

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Table 1. Spikevax bivalent Original/Omicron BA.1 qualitative and quantitative composition

| Strength | Container | Dose(s) | Composition per dose |
|--|---|-------------------------|--|
| Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection | Multidose 2.5 mL vial (blue flip-off cap) | 5 doses of 0.5 mL each | One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). |
| | Multidose 5 mL vial (blue flip-off cap) | 10 doses of 0.5 mL each | |

Elasomeran 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.

Imelasomeran contains mRNA, 5'-capped, encoding a full-length, codon-optimised pre-fusion stabilised conformation variant (K983P and V984P) of the SARSCoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
White to off white dispersion (pH: 7.0 – 8.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spikevax bivalent Original/Omicron BA.1 is indicated as a 50 microgram booster dose in adults who previously received the primary vaccination or a primary vaccination with first booster dose of an original monovalent vaccine.

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

4.2 Posology and method of administration

Posology

The dose of Spikevax bivalent Original/Omicron BA.1 is 0.5 mL given intramuscularly.

There should be an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine.

Spikevax bivalent Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

For details on the primary vaccination course for ages 12 and above, please refer to the Summary of Product Characteristics for Spikevax 0.2 mg/mL dispersion for injection.

Paediatric population

The safety and efficacy of Spikevax in children less than 6 years of age have not yet been established. No data are available.

Elderly population

No dosage 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. 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. The second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax.

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 after the second dose, and more often in younger males (see section 4.8). The risk profile appears to be similar for the second and the third dose.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

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. 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.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Spikevax may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with Spikevax may not protect all vaccine recipients.

Excipients with known effect

Sodium

This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL 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 bivalent Original/Omicron BA.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Spikevax bivalent Original/Omicron BA.1 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, Spikevax bivalent Original/Omicron BA.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Spikevax bivalent Original/Omicron BA.1 during breastfeeding.

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to Spikevax is negligible. Observational data from women who were breastfeeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Spikevax bivalent Original/Omicron BA.1 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

Spikevax bivalent Original/Omicron BA.1 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

Participants 18 years of age and older

The safety of Spikevax was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of

age and older who received at least one dose of Spikevax (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 in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 3,726 participants 12 through 17 years of age who received at least one dose of Spikevax (n=2,486) or placebo (n=1,240) (NCT04649151). Demographic characteristics were similar among participants who received Spikevax 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%).

Children 6 through 11 years of age

Safety data for Spikevax in children were collected in an ongoing Phase 2/3 two-part randomised, observer-blind clinical trial conducted in the United States and Canada (NCT04796896). Part 1 is an open-label phase of the trial for safety, dose selection, and immunogenicity and included 380 participants 6 through 11 years of age who received at least 1 dose (0.25 mL) of Spikevax. Part 2 is the placebo-controlled phase for safety and included 4,016 participants 6 through 11 years of age who received at least one dose (0.25 mL) of Spikevax (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 and those who received placebo.

The most frequent adverse reactions in participants 6 through 11 years of age following administration of the primary series 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%).

Tabulated list of adverse reactions from clinical studies and post authorisation experience in children and individuals 6 years of age and older

The safety profile presented below is based on data generated in a placebo- controlled clinical study on 30,351 adults \geq 18 years of age, another placebo-controlled clinical study with 3,726 participants 12 through 17 years of age, another clinical study with 4,002 participants 6 through 11 years of age, and post-marketing experience.

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

Very common (\geq 1/10)

Common (\geq 1/100 to <1/10)

Uncommon (\geq 1/1,000 to <1/100)

Rare (\geq 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 2).

Table 2. Adverse reactions from Spikevax clinical trials and post authorisation experience in children and individuals 6 years 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 |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness |
| | Rare | Acute peripheral facial paralysis** Hypoesthesia Paraesthesia |
| Cardiac disorders | Very rare | Myocarditis Pericarditis |
| Gastrointestinal disorders | Very common | Nausea/vomiting |
| | Uncommon | Abdominal pain*** |
| Skin and subcutaneous tissue disorders | Common | Rash |
| | Rare | Acute and delayed urticaria |
| Musculoskeletal and connective tissue disorders | Very common | Myalgia Arthralgia |
| 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***** |

*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.

**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.

*** Abdominal pain was observed in the paediatric population (5 to 11 years of age): 0.2% in the Spikevax group and 0% in the placebo group.

****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 1 and 2 days, respectively, after vaccination

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

Participants 18 years of age and older (booster dose)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax 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 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). No new safety signals were identified.

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. 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.

Call for reporting:

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.

Please report adverse drug events to:

The National Pharmacovigilance Centre (NPC):

Fax: +966-11-205-7662

SFDA Call Center: 19999

E-mail: npc.drug@sfd.gov.sa

Website: <https://ade.sfd.gov.sa>

You can also report any suspected adverse reactions to:

Pharmacovigilance department in Tabuk Pharmaceuticals:

E-mail: pv.info@tabukpharmaceuticals.com

Tel: +966 4774946; Ext 233

4.9 Overdose

No case of overdose has been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

Spikevax (elasomeran) and Spikevax bivalent Original/Omicron BA.1 (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.

Clinical efficacy

Immunogenicity in participants 18 years of age and older – 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 bivalent Original/Omicron BA.1 (25 micrograms/25 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 6422.3 (5990.1, 6885.7) and 5286.6 (4887.1, 5718.9) 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 \geq 0.67).

The estimated Day 29 neutralising antibody GMTs against Omicron, BA.1 were 2479.9 (2264.5, 2715.8) and 1421.2 (1283.0, 1574.4) 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).

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. 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.

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 (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 3.

