# PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

For

## Spikevax (elasomeran)

Marketing Authorization Number 68267

## and

## Spikevax Bivalent Original / Omicron

## (elasomeran / imelasomeran)

Marketing Authorisation Number 69009

Dispersion for injection

Document Version: 2.0

Document Date: 20 October 2022

Based on Part VI of EU RMP version 4.2, dated 26 August 2022

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## List of Abbreviations

| Acronym | Definition |
|---|---|
| 2019-nCoV | 2019 novel coronavirus |
| Ab | antibody |
| AESI | adverse event of special interest |
| AR | adverse reaction |
| COVID-19 | disease caused by the novel 2019 coronavirus |
| CoV | coronaviruses |
| EMA | European Medicine Agency |
| EPAR | European Public Assessment Report |
| EU/EEA | European Union/European Economic Area |
| Ig | immunoglobulin |
| mRNA | messenger ribonucleic acid |
| PL | patient leaflet |
| RMP | risk management plan |
| SARS | severe acute respiratory syndrome |
| SCRI | self-controlled risk interval |
| SmPC | Summary of Product Characteristics |
| VAED | vaccine associated enhanced disease |
| VAERD | vaccine-associated enhanced respiratory disease |

**Overview**

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Spikevax Bivalent Original / Omicron is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Spikevax Bivalent Original / Omicron in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Moderna Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Spikevax Bivalent Original / Omicron.

**Summary of the Risk Management Plan**

This is a summary of the risk management plan (RMP) for Spikevax and Spikevax bivalent Original/Omicron BA.1. The RMP details important risks of Spikevax and Spikevax bivalent Original/Omicron BA.1, how these risks can be minimised, and how more information will be obtained about Spikevax's and Spikevax bivalent Original/Omicron BA.1's risks and uncertainties (missing information).

Spikevax's and Spikevax bivalent Original/Omicron BA.1's summary of product characteristics (SmPC) and their package leaflet give essential information to healthcare professionals and patients on how Spikevax and Spikevax bivalent Original/Omicron BA.1 should be used.

This summary of the RMP for Spikevax and Spikevax bivalent Original/Omicron BA.1 should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Spikevax's and Spikevax bivalent Original/Omicron BA.1's RMP.

## I The Medicine and What it is Used for

Spikevax is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older. Spikevax bivalent Original/Omicron BA.1 is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older, after primary COVID-19 immunisation. The active substance in Spikevax is mRNA encoding the SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and it is given by intramuscular route. The active substances in Spikevax bivalent Original/Omicron BA.1 are mRNA encoding the original SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and mRNA encoding the SARS-CoV-2 Spike protein of the Omicron variant embedded in lipid nanoparticles (imelasomeran) and it is given by intramuscular route.

Further information about the evaluation of Spikevax and Spikevax bivalent Original/Omicron BA.1 benefits can be found in the Spikevax EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: www.ema.europa.eu/en/medicines/human/EPAR/spikevax

## II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Spikevax and Spikevax bivalent Original/Omicron BA.1, together with measures to minimise such risks and the proposed studies for learning more about Spikevax and Spikevax bivalent Original/Omicron BA.1's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about Adverse Reactions (ARs) is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of Spikevax is not yet available, it is listed under "missing information" below.

In the case of Spikevax and Spikevax bivalent Original/Omicron BA.1, these measures are supplemented with additional pharmacovigilance activities mentioned under the relevant important risks below.

### *II.A List of Important Risks and Missing Information*

Important risks of Spikevax and Spikevax bivalent Original/Omicron BA.1 are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spikevax and Spikevax bivalent Original/Omicron BA.1. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**Table 1: List of Important Risks and Missing Information**

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Myocarditis<br>Pericarditis |
| Important potential risks | Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) |
| Missing information | Use in pregnancy and while breast-feeding Long-term safety<br>Use in immunocompromised subjects<br>Interaction with other vaccines<br>Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in subjects with autoimmune or inflammatory disorders |

## *II.B Summary of Important Risks*

**Table 2: Important Identified Risk: Myocarditis**

| **Important Identified Risk: Myocarditis** | |
|---|---|
| Evidence for linking the risk to the medicine | Data to evaluate the safety concern were derived from clinical trials and the post- authorisation safety. |
| Risk factors and risk groups | Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases.<br>Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. |

| **Important Identified Risk: Myocarditis** | |
|---|---|
| | The spontaneous reports included in the global safety database included 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis. |
| Risk minimisation measures | Routine risk minimisation measures:<br><br>SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects<br><br>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. (SmPC Section 4.4).<br><br>Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).<br><br>Additional risk minimisation measures: None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>Study mRNA-1273-P903<br>Study mRNA-1273-P904<br>Study mRNA-1273-P204<br>Study mRNA-1273-P910<br>Study mRNA-1273-P911<br>Study mRNA-1273-P301<br>Study mRNA-1273-P304<br>Study mRNA-1273-P203<br>Study 20-0003 |

| **Important Identified Risk: Myocarditis** | |
|---|---|
| | Study mRNA-1273-P201 |

