‡ Hypoaesthesia Paraesthesia
Cardiac disorders	Very rare	Myocarditis Pericarditis
Gastrointestinal disorders	Very common	Nausea/vomiting
	Common	Diarrhoea

MedDRA system organ class	Frequency	Adverse reactions
	Uncommon	Abdominal pain§
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria¶
	Not known	Erythema multiforme Mechanical urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding#
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling Injection site erythema
	Common	Injection site urticaria Injection site rash Delayed injection site reaction♠
	Uncommon	Injection site pruritus
	Rare	Facial swelling♥
	Not known	Extensive swelling of vaccinated limb

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases.

† Observed in the paediatric population (6 months to 5 years of age).

‡ Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the Spikevax (original) 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.

§ Abdominal pain was observed in the paediatric population (6 to 11 years of age): 0.2% in the Spikevax (original) group and 0% in the placebo group.

¶ Urticaria has been observed with either acute onset (within a few days after vaccination) or delayed onset (up to approximately two weeks after vaccination).

Most cases appeared to be non-serious and temporary in nature.

♠ Median time to onset was 9 days after the first injection, and 11 days after the second injection. Median duration was 4 days after the first injection, and 4 days after the second injection.

♥ 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.

The reactogenicity and safety profile in 343 subjects receiving Spikevax (original), that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Adults (booster dose)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax (original) are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax (original) vaccine primary series. In an open-label phase of this study, 167 of those participants received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose of the primary series. The solicited adverse reaction profile for the booster dose (0.25 mL, 50 micrograms) was similar to that after the second dose in the primary series.

Spikevax bivalent Original/Omicron BA.1 (booster dose)

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 Original/Omicron BA.1 50 microgram booster dose, and 377 participants received the

Spikevax (original) 50 microgram booster dose.

Spikevax bivalent Original/Omicron BA.1 had a reactogenicity profile similar to that of the Spikevax (original) booster given as a second booster dose. The frequency of adverse reactions after immunisation with Spikevax bivalent Original/Omicron BA.1 was also similar or lower relative to that of a first booster dose of Spikevax (original) (50 micrograms) and relative to the second dose of the Spikevax (original) primary series (100 micrograms). The safety profile of Spikevax bivalent Original/Omicron BA.1 (median follow-up period of 113 days) was similar to the safety profile of Spikevax (original) (median follow-up period of 127 days).

Spikevax bivalent Original/Omicron BA.4-5 (booster dose)
The safety, reactogenicity, and immunogenicity of a bivalent booster dose of Spikevax bivalent Original/Omicron BA.4-5 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, 511 participants received a booster dose of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms), and 376 participants received a booster dose of Spikevax (original) (50 micrograms).

Spikevax bivalent Original/Omicron BA.4-5 had a reactogenicity profile similar to that of the Spikevax (original) booster given as a second booster dose.

Spikevax XBB 1.5 (booster dose)
The safety, reactogenicity and immunogenicity of a booster dose of Spikevax XBB.1.5 are evaluated in an ongoing Phase 2/3 open-label study in adults (mRNA-1273-P205, Part J). In this study, 50 participants received a booster dose of Spikevax XBB.1.5 (50 micrograms) and 51 participants received a booster dose of an investigational bivalent Omicron XBB.1.5/BA.4-5 vaccine (50 micrograms).

The reactogenicity profile of Spikevax XBB.1.5 was similar to that of Spikevax (original) and Spikevax bivalent Original/Omicron BA.4-5. The median follow-up time for both vaccine groups in this interim analysis was 20 days (range of 20 to 22 days with data cut-off date of 16 May 2023).

Spikevax (original) in solid organ transplant recipients
The safety, reactogenicity, and immunogenicity of Spikevax (original) were evaluated in a two-part Phase 3b open-label study in adult solid organ transplant (SOT) recipients, including kidney and liver transplants (mRNA-1273-P304). A 100 microgram (0.5 mL) dose was administered, which was the dose authorised at the time of study conduct.

In Part A, 128 SOT recipients received a third dose of Spikevax (original). In Part B, 159 SOT recipients received a booster dose at least 4 months after the last dose (fourth dose for mRNA vaccines and third dose for non-mRNA vaccines).

Reactogenicity was consistent with the known profile of Spikevax (original). There were no unexpected safety findings.

Description of selected adverse reactions

Myocarditis
The increased risk of myocarditis after vaccination with Spikevax (original) is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Spikevax (original). One study showed that in a period of 7 days after the second dose, there were about 1.316 (95% CI: 1.299, 1.333) extra cases of myocarditis in 12 to 29 year-old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose, there were 1.88 (95% CI: 0.956, 2.804) extra cases of myocarditis in 16 to 24 year-old males per 10 000 compared to unexposed persons.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions and include batch/Lot number if available.

