▼ 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 dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each.

One dose (0.5 mL) of the primary series contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

One dose (0.25 mL) of the booster contains 50 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcriptionfrom the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 embedded in the SM-102 lipid nanoparticles [composed of the lipids, Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (SM-102)].

Spikevax does not contain any preservatives, antibiotics, adjuvants, or human- or animal-derived materials. The vial stopper does not contain natural rubber latex.

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 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary series

Individuals 12 years of age and older
Spikevax (100micrograms, 0.5mL) is a two-dose regimen

Individuals 6 through 11 years of age
Spikevax is administered as a course of 2 (two) 50 microgram doses (0.25mL each).

The second dose should be administered one month after the first dose (see sections 4.4 and 5.1).

Immunocompromised individuals
A third dose of the Spikevax (0.5 mL) administered at least 28 days following the first two doses of this vaccine is authorised for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster dose
Individuals 12 years of age and older
Spikevax is administered intramuscularly as a single dose (0.25 mL) at least 3 months after completing a primary series. Local health authority recommendations for booster interval should be followed.

Interchangeability
Primary series

The interchangeability of Spikevax with other COVID-19 vaccines to complete the primary vaccination course has not been established.

Individuals who have received one dose of Spikevax (0.5 mL, 100 micrograms) should receive a second dose of Spikevax (0.5 mL, 100 micrograms) to complete the primary vaccination course.

Children aged 6 through 11 years who have received one dose of Spikevax (0.25 mL, 50 micrograms) should receive a second dose of Spikevax (0.25 mL, 50 micrograms) to complete the primary vaccination course.

Booster dose in individuals 12 years of age and older
A single booster dose of Spikevax (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorised or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorised for a booster dose of Spikevax.

Paediatric population
The safety and efficacy of Spikevax in children and adolescents less than 12 years of age have not yet been established. No data are available.

Elderly population
Clinical studies of Spikevax included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In the ongoing adult study of primary series dosing (0.5 mL), 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of

participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 86.4% (95% CI 61.4, 95.2) compared to 95.6% (95% CI 90.6, 97.9) in participants 18 to <65 years of age. Overall, there were no notable differences in the safety profiles observed in participants 65 years of age and older and younger participants.

In the ongoing clinical study of a single booster dose (0.25 mL), 22.2% (n=38) of participants were 65 years of age and older. This study did not include sufficient numbers of participants 65 years of age and older to determine whether they respond differently than younger participants. Some local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older compared to participants 18 through 64 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

Spikevax is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or to a previous dose of Spikevax. See excipients listed in 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 bereadily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation is recommended following vaccination as follows:

- 30 minutes:
  - People with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy.
  - People with a history of anaphylaxis due to any cause.
- 15 minutes:

- All other persons.

A 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 have been very rare reports of myocarditis and pericarditis occurring after vaccination with Spikevax. The majority of the cases have been reported in young males, and shortly after the second primary dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

Altered immunocompetence

If Spikevax is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response to the vaccine may be diminished.

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), safety and effectiveness of a third dose of Spikevax have been evaluated in participants who received solid organ transplants. The administration of a third vaccine dose (0.5 mL) appears to be only moderately effective in increasing antibody titers. Patients should be counselled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated as appropriate for their health status.

Persons at risk of bleeding

As with other intramuscular injections, Spikevax should be given with caution in individuals with bleeding disorders, such as haemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of haematoma following the injection.

Acute illness

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

Limitations of vaccine effectiveness

Vaccination with Spikevax may not protect all recipients.

Excipients with known effect

Sodium

This vaccine contains 0.033 mg of sodium per 0.5 mL dose and is considered 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Other vaccines

There are no data to assess the concomitant administration of Spikevax with other vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate and well-controlled studies of Spikevax use in pregnant women have been conducted. Available data on Spikevax administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

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

Breastfeeding

Data are not available to assess the effects of Spikevax on the breasfed infant or on milk production/excretion. Pregnant or breastfeeding mothers are advised to discuss their options with their healthcare providers.

Fertility

No data are available on fertility in humans with use of Spikevax.