**Table 3: Important Identified Risk: Pericarditis**

| **Important Identified Risk: Pericarditis** | |
|---|---|
| Evidence for linking the risk to the medicine | Data to evaluate the safety concern were derived from the clinical trials and post- authorisation safety data. |
| Risk factors and risk groups | In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely result in cardiac tamponade.<br><br>Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults.<br><br>A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65.<br><br>Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare. |
| Risk minimisation measures | <u>Routine risk minimisation measures:</u><br><br>SmPC Section 4.4 Special Warnings a nd Precautions for Use and 4.8 Undesirable Effects<br><br>PL 2. What you need to know before you are given Spikevax; 4 Possible side effects<br><br>Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should |

| **Important Identified Risk: Pericarditis** | |
|---|---|
| | 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. (SmPC Section 4.4).<br><br>Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).Additional risk minimisation measures: None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>Study mRNA-1273-P903<br>Study mRNA-1273-P904<br>Study mRNA-1273-P204<br>Study mRNA-1273-P301<br>Study mRNA-1273-P304<br>Study mRNA-1273-P203<br>Study 20-0003<br>Study mRNA-1273-P201<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 4: Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD) Disease**

| **Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associatedEnhanced Respiratory Disease (VAERD)** | |
|---|---|
| Evidence for linking the risk to the medicine | No evidence of harm has been identified in nonclinical studies nor from thePhase 3 mRNA-1273-P301 harm monitoring at the time of the data lock point for the risk management plan where safety follow up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. As of 30 June 2021, no new information has been identified through post-authorisation safety data. |
| Risk factors and risk groups | This is a potential risk and no increased risk to elasomeranhas been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease. |
| Risk minimisation measures | Routine risk minimisation measures:<br>None<br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Study mRNA-1273-P903<br>Study mRNA-1273-P904<br>Study mRNA-1273-P204<br>Study mRNA-1273-P301<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 5: Missing information: Use in Pregnancy and While Breast-Feeding**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: SmPC Sections<br>4.6 Fertility, pregnancy and lactation<br>5.3 Preclinica l safety data PL Section 2<br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Study mRNA-1273-P905<br>Study mRNA-1273-P919<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 6: Missing information: Long-Term Safety**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>None<br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Study mRNA-1273-P903<br>Study mRNA-1273-P904<br>Study mRNA-1273-P204<br>Study mRNA-1273-P301<br>Study 20-0003<br>Study mRNA-1273-P203<br>Study mRNA-1273-P205<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 7: Missing information: Use in Immunocompromised Subjects**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br><br>SmPC Section<br>4.4 Special Warnings and Precautions for Use PL Section 2<br><br>Additional risk minimisation measures:<br><br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>Study mRNA-1273-P901<br>Study mRNA-1273-P304<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 8: Missing information: Interaction with Other Vaccines**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br><br>SmPC Section<br>4.5 Interaction with other medicinal products and other forms of interaction PL Section 2<br><br>Additional risk minimisation measures:<br><br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>Study mRNA-1273-P901<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 9: Missing information: Use in Frail Subjects With Unstable Health Conditions and Co-morbidities (e.g. Chronic Obstructive Pulmonary Disease (COPD), Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Study mRNA-1273-P901<br>Study mRNA-1273-P904<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 10: Missing information: Use in Subjects With Autoimmune or Inflammatory Disorders**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>PL Section 2<br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Study mRNA-1273-P901<br>Study mRNA-1273-P904<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

## *II.C Post-Authorisation Development Plan*

### II.C.1 Studies Which are Conditions of the Marketing Authorisation

| Study Title and Number | Purpose of the Study |
|---|---|
| Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older<br>(mRNA-1273-P301) | Long-term safety data and durability of vaccine effectiveness (VE). |
| A Phase 2/3, Randomized, Observer-Blind, Placebo- Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age<br>(mRNA-1273-P203) | Evaluate the safety, reactogenicity, and effectiveness |
| Phase 2/3, two-part, open-label, dose-escalation, age de- escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age<br>(mRNA-1273-P204) | Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of mRNA-1273 administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age |
| Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants<br>(mRNA-1273-P205) | Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA- 1273.617.2, mRNA-1273.213, mRNA-1273.529, and Spikevax bivalent |

### II.C.2 Other Studies in Post-Authorisation Development Plan

The following studies are considered ongoing and/or planned additional pharmacovigilance activities:

| Study Title and Number | Purpose of the Study |
|---|---|
| Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (DMID Protocol No. 20-0003 [NCT04283461]) | Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses. |
| A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years<br>(mRNA-1273-P201) | Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster. |
| A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls<br>(mRNA-1273-P304) | Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of SARS-CoV-2 mRNA-1273 vaccine. Immunogenicity: neutralizing and binding antibody titers as surrogate endpoints expected to predict clinical benefit. |
| Post-Authorisation Safety of SARS-CoV-2 mRNA- 1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity<br>(mRNA-1273-P903) | Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives:<br>• Estimation of background rates for AESI and other outcomes in the cohort<br>• Assessment of observed versus expected rates<br>• Self-controlled risk interval analysesfor adverse events that meet specific threshold criteria. |

| | |
|---|---|
| Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU<br>(mRNA-1273-P904) | The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? |
| Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries<br>(mRNA-1273-P905) | The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? |
| Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the U.S<br>(mRNA-1273-P901) | Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disea se (hospitaliza tions and mortality). |
| Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA)<br>(mRNA-1273-P911) | The overarching goal of this study is to characterize long-term outcomes of myocarditis tempora ly associated with administration of ela someran (SPIKEVAX). |
| An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy<br>(mRNA-1273-P919) | To assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is associated with prenatal exposure to Spikevax. |