4.9 Overdose

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, COVID-19 vaccines, ATC code: J07BN01

Mechanism of action

Elasomeran and elasomeran/imelasomeran both contain mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19. The nucleoside-modified mRNA in elasomeran/davesomeran and in andusomeran is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

Clinical efficacy

Immunogenicity in adults – after Spikevax XBB.1.5 dose (0.5 mL, 50 micrograms) versus an investigational bivalent XBB.1.5/BA.4-5 dose (0.5 mL, 25 micrograms/25 micrograms)
The safety, reactogenicity and immunogenicity of Spikevax XBB.1.5 50 micrograms and of a bivalent vaccine that contains equal mRNA amounts of Omicron XBB.1.5 and Omicron BA.4-5 spike proteins (25 micrograms XBB.1.5 / 25 micrograms BA.4-5) are evaluated in a Phase 2/3 open-label study in adults. In this study, 50 participants received Spikevax XBB.1.5 and 51 participants received the investigational bivalent XBB.1.5/BA.4-5 (mRNA-1273- P205, Part J). The two groups were randomised 1:1.

The vaccines were administered as a fifth dose to adults who previously received a two-dose primary series of any mRNA COVID-19 vaccine, a booster dose of any mRNA COVID-19 vaccine, and a booster dose of any mRNA bivalent Original/Omicron BA.4-5 vaccine.

Spikevax XBB.1.5 and bivalent XBB.1.5/BA.4-5 elicited potent neutralising responses at Day 15 against XBB.1.5, XBB.1.16, BA.4-5, BQ.1.1 and D614G. In the per-protocol immunogenicity set that includes all participants, with and without prior SARS-CoV-2 infection (N=49 and N=50 for Spikevax XBB.1.5 and bivalent XBB.1.5/BA.4-5 groups, respectively), the Day 15 GMFR (95% CI) for

Spikevax XBB.1.5 and bivalent XBB.1.5/BA.4-5 was 16.7 (12.8, 21.7) and 11.6 (8.7, 15.4), respectively, against XBB.1.5 and 6.3 (4.8, 8.2) and 5.3 (3.9, 7.1) against BA.4-5.

For variants not contained in the vaccines, the Day 15 GMFR (95% CI) for Spikevax XBB.1.5 and bivalent XBB.1.5/BA.4-5 was 11.4 (8.5, 15.4) and 9.3 (7.0, 12.3) against XBB.1.16; 5.8 (4.7, 7.3) and 6.1 (4.6, 7.9) against BQ.1.1 and 2.8 (2.2, 3.5) and 2.3 (1.9, 2.8) against D614G.

Immunogenicity in participants 18 years of age and older – after Spikevax bivalent Original/Omicron BA.4-5 booster dose (0.5 mL, 25 micrograms/25 micrograms)
The safety, reactogenicity, and immunogenicity of a Spikevax bivalent Original/Omicron BA.4-5 booster dose 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, 511 participants received the Spikevax bivalent Original/Omicron BA.4-5 50 microgram booster dose, and 376 participants received the Spikevax (original) 50 microgram booster dose.

Study P205 Part H evaluated the safety, reactogenicity and immunogenicity of Spikevax bivalent Original/Omicron BA.4-5 when administered as a second booster dose to adults who previously received 2 doses of Spikevax (original) (100 microgram) as a primary series and a first booster dose of Spikevax (original) (50 micrograms). In P205 Part F, study participants received Spikevax (original) (50 micrograms) as a second booster dose and the Part F group serves as a within-study, non-contemporaneous comparator group to the Spikevax bivalent Original/Omicron BA.4-5 group. In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the observed geometric mean titre (GMT) (95% CI) at pre-booster was 87.9 (72.2, 107.1) and increased to 2 324.6 (1 921.2, 2 812.7) 28 days after the Spikevax bivalent Original/Omicron BA.4-5 booster dose. The Day 29 GMR for Spikevax Original/Omicron BA.4-5 50 microgram booster dose versus the Spikevax (original) 50 microgram booster dose was 6.29 (5.27, 7.51), meeting the pre-specified criterion for superiority (lower bound of CI >1).