4.7 Effects on ability to drive and use machines

No studies on the effects of the Spikevax on the ability to drive and use machines have been performed.

Some of the effects mentioned under section 4.8 "Undesirable Effects" may 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 profile presented below is based on data generated in a placebo-controlled clinical study on 30,351 participants ≥ 18 years of age.

Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants. The most frequently reported adverse

reactions after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70.1% any grade; 10.1% grade ≥ 3), headache (64.9% any grade; 5.8% grade ≥ 3), myalgia (61.6% any grade; 9.1% grade ≥ 3) arthralgia (46.5%; 5.4% grade ≥ 3), and chills (45.5% any grade; 1.4% grade ≥ 3). The majority of local and systemic adverse reactions had a median duration of 1 to 3 days.

Overall, there was a higher reported rate of adverse reactions in adults aged 18 to < 65 years than in those aged 65 years and above.
Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. In the participants who received the vaccine, solicited systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1. Grade 3 systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1.

Immunocompromised participants 18 years of age and older
From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*) in 60 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported.

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 trial (Study 2, NCT04649151) 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). Overall, 51.4% were male, 48.6% were female, 11.6% were Hispanic or Latino, 83.9% were White, 3.4% were African American, 5.9% were Asian, 0.5% were American Indian or Alaska Native, <0.1% were Native Hawaiian or Pacific Islander, 1.0% were other races, and 4.5% were multiracial. Demographic characteristics were similar among participants who received Spikevax and those who received placebo.

In a clinical study, the most frequent adverse reactions in participants 12 through 17 years of age were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%), chills (49.1%), arthralgia (34.6%) axillary swelling/tenderness (34.6%), nausea/vomiting (29.3%), swelling at the injection site (27.7%), erythema at the injection site (25.8%), and fever (13.7%).

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 4,002 participants 6 through 11 years of age who received at least one dose (0.25 mL) of Spikevax (n=3,007) or placebo (n=995). 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 children 6 through 11 years of age following administration of the primary series were injection site pain (98.4%), fatigue (73%), headache (62%), myalgia (35.2%), chills (34.6%), nausea/vomiting (29.2%), axillary swelling/tenderness (26.9%), fever (25.9%), injection site erythema (24.3%), injection site swelling (22.5%), and arthralgia (21.2%).

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

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,346 adults ≥ 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 (≥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 clinical trials and post authorisation experience in individuals 6 years of age and older

MedDRA system organ class	**Frequency**	**Adverse reaction(s)**
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** Hypoaesthesia/ paraesthesia
Cardiac disorders	Very rare	Myocarditis Pericarditis
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
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

MedDRA system organ class	Frequency	Adverse reaction(s)
		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 vaccine group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
***There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination.

Booster dose participants
Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of Spikevax in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 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) at least 6 months after receiving the second dose of the primary series. The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series.

Booster dose following primary vaccination with another authorised or approved COVID-19 vaccine
The safety of Spikevax (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of Spikevax (0.25 mL) booster dose administered following completion of a Spikevax primary series (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of Spikevax. In this study, adults who had completed primary vaccination with Spikevax 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2- dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARSCoV-2 infection were randomised 1:1:1 to receive a booster dose of one of three vaccines: Spikevax (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following Spikevax heterologous booster dose (0.5 mL) did not identify any new safety concerns, as compared with adverse reactions reported following Spikevax primary series doses or homologous booster dose (0.25 mL).

Post-authorisation experience

Anaphylaxis, myocarditis, and pericarditis have been reported following Spikevax administration (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. Itallows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the FDA at (02) 8809 5596 or report online to https://www.fda.gov.ph/covid-19-vaccine-report-a-side-effect/ and include batch/lot number if available.

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 encodes for the pre-fusion stabilised Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection.

