

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial that contains 5 doses of 0.5 mL or 10 doses of 0.25 mL each.

One dose (0.5 mL) contains 25 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles) and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

One dose (0.25 mL) contains 12.5 micrograms of elasomeran and 12.5 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

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 is a single-stranded 5'-capped messenger RNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1).

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 booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older, who have previously received at least a primary vaccination course against COVID-19 (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

12 years of age and older

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

6 years through 11 years of age

The dose of Spikevax bivalent Original/Omicron BA.1 is 0.25 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 mRNA 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 individuals 6 years of age and older, please refer to the Summary of Product Characteristics for Spikevax (original).

Paediatric population

The safety and efficacy of Spikevax bivalent Original/Omicron BA.1 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.

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 the vaccine should not be given to those who have experienced severe allergic reactions (e.g. anaphylaxis, generalised urticaria) to an earlier dose of Spikevax (original) or Spikevax bivalent Original/Omicron BA.1.

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.

Immunocompromised individuals

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

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

As with all vaccines, vaccination with Spikevax bivalent Original/Omicron BA.1 may not protect all vaccine recipients.

Excipients with known effect

Sodium

This vaccine contains less than 1 mmol sodium (23 mg), 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 (original) or 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.

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. 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

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.

If required, symptomatic treatment with analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used.

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 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 (original). 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 (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 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 (original) 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.

Tabulated list of adverse reactions

The safety profile presented below is based on data generated in several placebo-controlled clinical studies of Spikevax (original):

- 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
- 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 1).

Table 1. Adverse reactions from Spikevax (original) clinical trials and post-authorisation experience in children and individuals 6 years of age and older

MedDRA System Organ Class	Frequency	Adverse reactions
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Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis
	Not known	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
	Common	Diarrhoea
	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.

† 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.

Spikevax (original) booster dose - Adults

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 – Adults

The safety, reactogenicity, and immunogenicity of a second 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 Spikevax (original) 50 microgram booster dose.

Spikevax bivalent Original/Omicron BA.1 had a reactogenicity and safety profile similar to that of Spikevax (original) given as a second booster dose (median follow-up period of 113 days and 127 days, respectively). The frequency of adverse reactions after immunisation with Spikevax bivalent Original/Omicron BA.1 was also similar 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).

Description of selected adverse reactions

Myocarditis

The increased risk of myocarditis after vaccination with Spikevax (original) or Spikevax bivalent Original/Omicron BA.1 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. If you are concerned about an adverse event, it should be reported on a Yellow Card. Reporting forms and information can be found at <https://coronavirus-yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store and include the vaccine brand and batch/Lot number if available. Alternatively, adverse events of concern in association with Spikevax (original) or Spikevax bivalent Original/Omicron BA.1 can be reported to Moderna on the toll-free number: 08000857562 or via www.modernacovid19global.com. Please do not report the same adverse event(s) to both systems as all reports will be shared between Moderna and MHRA (in an anonymised form) and dual reporting will create unnecessary duplicates.

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: Vaccine, other viral vaccines, ATC code: J07BN01

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

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 (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% 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.

The level of protection gained after dose 1 was assessed in a post-hoc analysis in the mITT Set. In the interval 14 days after dose 1 to dose 2, there were 35 cases of COVID-19 on placebo and only 2 in the vaccine group. This indicates that the vaccine may provide some level of protection from 14 days after the first dose and before receiving dose 2. For optimal protection, two doses should be administered one month apart.

Clinical efficacy of Spikevax (original) 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 of Spikevax (original) in adolescents 12 through 17 years of age

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% 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 7172.0 (95% CI: 6610.4, 7781.4). 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 of Spikevax (original) in children 6 years 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 efficacy of Spikevax (original) 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 (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 of Spikevax (original) in children 6 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 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 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 through 11-year-olds 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 5847.5 (95% CI: 4999.6, 6839.1). The SRR was 100 (95% CI: 95.9, 100.0). Serum nAb levels for children 6 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.