The estimated neutralising antibody GMTs (95% CI) against Omicron BA.4/BA.5 adjusted for pre-booster titre and age group were 2 747.3 (2 399.2, 3 145.9) and 436.7 (389.1, 490.0) 28 days after Spikevax bivalent Original/Omicron BA.4-5 and Spikevax (original) booster doses, respectively, and the GMR (95% CI) was 6.29 (5.27, 7.51), meeting the pre-specified criterion for non-inferiority (lower bound of CI >0.667).

Immunogenicity in adults – after Spikevax bivalent Original/Omicron BA.1 booster dose (0.5 mL, 25 micrograms/25 micrograms)
The safety, reactogenicity, and immunogenicity of a 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 (mRNA-1273-P205). In this study, 437 participants received the Spikevax bivalent Original/Omicron BA.1 50 microgram booster dose, and 377 participants received the Spikevax (original) 50 microgram booster dose.

Study P205 Part G evaluated the safety, reactogenicity and immunogenicity of Spikevax bivalent Original/Omicron BA.1 when administered as a second booster dose to adults who previously received 2 doses of Spikevax (original) (100 microgram) as a primary series and a booster dose of Spikevax (original) (50 micrograms) at least 3 months prior to enrolment. In P205 Part F, study participants received Spikevax (original) (50 micrograms) as a second booster dose and the Part G group serves as a within-study, non-contemporaneous comparator group to the Spikevax bivalent Original/Omicron BA.1 group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the original SARS-CoV-2 estimated neutralising antibody geometric mean titre (GMT) and corresponding 95% CI was 6 422.3 (5 990.1, 6 885.7) and 5 286.6 (4 887.1, 5 718.9) 28 days after the Spikevax bivalent Original/Omicron BA.1 and Spikevax (original) booster doses, respectively. These GMTs represent the ratio between response of Spikevax bivalent

Original/Omicron BA.1 versus Spikevax (original) against the ancestral SARS-CoV-2 (D614G) strain. The GMR (97.5% CI) was 1.22 (1.08, 1.37) meeting the pre-specified criterion for non-inferiority (lower bound of 97.5% CI ≥0.67).

The estimated Day 29 neutralising antibody GMTs against Omicron, BA.1 were 2 479.9 (2 264.5, 2 715.8) and 1 421.2 (1 283.0, 1 574.4) in the Spikevax bivalent Original/Omicron BA.1 and Spikevax (original) booster groups, respectively, and the GMR (97.5% CI) was 1.75 (1.49, 2.04), which met the pre-specified superiority criterion (lower bound of CI >1).

Three-month antibody persistence of Spikevax bivalent Original/Omicron BA.1 booster vaccine against COVID-19
Participants in Study P205 Part G were sequentially enrolled to receive 50 micrograms of Spikevax (original) (n = 376) or Spikevax bivalent Original/Omicron BA.1 (n = 437) as second booster doses. In participants with no pre-booster incidence of SARS-CoV-2, Spikevax bivalent Original/Omicron BA.1 elicited Omicron-BA.1-neutralising antibody titres (observed GMT) that were significantly higher (964.4 [834.4, 1 114.7]) than those of Spikevax (original) (624.2 [533.1, 730.9]) and similar between boosters against ancestral SARS-CoV-2 at three months.

Clinical efficacy in adults
The adult study was a randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) that excluded individuals who were immunocompromised or had received immunosuppressants within 6 months, as well as participants who were pregnant, or with a known history of SARS-CoV-2 infection. Participants with stable HIV disease were not excluded. Influenza vaccines could be administered 14 days before or 14 days after any dose of Spikevax (original). Participants were also required to observe a minimum interval of 3 months after receipt of blood/plasma products or immunoglobulins prior to the study in order to receive either placebo or Spikevax (original).

A total of 30 351 subjects were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28 207 subjects who received either Spikevax (original) (n=14 134) or placebo (n=14 073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS. 98% of vaccine recipients received the second dose 25 days to 35 days after dose 1 (corresponding to -3 to +7 days around the interval of 28 days).

COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy overall and by key age groups are presented in Table 5.

Table 5. Vaccine efficacy analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – PPS

Age group (years)	Spikevax (original)			Placebo			
	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1 000 person-years	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1 000 person-years	% Vaccine efficacy (95% CI)*
Overall (≥18)	14 134	11	3.328	14 073	185	56.510	94.1 (89.3, 96.8)**
18 to <65	10 551	7	2.875	10 521	156	64.625	95.6 (90.6, 97.9)

Age group (years)	Spikevax (original)			Placebo			
	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1 000 person-years	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1 000 person-years	% Vaccine efficacy (95% CI)*
≥65	3 583	4	4.595	3 552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2 953	4	5.586	2 864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

[#]COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*Vaccine efficacy and 95% confidence interval (CI) from the stratified Cox proportional hazard model
** CI not adjusted for multiplicity. Multiplicity adjusted statistical analyses were carried out in an interim analysis based on less COVID-19 cases, not reported here.