The expressed Spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

5.2 Clinical studies

Efficacy in adults 18 years of age and older

Study 1 was randomised, placebo-controlled, observer-blind clinical study conducted in participants 18 years of age and older who were at increased risk of COVID-19 disease (NCT04470427). In addition, pre-specified cohorts of participants who were either ≥65 years of age or 18 to < 65 years of age with comorbid medical conditions were included. A total of 30,351 participants 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 a 2-dose regimen (at 0 and 1 month) of either Spikevax (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-

2 status, and did not develop confirmed COVID-19 within 14 days after the second dose (Table 2).
The PPS study population included 47.4% female, 52.6% male, 79.5% White, 19.7% Hispanic or Latino, and 9.7% African American, 4.6% Asian, and 6.2% other. The median age of participants was 53 years (range 18-95). Of the study participants, 22.6% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection). 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.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) and by a clinical adjudication committee.

Table 2: Primary 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)*
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants 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)

[#] COVID-19: symptomatic COVID-19 requiring positive RT-PCR (reverse transcription-polymerase chain reaction) result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*VE and 95% CI from the stratified Cox proportional hazard model

Efficacy against severe COVID-19

Among all participants in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 persons/years). Vaccine efficacy against severe COVID-19 was 100% (Table 3).

Table 3: Secondary efficacy analysis: confirmed severe COVID-19[#] cases starting 14 days after the 2nd dose – per-protocol set

Endpoint	Spikevax			Placebo			% Vaccine efficacy (95%
	Participants N	COVID-19 cases n	Incidence rate of COVID-	Participants N	COVID-19 cases n	Incidence rate of COVID-	

			19 per 1,000 person-years			19 per 1,000 person-years	CI)*
Severe* cases 14 days after Dose 2	14,134	0	NA	14,073	30	9.138	100%

#Severe COVID-19 cases are defined as a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:
-Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
-Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
-Significant acute renal, hepatic or neurologic dysfunction, OR
-Admission to an intensive care unit or death.
* VE and 95% CI from the stratified Cox proportional hazard model

Additional efficacy analyses

Subgroup analyses of vaccine efficacy 14 days after Dose 2 can be found in Table 4.

Table 4: Subgroup analyses of vaccine efficacy - COVID-19 14 days after Dose 2 per adjudication committee assessments (primary efficacy analysis set) – per-protocol set

Subgroup	Spikevax			Placebo			% Vaccine efficacy (95% CI)**
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	
Overall High risk*	3,206	4	5.227	3,167	43	57.202	90.9 (74.7, 96.7)
High risk 18 to <65	2,155	2	3.947	2,118	35	70.716	94.4 (76.9, 98.7)
Not High risk 18 to <65	8,396	5	2.594	8,403	121	63.054	95.9 (90.0,98.3)
Females	6,768	7	4.364	6,611	98	62.870	93.1 (85.2,96.8)
Males	7,366	4	2.352	7,462	87	50.730	95.4 (87.4,98.3)

* Participants at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age
** VE and 95% CI from the stratified Cox proportional hazard model

Immunogenicity in immunocompromised recipients
From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), a separate randomised controlled study has been conducted in 120 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years). A third dose (0.5 mL) of Spikevax was administered to 60 participants approximately 2 months after they had received a second dose; saline placebo was given to 60 individuals for comparison (NCT04885907). Significant increases in levels of SARS-CoV-2 antibodies occurred four weeks after the third dose in 55.0% of participants in the Spikevax group (33 of 60) and 17.5% of participants in the placebo group (10 of 57).

Efficacy in adolescents 12 through 17 years of age
Study 2 is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of Spikevax in adolescents ages 12 to 17 years in the United States (NCT04649151). 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. Participants will be followed for efficacy and safety until 1 year after the second dose.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Spikevax (n=2,163) or placebo (n=1,073), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set). In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races. 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 the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription-polymerase chain reaction). Listed symptoms were fever (temperature $> 38^{\circ}C/\geq 100.4^{\circ}F$), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea.

There were 2 COVID-19 cases in the Spikevax group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% confidence interval of 67.8% to 99.2%) (Table 5).

Table 5: Efficacy analysis: COVID-19* in participants 12 to 17 years of age starting 14 days after Dose 1 – modified intent-to-treat set

Spikevax			Placebo			% Vaccine efficacy (95% CI)†
Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per	Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per	
2,163	2	3.828	1,073	13	52.473	92.7 (67.8, 99.2)

* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.