Immunogenicity in adults – after Spikevax (original) 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 in adults – after Spikevax bivalent Original/Omicron BA.1 booster dose (0.5 mL, 50 micrograms)

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). Study P205 Part G and Part F enrolled participants who had previously received 2 doses of Spikevax (original) (100 micrograms) as a primary series and a booster dose of Spikevax (original) (50 micrograms) at least 3 months prior to enrollment. In Part G, 437 participants received a second booster dose of Spikevax bivalent Original/Omicron BA.1 (50 micrograms). In Part F, 377 participants received a second booster dose of Spikevax (original) (50 micrograms). The Part F 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 that includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster) (Table 3).

Table 3. Ancestral SARS-CoV-2 (D614G) and Omicron (BA.1) neutralising antibody titres (ID₅₀) - Spikevax bivalent Original/Omicron BA.1 50 µg and Spikevax (original) 50 µg administered as second booster doses

Antibody: PsVNA nAb ID ₅₀ titres	Omicron variant		Ancestral SARS-CoV-2	
	P205 Part G Spikevax bivalent Original/ Omicron BA.1 50 µg (N=334)	P205 Part F Spikevax (original) 50 µg (N=260)	P205 Part G Spikevax bivalent Original/ Omicron BA.1 50 µg (N=334)	P205 Part F Spikevax (original) 50 µg (N=260)
	Pre-booster, n	334	260	334
Observed GMT (95% CI) ^a	298.1 (258.8, 343.5)	332.0 (282.0, 390.9)	1266.7 (1120.2, 1432.5)	1521.0 (1352.8, 1710.2)
Day 29, n	334	260	334	260
Observed GMT (95% CI) ^a	2372.4 (2070.6, 2718.2)	1473.5 (1270.8, 1708.4)	5977.3 (5321.9, 6713.3)	5649.3 (5056.8, 6311.2)
Observed GMFR (95% CI) ^a	8.0 (7.2, 8.8)	4.4 (4.0, 5.0)	4.7 (4.4, 5.1)	3.7 (3.4, 4.0)
GLSM [estimated GMT] (95% CI) ^b	2479.9 (2264.5, 2715.8)	1421.2 (1283.0, 1574.4)	6422.3 (5990.1, 6885.7)	5286.6 (4887.1, 5718.9)
GMR (97.5% CI)^b	1.7 (1.5, 2.0)		1.2 (1.1, 1.4)	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold-rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID₅₀ = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome-2; n = number of participants with non-missing data at the corresponding timepoint.

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

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

In this immunogenicity set, GMRs remained similar at 3 months to those observed at Day 29. Omicron-BA.1-neutralising antibody estimated GMT was significantly higher (997.5 [898.4, 1107.4]) than that of Spikevax (original) (602.7 [534.7, 679.4]) with a GMR of 1.7 [1.4, 2.0]. SARS-CoV-2 (D614G)-neutralising antibody estimated GMTs were 3595.6 [3334.8, 3876.8] and 3257.3 [2986.3, 3552.9], respectively, with a GMR of 1.10 [0.97, 1.26].

Observed neutralising antibody titres for Omicron subvariants BA.4/5 after Spikevax bivalent Original/Omicron BA.1 booster dose

Table 4 presents the summary of the observed neutralising antibody GMTs and GMFRs against Omicron BA.4/BA.5 for participants who received either the Spikevax bivalent Original/Omicron BA.1 50 microgram booster vaccine (Part G) or the Spikevax (original) 50 microgram booster vaccine (Part F) as a second booster dose (4th dose). This exploratory analysis was conducted in the immunogenicity set that includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster).