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

The vaccine efficacy of Spikevax (original) to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% CI: 88.6, 96.5).

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Immunogenicity in adults – after booster dose (0.25 mL, 50 micrograms)
The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax (original) are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax (original) vaccine as primary series. In an open-label phase, 149 of those participants (Per Protocol Set) received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose in the primary series. A single booster dose (0.25 mL, 50 micrograms) was shown to result in a geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29) in neutralising antibodies from pre-booster compared to 28 days after the booster dose. The GMFR in neutralising antibodies was 1.53 (95% CI: 1.32, 1.77) when compared 28 days post dose 2 (primary series) to 28 days after the booster dose.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine in adults
Safety and immunogenicity of a heterologous booster with Spikevax (original) were studied in an investigator-initiated study with 154 participants. The minimum time interval between primary series using a vector-based or RNA-based COVID-19 vaccine and booster injection with Spikevax (original) was 12 weeks (range: 12 weeks to 20.9 weeks). The dose used for boosting in this study was 100 micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were

assessed on Day 1 prior to administration and at Day 15 and Day 29 after the booster dose. A booster response was demonstrated regardless of primary vaccination.

Only short-term immunogenicity data are available; long-term protection and immunological memory are currently unknown.

Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) in the UK
COV-BOOST is a multicentre, randomised Phase 2 investigator-initiated study of third dose booster vaccination against COVID-19 with a subgroup to investigate detailed immunology. Participants were adults aged 30 years or older, in good physical health (mild to moderate well-controlled co-morbidities were permitted), who had received two doses of either Pfizer–BioNTech or Oxford–AstraZeneca (first dose in December 2020, January 2021 or February 2021), and were at least 84 days post second dose by the time of enrolment. Spikevax (original) boosted antibody and neutralising responses and was well tolerated regardless of the prime series. The dose used for boosting in this study was 100 micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were assessed on Day 28 after the booster dose.

Clinical efficacy in adolescents 12 through 17 years of age
The adolescent study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study (NCT04649151) to evaluate the safety, reactogenicity, and efficacy of Spikevax (original) in adolescents 12 to 17 years of age. Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3 732 participants were randomised 2:1 to receive 2 doses of Spikevax (original) or saline placebo 1 month apart.

A secondary efficacy analysis was performed in 3 181 participants who received 2 doses of either Spikevax (original) (n=2 139) or placebo (n=1 042) and had a negative baseline SARS-CoV-2 status in the Per Protocol Set. Between participants who received Spikevax (original) and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose.

There were zero symptomatic COVID-19 cases in the Spikevax (original) group and 4 symptomatic COVID-19 cases in the placebo group.

Immunogenicity in adolescents 12 to 17 years of age – after Spikevax primary vaccination
A non-inferiority analysis evaluating SARS-CoV-2 50% neutralising titres and seroresponse rates 28 days after Dose 2 was conducted in the per-protocol immunogenicity subsets of adolescents aged 12 through 17 (n=340) in the adolescent study and in participants aged 18 through 25 (n=296) in the adult study. Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The geometric mean ratio (GMR) of the neutralising antibody titres in adolescents 12 to 17 years of age compared to the 18- to 25-year-olds was 1.08 (95% CI: 0.94, 1.24). The difference in seroresponse rate was 0.2% (95% CI: -1.8, 2.4). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Immunogenicity in adolescents 12 years through 17 years of age – after Spikevax (original) booster dose
The primary immunogenicity objective of the booster phase of this study was to infer efficacy of the booster dose in participants 12 years through 17 years of age by comparing post-booster immune responses (Day 29) to those obtained post-dose 2 of the primary series (Day 57) in young adults (18 to 25 years of age) in the adult study. Efficacy of the 50 microgram Spikevax booster dose is inferred if post-booster dose immune responses (nAb geometric mean concentration [GMC] and seroresponse rate [SRR]) meet prespecified noninferiority criteria (for both GMC and SRR) compared to those measured following completion of the 100 microgram Spikevax primary series among a subset of young adults (18 to 25 years) in the pivotal adult efficacy study.

In an open-label phase of this study, participants 12 years through 17 years of age received a single booster dose at least 5 months after completion of the primary series (two doses 1 month apart). The primary immunogenicity analysis population included 257 booster dose participants in this study and a random subset of 295 participants from the young adult study (ages ≥18 to ≤25 years) who previously completed a primary vaccination series of two doses 1 month apart of Spikevax. Both groups of participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively.