Table 3. Vaccine efficacy analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – per-protocol set

| Age group (years) | Spikevax | | | Placebo | | | % Vaccine efficacy (95% CI)* |
|-------------------|------------|------------------|---|------------|------------------|---|------------------------------|
| | 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 | |
| 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) |
| ≥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 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% confidence interval 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.

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 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 or saline placebo 1 month apart.

A secondary efficacy analysis was performed in 3,181 participants who received 2 doses of either Spikevax (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 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 group and 4 symptomatic COVID-19 cases in the placebo group.

Immunogenicity in adolescents 12 to 17 years of age

A non-inferiority analysis evaluating SARS-CoV-2 50% neutralising titers 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 titers 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.

Clinical efficacy in children 6 through 11 years of age

The paediatric study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of Spikevax in children ages 6 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 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 (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 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 group and four COVID-19 cases (0.5%) in the placebo group.

Immunogenicity in children 6 through 11 years of age

An analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in a subset of children aged 6 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 titers in children 6 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 participants 18 years of age and older – after booster dose (0.25 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax 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 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 18 years of age and older

Safety and immunogenicity of a heterologous booster with Spikevax were studied in an investigator-initiated trial 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 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 trial 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 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.

Pre-boost and post-boost neutralising antibody against the B.1.617.2 (Delta) variant in adults

Results of the pseudovirus neutralisation assay (PsVNA) against the B.1.617.2 (Delta) variant determined pre-booster and on Day 29 post-booster showed that administration of a booster dose of Spikevax (0.25 mL, 50 micrograms) in adults induced a 17-fold rise in neutralising antibodies against the Delta variant compared with pre-booster levels (GMFR = 17.28; 95% CI: 14.38, 20.77; n=295).

Neutralising antibody against the B.1.617.2 (Delta) variant in children 6 through 11 years of age
Serum samples of the per-protocol immunogenicity subset (n=134) of the ongoing paediatric study obtained at baseline and on Day 57 were tested in a PsVNA based on the B.1.617.2 (Delta) variant. In children 6 through 11 years of age, the GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant (measured by PsVNA). Furthermore, 99.3% of children met the definition of seroresponse.

Elderly population

Spikevax was assessed in individuals 12 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of Spikevax was consistent between elderly (≥ 65 years) and younger adult subjects (18-64 years).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with the Spikevax in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

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 repeat 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 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 mRNA-1273 vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid SM-102

Cholesterol

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)

1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (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 bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection]

9 months at -25°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days. Within this period, up to 12 hours may be used for transportation.

Once thawed, the vaccine should not be re-frozen.

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

Punctured multidose vial [Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection]

Chemical and physical in-use stability has been demonstrated for 19 hours at 2°C to 25°C after initial puncture (within the allowed use period of 30 days at 2°C to 8°C and 24 hours at 8°C to 25°C). 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

Multidose vials [Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection]

Store frozen between -50°C to -15°C.

Keep the vial in the outer carton to protect from light.

For storage conditions after thawing and first opening, see section 6.3.

Transportation of thawed 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

Multidose vials [Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection]

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

Each vial contains 2.5 mL.

Pack size: 10 multidose vials

Spikevax 0.1 mg/mL dispersion for injection

2.5 mL dispersion in a (type 1 glass or type 1 equivalent glass or cyclic olefin polymer with inner barrier coating) multidose vial with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal).

Each vial contains 2.5 mL.

Pack size: 10 multidose vials

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 dispersion.

Vials are stored frozen between -50°C to -15°C.

Frozen Storage



Multidose vials [Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection]

The vaccine comes ready to use once thawed.

Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal. Pierce the stopper preferably at a different site each time.

An additional overfill is included in each vial to ensure that 5 doses of 0.5 mL can be delivered.


Verify that the vial has a blue flip-off cap and the product name is Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection. If the vial has a blue flip-off cap and the product name is Spikevax 0.1 mg/mL dispersion for injection, please make reference to the Summary of Product Characteristics for that formulation.

Thaw each vial before use

Images for illustrative purposes only

2 hours and 30 minutes in refrigerator

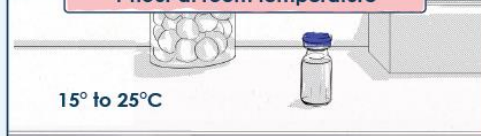
2° to 8°C
(within the 30 days shelf life at 2° to 8°C)



OR

1 hour at room temperature

15° to 25°C



Let vial sit at room temperature for 15 minutes before administering

Instructions Once Thawed

Unpunctured Vial

Maximum times

30 days Refrigerator
2° to 8°C

24 hours Cool storage up to room temperature
8° to 25°C



After first dose has been withdrawn

Maximum time

19 hours Refrigerator or room temperature

Vial should be held between 2° to 25°C. Record the date and time of discard on the vial label.
Discard punctured vial after 19 hours.



Withdraw each dose of vaccine from the vial using a new sterile needle and syringe for each injection to prevent transmission of infectious agents from one person to another.
The dose in the syringe should be used immediately.

Once the vial has been punctured to withdraw the initial dose, the vaccine should be used immediately and be discarded after 19 hours.

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

NEVER refreeze thawed vaccine

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

Administration


Swirl vial gently after thawing and before each withdrawal.
The vaccine comes ready to use once thawed. Do not shake or dilute.

Prior to injection, inspect each dose to:

- Confirm liquid is white to off-white in colour in both vial and syringe.
- Verify syringe volume.

The vaccine may contain white or translucent product-related particulates.

If dosage is incorrect, or discolouration and other particulate matter is present, do not administer the vaccine.



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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1507/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2021
Date of latest renewal: 03 October 2022

10. DATE OF REVISION OF THE TEXT

10/2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.