Table 4. Summary of neutralising antibody geometric mean titres for the Omicron BA.4/BA.5 variant - comparison between Spikevax bivalent Original/Omicron BA.1 50 µg and Spikevax (original) 50 µg booster doses

	PPSI - Neg	
	P205 Part G Spikevax bivalent Original/Omicron BA.1 50 µg (N=334)	P205 Part F Spikevax (original) 50 µg (N=260)
Pre-booster, n^a	334	260
Observed GMT (95% CI) ^{a,b}	115.6 (98.5, 135.6)	139.7 (119.5, 163.3)
Day 29, n^a	333	260
Observed GMT (95% CI) ^{a,b}	727.4 (632.8, 836.1)	492.1 (431.1, 561.9)
Observed GMFR (95% CI) ^{a,b}	6.3 (5.7, 6.9)	3.5 (3.2, 3.9)
GLSM [Estimated GMT] (95% CI) ^b	776.4 (719.5, 837.9)	458.3 (420.6, 499.3)
GMR (95% CI)^b	1.7 (1.5, 1.9)	

Abbreviations: CI = confidence interval; GLSM=geometric least squares mean; GMFR = geometric mean fold-rise (post-baseline/baseline titres); GMT = geometric mean titre; ID₅₀ = 50% inhibitory dilution; LOD = limit of detection; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PPSI = per-protocol set for immunogenicity; PPSI – Neg = per-protocol Set for immunogenicity – SARs-CoV-2 Negative at baseline; PPSI – Pos = per-protocol Set for immunogenicity – SARS-CoV-2 Positive at baseline; PsVNA = pseudotyped virus neutralization assay.

Note: antibody values reported as below the lower limit of detection are replaced by 0.5 x LOD.

^a Number of subjects with non-missing data at the timepoint (baseline or post-baseline).

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

Immunogenicity of a booster dose of Spikevax (original) 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 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 (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 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 (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.

Spikevax (original) - 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 (original) (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).

Spikevax (original) - 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 (original) was assessed in individuals 6 years 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). Spikevax bivalent Original/Omicron BA.1 was assessed in 437 individuals 18 years of age and older (P205 Part G, safety analysis set), including 38 subjects 75 years of age and older. A total of 174 of the 437 participants (39.8%) were ≥ 65 years of age.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with Spikevax (original) and Spikevax bivalent Original/Omicron BA.1 in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. New information on this medicinal product will be reviewed at least every year and this SmPC will be updated as necessary.

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 (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

This vaccine contains polyethylene glycol/macrogol (PEG) as part of PEG2000-DMG.

SM-102 (heptadecan-9-yl 8-{{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate)

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

9 months at -50°C to -15°C.

Within the period of 9 months, after removal from the freezer, the unopened vaccine 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).

Chemical and physical stability has also been demonstrated for unopened vaccine vials when stored for 12 months at -50°C to -15°C **provided that once thawed and stored at 2°C to 8°C**, protected from light, **the unopened vial will be used up within a maximum of 14 days** (instead of 30 days, when stored at -50°C to -15°C for 9 months), but not exceeding a total storage time of 12 months.

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

Chemical and physical in-use stability has been demonstrated for 6 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

Store frozen between -50°C to -15°C.

Store in the original carton 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 or 14 days shelf life, respectively, 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 vial (0.1 mg/mL)

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

6.6 Special precautions for disposal

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.

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.

Spikevax bivalent Original/Omicron BA.1 vials are multidose.

Five (5) doses (of 0.5 mL each) or ten (10) doses (of 0.25 mL each) can be withdrawn from each vial. An additional overfill is included in each vial to ensure that 5 doses of 0.5 mL or 10 doses of 0.25 mL can be delivered.

Thaw each multidose vial before use following the instructions below (Table 5). When the vial is thawed in the refrigerator, let it sit at room temperature for 15 minutes before administering.

Table 5. 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

Verify that the vial has a blue flip-off cap and the product name is Spikevax bivalent Original/Omicron BA.1. 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.

Thawed vials and filled syringes can be handled in room light conditions.

Thaw each vial before use
Images for illustrative purposes only

2 hours and 30 minutes in refrigerator

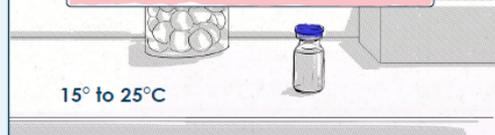
2° to 8°C
(within the 30 days shelf life at 2° to 8°C)



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



Cool storage up to room temperature

8° to 25°C

After first dose has been withdrawn

Maximum time

6

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 6 hours.



NEVER refreeze thawed vaccine

Administration

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

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.



7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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