The GMR of the adolescent booster dose Day 29 GMC compared with young adults: Day 57 GMR was 5.1 (95% CI: 4.5, 5.8), meeting the noninferiority criteria (i.e., lower bound of the 95% CI >0.667 (1/1.5); point estimate ≥0.8); the SRR difference was 0.7% (95% CI: -0.8, 2.4), meeting the noninferiority criteria (lower bound of the 95% of the SRR difference >-10%).

In the 257 participants, pre-booster (booster dose-Day 1) nAb GMC was 400.4 (95% CI: 370.0, 433.4); on BD-Day 29, the GMC was 7 172.0 (95% CI: 6 610.4, 7 781.4). Post-booster booster dose-Day 29 GMC increased approximately 18-fold from pre-booster GMC, demonstrating the potency of the booster dose to adolescents. The SRR was 100 (95% CI: 98.6, 100.0).

The prespecified success criteria for the primary immunogenicity objective were met, thus enabling the inference of vaccine efficacy from the adult study.

Clinical efficacy in children 6 years through 11 years of age
The paediatric study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical study to evaluate the safety, reactogenicity, and efficacy of Spikevax (original) in children aged 6 years through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4 011 participants were randomised 3:1 to receive 2 doses of Spikevax (original) or saline placebo 1 month apart.

A secondary efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of 10 November 2021 was performed in 3 497 participants who received two doses (0.25 mL at 0 and 1 month) of either Spikevax (original) (n=2 644) or placebo (n=853) and had a negative baseline SARS-CoV-2 status in the Per Protocol Set. Between participants who received Spikevax (original) and those who received placebo, there were no notable differences in demographics.

COVID-19 was defined as symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose.

There were three COVID-19 cases (0.1%) in the Spikevax (original) group and four COVID-19 cases (0.5%) in the placebo group.

Immunogenicity in children 6 years through 11 years of age
An analysis evaluating SARS-CoV-2 50% neutralising titres and seroresponse rates 28 days after Dose 2 was conducted in a subset of children aged 6 years through 11 years (n=319) in the paediatric study and in participants aged 18 through 25 years (n=295) in the adult study. Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralising antibody titres in children 6 years through 11 years of age compared to the 18- to 25-year-olds was 1.239 (95% CI: 1.072, 1.432). The difference in seroresponse rate was 0.1% (95% CI: -1.9, 2.1). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Immunogenicity in children 6 years through 11 years of age – after Spikevax (original) booster dose
The primary immunogenicity objective of the booster phase of this study is to infer efficacy of the booster dose in participants 6 years through 11 years of age by comparing post-booster dose immune responses (Day 29) to those obtained post dose 2 of the primary series (Day 57) in young adults (18 to 25 years of age) in that study, where 93% efficacy was demonstrated. Efficacy of the 25 microgram Spikevax booster dose is inferred if post-booster dose immune responses (neutralising antibody [nAb]

geometric mean concentration [GMC] and seroresponse rate [SRR]) meet pre-specified non-inferiority criteria (for both GMC and SRR) compared to those measured following completion of the 100 microgram Spikevax primary series among a subset of young adults (18 to 25 years) in the pivotal adult efficacy trial.

In an open-label phase of this study, participants 6 years through 11 years of age received a single booster dose at least 6 months after completion of the primary series (two doses 1 month apart). The primary immunogenicity analysis population included 95 booster dose participants in 6 years through 11 years and a random subset of 295 participants from the young adult study who received two doses 1 month apart of Spikevax. Both groups of participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively.

In the 95 participants, on booster dose-Day 29, the GMC was 5 847.5 (95% CI: 4 999.6, 6 839.1). The SRR was 100 (95% CI: 95.9, 100.0). Serum nAb levels for children 6 years through 11 years in the per-protocol immunogenicity subset with pre-booster SARS-CoV-2 negative status and the comparison with those from young adults (18 to 25 years of age) were studied. The GMR of booster dose Day 29 GMC compared to young adults Day 57 GMC was 4.2 (95% CI: 3.5, 5.0), meeting the noninferiority criteria (i.e., lower bound of the 95% CI > 0.667); the SRR difference was 0.7% (95% CI: -3.5, 2.4), meeting the noninferiority criteria (lower bound of the 95% of the SRR difference > -10%).

The prespecified success criteria for the primary immunogenicity objective were met, thus enabling the inference of booster dose vaccine efficacy. The brisk recall response evident within 4 weeks of booster dosing is evidence of the robust priming induced by the Spikevax primary series.