† Vaccine efficacy defined as 1 — ratio of incidence rate (Spikevax vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Immunogenicity in adolescents 12 through 17 years of age

In Study 2 (NCT04649151), an analysis was conducted of SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in Study 2 and in participants aged 18 through 25 in Study 1 who had no immunologic or virologic evidence of prior COVID-19 at baseline. Noninferior immune responses and seroresponse rates were demonstrated in a comparison of adolescents aged 12 through 17 years to participants aged 18 through 25 (Table 6).

Table 6: Summary of geometric mean titer and seroresponse rate – comparison of adolescents aged 12 through 17 to participants aged 18 through 25 – per-protocol immunogenicity subset

Assay	Time point	Spikevax		12 through 17 years/ 18 through 25 years	
		12 through 17 years n=340	18 through 25 years n=305		
		GLSM (95% CI)*	GLSM (95% CI)*	GMR (95% CI)†	Met noninferiority objective (Y/N)‡
SARS-CoV-2 neutralisation assay – ID50 (titer)§	28 days after Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	1.08 (0.94, 1.24)	Y
		Seroresponse % (95% CI)¶	**Seroresponse % (95% CI)¶**	**Difference in seroresponse rate % (95% CI)#**	
		98.8 (97.0, 99.7)	98.6 (96.6, 99.6)	0.2 (-1.8, 2.4)	

GLSM = Geometric least squares mean

GMR = Geometric mean ratio

n = Number of subjects with non-missing data at the corresponding timepoint

* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
† The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in Study 2 and young adults in Study 1) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
‡ Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.
§ SARS-CoV-2 50% inhibitory dose (ID50) neutralisation titers were determined using a SARS-CoV-2 Spike-Pseudotyped Virus Neutralisation Assay. Quantification of SARS-CoV-2 neutralising antibodies utilises lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Neutralisation is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.
¶ Seroresponse due to vaccination specific to pseudovirus neutralising antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
# Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

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 Spiekvax or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until 1 year after the second dose.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of October 6, 2021 was performed in 3,556 participants who received two doses (0.25 mL at 0 and 1 month) of either Spikevax (n=2,678) or placebo (n=878), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set [mITT]). Between participants who received Spikevax and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 7.

Table 7: Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1 – modified intent-to-treat set

	Spikevax N=2,672		**Placebo** N=877		**% Vaccine Efficacy (95% CI)***
	Cases (n)	**Incidence Rate of COVID-19 per 1,000 Person-Years**	**Cases (n)**	**Incidence Rate of COVID-19 per 1,000 Person-Years**	
COVID-19 Cases -	0	0	13	152.027	100.0 (89.3, NE)
COVID-19 Cases -	3	11.399	14	163.810	93.0 (75.1, 98.7)
SARS-CoV-2 Infections (regardless of symptoms)[c]	16	60.958	26	306.853	80.1 (61.5, 90.0)
Asymptomatic SARS-CoV-2 Infections[d]	13	49.529	12	141.625	65.0 (16.1, 85.3)

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.

NE = Not estimable

***** Vaccine efficacy defined as 1 — ratio of incidence rate (Spikevax vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

[a] Participant must have experienced at least two of the following systemic symptoms: fever (≥38°C / ≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR.

[b] Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

[c] A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.

[d] Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

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 subset of children aged 6 through 11 (n=134) in the paediatric study and in participants aged 18 through 25 (n=296) in the adult

study (NCT04796896). 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 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). 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 booster dose participants
Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of Spikevax in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Spiekvax primary series. In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL) at least 6 months after receiving the second dose in the primary series. A single booster dose (0.25 mL) was shown to be immunogenic at Day 29 post-booster dose and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in Study 1.

Immunogenicity of a booster dose following primary vaccination with another authorised or approved COVID-19 vaccine in adults 18 years of age and older
Effectiveness of Spikevax (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of Spikevax (0.25 mL) booster dose administered following completion of a Spikevax primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of Spikevax. In this study, adults who had completed primary vaccination with Spikevax 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Spikevax, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to Spikevax (0.5 mL) was demonstrated regardless of primary vaccination.