Clinical efficacy in children 6 months through 5 years of age
An ongoing Phase 2/3 study was conducted to evaluate the safety, tolerability, reactogenicity, and efficacy of Spikevax in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of 21 February 2022 was performed in 5 476 participants 6 months through 5 years of age who received two doses (at 0 and 1 month) of either Spikevax (n=4 105) or placebo (n=1 371) and had a negative baseline SARS-CoV-2 status (referred to as the Per Protocol Set for Efficacy). Between participants who received Spikevax and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy post-Dose 2 was 71 days for participants 2 years through 5 years of age and 68 days for participants 6 months through 23 months of age.

Vaccine efficacy in this study was observed during the period when the B.1.1.529 (Omicron) variant was the predominant variant in circulation.

Vaccine efficacy (VE) in Part 2 for the Per Protocol Set for Efficacy for COVID-19 cases 14 days or more after dose 2 using the “COVID-19 P301 case definition” (i.e., the definition employed in the pivotal adult efficacy study) was 46.4% (95% CI: 19.8, 63.8) for children 2 years through 5 years of age and 31.5% (95% CI: -27.7, 62.0) for children 6 months through 23 months of age.

Immunogenicity in children 6 months through 5 years of age
For children aged 2 years through 5 years of age, comparison of Day 57 nAb responses in this Part 2 per-protocol immunogenicity subset (n = 264; 25 micrograms) to those of young adults (n = 295; 100 micrograms) demonstrated a GMR of 1.014 (95% CI: 0.881, 1.167), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The geometric mean fold rise (GMFR) from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in seroresponse rates (SRR) between the children and young adults was -0.4%

(95% CI: -2.7%, 1.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%).

For infants and toddlers from 6 months through 23 months of age, comparison of Day 57 nAb responses in this Part 2 per-protocol immunogenicity subset (n = 230; 25 micrograms) to those of young adults (n = 295; 100 micrograms) demonstrated a GMR of 1.280 (95% CI: 1.115, 1.470), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The difference in SRR rates between the infants/toddlers and young adults was 0.7% (95% CI: -1.0%, 2.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Accordingly, the prespecified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 micrograms to be inferred in both children 2 years through 5 years and infants and toddlers aged 6 months through 23 months (Tables 6 and 7).

Table 6. Summary of geometric mean concentration ratio and seroresponse rate – comparison of individuals 6 months through 23 months of age to participants 18 years through 25 years of age – per-protocol immunogenicity set

		6 months through 23 months n=230	**18 years through 25 years n=291**	**6 months through 23 months/ 18 years through 25 years**	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralisation assay[c]	28 days after Dose 2	1 780.7 (1 606.4, 1 973.8)	1 390.8 (1 269.1, 1 524.2)	1.3 (1.1, 1.5)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		100 (98.4, 100)	99.3 (97.5, 99.9)	0.7 (-1.0, 2.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
[a] The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.
[c] Final geometric mean antibody concentrations (GMC) in AU/mL were determined using SARS-CoV-2 microneutralisation assay.
[d] Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralising antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
[e] Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Table 7. Summary of geometric mean concentration ratio and seroresponse rate – comparison of individuals 2 years through 5 years of age to participants 18 years through 25 years of age – per-protocol immunogenicity set

		2 years through 5 years n=264	18 years through 25 years n=291	2 years through 5 years/ 18 years through 25 years	
Assay	**Time Point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC Ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralisation assay[c]	28 days after Dose 2	1 410.0 (1 273.8, 1 560.8)	1 390.8 (1 262.5, 1 532.1)	1.0 (0.9, 1.2)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		98.9 (96.7, 99.8)	99.3 (97.5, 99.9)	-0.4 (-2.7, 1.5)	

GMC = Geometric mean concentration

n = number of participants with non-missing data at baseline and at Day 57

* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.

[a] The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.

[c] Final geometric mean antibody concentrations (GMC) in AU/mL were determined using SARS-CoV-2 microneutralisation assay.

[d] Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.

[e] Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Immunogenicity in solid organ transplant recipients

The safety, reactogenicity, and immunogenicity of Spikevax (original) were evaluated in a two-part Phase 3b open-label study in adult solid organ transplant (SOT) recipients, including kidney and liver transplants (mRNA-1273-P304). A 100 microgram (0.5 mL) dose was administered, which was the dose authorised at the time of study conduct.

In Part A, 128 SOT recipients received a third dose of Spikevax (original). In Part B, 159 SOT recipients received a booster dose at least 4 months after the last dose.