Immunogenicity in adult participants against the B.1.617.2 (Delta) variant
Serum samples were obtained from participants in Study 3 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralisation assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of Spikevax booster (50 mcg) induced an 18-fold rise in neutralising titers against the Delta variant compared with pre-booster levels (Geometric mean fold rise (GMFR) = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall Study 3 (Part B) group (n = 293), the pre-booster neutralising antibodies (nAb) Geometric mean titre (GMT) for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n = 293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50 µg mRNA-1273 prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyses of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Spikevax booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Spikevax booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89]), it also was able to broaden and increase nAb levels against Delta variant.

Immunogenicity in children against the B.1.617.2 (Delta) variant
Additional data on the immunogenicity of Spikevax against the Delta variant comes from paediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per-protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 mcg of Spikevax
, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

5.2 Pharmacokinetic properties

Not applicable.

Carcinogenesis, mutagenesis, impairment of fertility
Conventional studies of repeat dose toxicity and reproductive and developmental toxicity in animals and *in vitro* did not reveal any risks for humans.

General toxicity
Intramuscular administration of mRNA to rats (up to 4 doses exceeding the human dose once every 2 weeks, resulting in higher doses in rats due to body weight differences) revealed some injection erythema and oedema and transient changes in haematology (neutrophils, eosinophils, lymphocytes, activated partial thromboplastin time, fibrinogen), chemistry (albumin and globulin), and increased cellularity and/or inflammation of lymphoid organs consistent with an inflammatory response, as well as vacuolation or hypertrophy in hepatocytes or Kupffer cells, without evidence of liver injury. All effects were reversible.

Genotoxicity/carcinogenicity
In vitro and in vivo genotoxicity studies were conducted with the novel lipid components of the vaccine. Results suggest the genotoxicity potential to humans is low. Carcinogenicity studies were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (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 injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
9 months at -50ºC to -15ºC.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30days.

Once thawed the vaccine should not be re-frozen.

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

Vials may be held for up to 12 hours at 2°C to 25ºC after initial puncture.

6.4 Special precautions for storage

Spikevax multiple-dose vials are stored frozen between -50º to -15ºC (-58º to 5ºF).

Any freezer that reliably maintains an average temperature between -50° and -15°C (-58° to 5°F) and has a separate sealed freezer door is acceptable for storing Spikevax.

Spikevax can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured). Do not refreeze.

The total storage time of a vial after removal from refrigerated conditions should not exceed 24 hours at 8° to 25°C (46° to 77°F). Do not refreeze.

Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 12 hours. Do not refreeze.

Protect from light.

Transportation of thawed vials in liquid state at 2°C to 8°C (36° to 46°F)

If transport at -50°C to -15°C C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2°C to 8°C (36° to 46°F)
and under routine road and air transport conditions with shaking and vibration minimised. Once thawed and transported in liquid state at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

6.5 Nature and contents of container

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

Each vial contains 5 mL.

Pack size: 10 multidose vials

6.6 Special precautions for disposal and other handling

Spikevax vials are for multiple use. Ten (10) doses of 0.5 mL volume each or a maximum of twenty (20) doses of 0.25 mL volume can be withdrawn from each multiple-dose vial.

Spikevax multiple-dose vials are stored frozen between -50°C to -15°C.

Spikevax can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured).

Thaw each vial before use:

- Thaw in refrigerated conditions between 2°C to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.
- Alternatively, thaw at room temperature between 15°C to 25°C for 1 hour.
- Do not re-freeze vials after thawing.

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

Spikevax is a white to off-white dispersion. It may contain white or translucent product-related particulates.