Immunogenicity in the study was assessed by measurement of neutralising antibodies against pseudovirus expressing the ancestral SARS-CoV-2 (D614G) strain at 1 month after Dose 2, Dose 3, booster dose and up to 12 months from the last dose in Part A, and up to 6 months from booster dose in Part B.

Three doses of Spikevax (original) induced enhanced neutralising antibody titres compared to pre-dose 1 and post-dose 2. A higher proportion of SOT participants who had received three doses achieved

seroresponse compared to participants who had received two doses. The neutralising antibody levels observed in SOT liver participants who had received three doses was comparable to the post-dose 2 responses observed in the immunocompetent, baseline SARS-CoV-2-negative adult participants. The neutralising antibody responses continued to be numerically lower post-dose 3 in SOT kidney participants compared to SOT liver participants. The neutralising levels observed one month after Dose 3 persisted through six months with antibody levels maintained at 26-fold higher and seroresponse rate at 67% compared to baseline.

A fourth (booster) dose of Spikevax (original) enhanced neutralising antibody response in SOT participants compared to post-dose 3, regardless of the previous vaccines received [mRNA-1273 (Moderna), BNT162b2 or any mRNA-containing combination]; however, SOT kidney participants had numerically lower neutralising antibody responses compared to SOT liver participants

Elderly

Spikevax (original) was assessed in individuals 6 months of age and older, including 3 768 subjects 65 years of age and older. The efficacy of Spikevax (original) was consistent between elderly (≥65 years) and younger adult subjects (18-64 years).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and reproductive and developmental toxicity.

General toxicity

General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low.

Genotoxicity/carcinogenicity

In vitro and *in vivo* genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low. Carcinogenicity studies were not performed.

Reproductive toxicity

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of Spikevax (original) 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. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of Spikevax (original) vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate)
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
Polyethylene glycol 2000 dimyristoyl glycerol (PEG2000-DMG)
Trometamol
Trometamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened multidose vial (Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms/2.5 mL)

9 months at -50ºC to -15ºC.

Within the period of 9 months, after removal from the freezer, the unopened vaccine vial may be stored refrigerated at 2°C to 8°C, protected from light, for a maximum of 30 days. Within this period, up to 12 hours may be used for transportation at 2°C to 8°C (see section 6.4).

Once thawed, the vaccine should not be refrozen.

The unopened vaccine may be stored at 8°C to 25°C up to 24 hours after removal from refrigerated conditions.

Punctured multidose vials (Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms /2.5 mL)

Chemical and physical in-use stability has been demonstrated for 12 hours at 2°C to 25ºC after initial puncture (within the allowed use period of 30 days, at 2°C to 8ºC and including 24 hours at 8°C to 25ºC). From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms/2.5 mL (multidose vials)

Store in a freezer at -50ºC to -15ºC.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after thawing, see section 6.3.
For storage conditions of the multidose vial after first opening, see section 6.3.

Transportation of thawed multidose vials in liquid state at 2°C to 8°C
If transport at -50°C to -15°C is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2°C to 8°C (within the 30 days shelf life at 2°C to 8°C). Once thawed and transported in liquid state at 2°C to 8°C, vials should not be refrozen and should be stored at 2°C to 8°C until use.

6.5 Nature and contents of container

Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms/2.5 mL (multidose vials)

2.5 mL suspension in a (type 1 glass) multidose vial with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal).

Pack size: 10 multidose vials. Each vial contains 2.5 mL.

6.6 Special precautions for disposal and other handling

The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the suspension.

Spikevax 2023-2024 Formula (XBB.1.5) Suspension for Injection 250 micrograms/2.5 mL

The vaccine comes ready to use once thawed.

Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

Verify that the vial has a blue flip-off cap and the product name is Spikevax 2023-2024 Formula. If the vial has a blue flip-off cap and the product name is Spikevax bivalent Original/Omicron BA.4-5, please make reference to the Summary of Product Characteristics for that formulation.