Inspect Spikevax vials visually for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

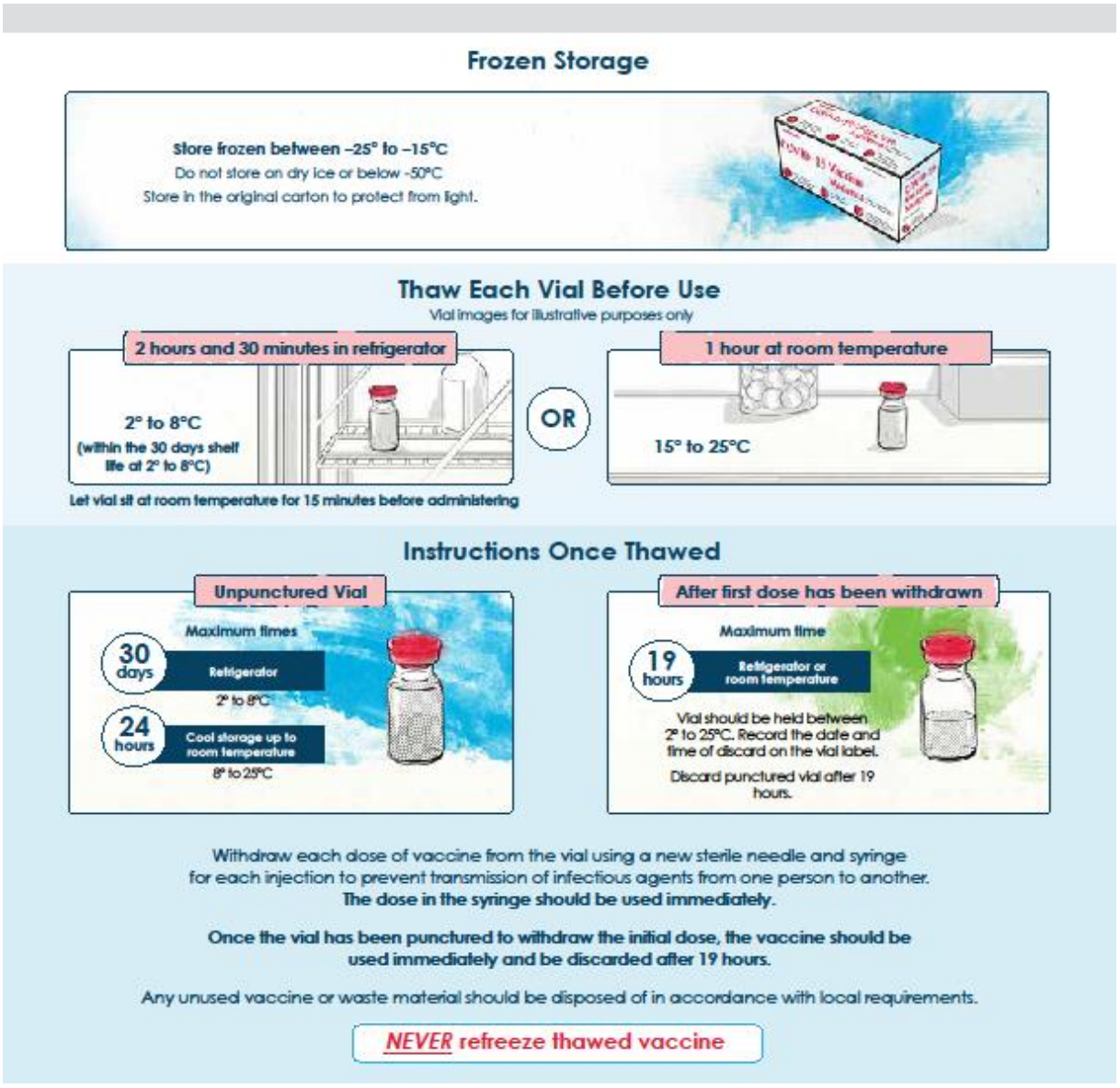
Withdraw each dose of vaccine from the vial using a new sterile needle and syringe (preferentially a low dead-volume syringe and/or needle) for each injection to prevent transmission of infectious agents from one person to another. Pierce the stopper, preferably at a different site each time. Do not puncture the vial more than 20 times. The dose in the syringe should be used promptly.

This product is preservative free. Once the vial has been entered (needle-punctured)

to withdraw the initial dose, the product should be used immediately and be discarded after 12 hours. Do not refreeze.

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

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



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

MODERNA BIOTECH SPAIN, S.L.
Calle Monte Esquinza 30
28010 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1507/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2021
Date of latest renewal: 04 October 2021

10. DATE OF REVISION OF THE TEXT

9 February 2022

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