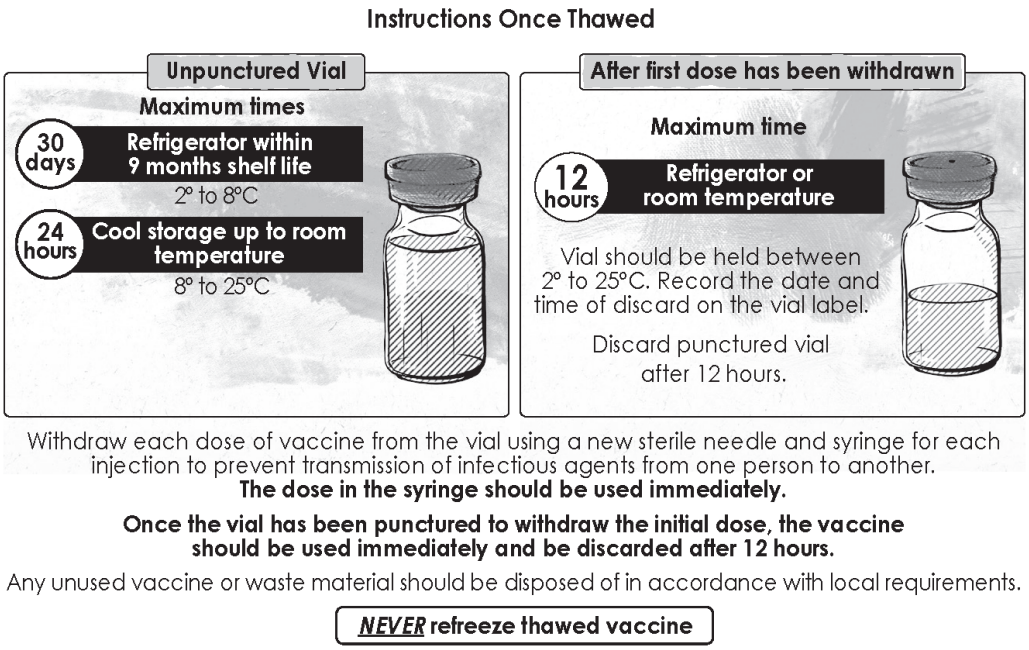
Pierce the stopper preferably at a different site each time.

An additional overfill is included in each multidose vial to ensure that 5 doses of 0.5 mL or a maximum of 10 doses of 0.25 mL can be delivered, depending on the individual's age.

Thaw each multidose vial before use following the instructions below (Table 8). When the vial is thawed in the refrigerator, let it sit at room temperature for 15 minutes before administering.

Table 8. Thawing instructions for multidose vials before use

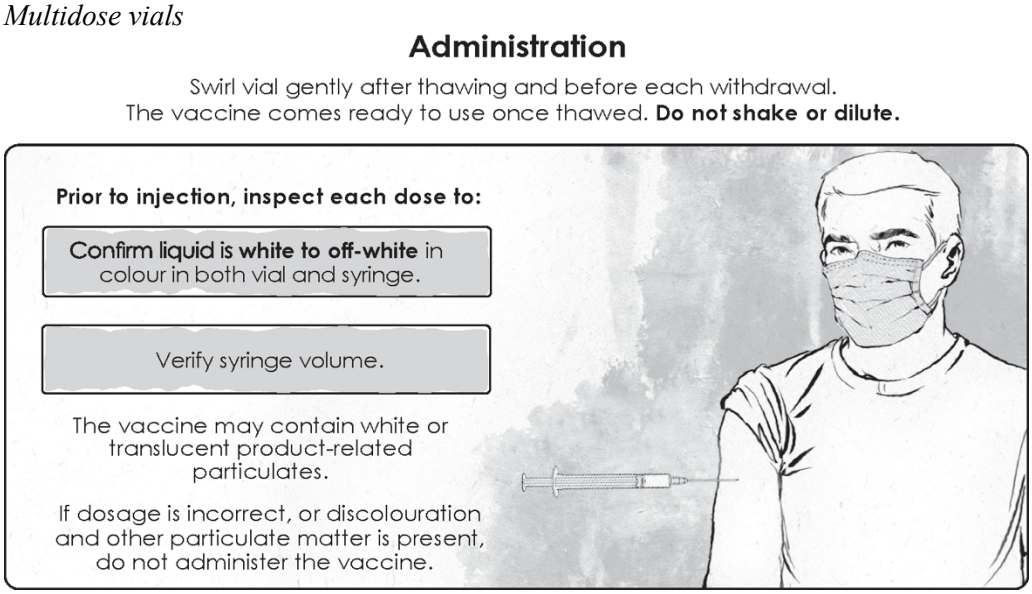
Configuration	Thaw instructions and duration			
	Thaw temperature (in a refrigerator)	**Thaw duration**	**Thaw temperature (at room temperature)**	**Thaw duration**
Multidose vial	2° – 8°C	2 hours and 30 minutes	15°C – 25°C	1 hour



Administration

The vaccine must be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm. Do not administer this vaccine intravascularly, subcutaneously or intradermally.

Multidose vials



Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Hong Kong
February 2024