26 April 2023
EMA/230596/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Invented name: Spikevax

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No.: EMEA/H/C/005791/II/0097/G

Marketing authorisation holder (MAH): Moderna Biotech Spain, S.L.

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AR | Adverse reaction |
| CCI | Commercially confidential information |
| CDC | US Centers for Disease Control and Prevention |
| CEAC | Cardiac event adjudication committee |
| CHMP | Committee for Medicinal Products for Human use |
| CI | Confidence interval |
| CMQ | Custom MedDRA Query |
| CNS | Central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| CoV | Coronavirus(es) |
| COVID-19 | Coronavirus disease 2019 |
| CSR | Clinical Study Report |
| DHHS | United States Department of Health and Human Services |
| EC | European Commission |
| eCTD | Electronic common technical document |
| eDiary | Electronic diary |
| EMA | European Medicines Agency |
| EoS | End of study |
| EMS | Emergency medical services |
| FDA | US Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer(s) |
| IM | Intramuscular(ly) |
| IV | Intravenous(ly) |
| LNP | Lipid nanoparticle |
| MAAE | Medically attended adverse event |
| MAH | Marketing authorisation holder |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| mRNA | messenger RNA |
| nAb | Neutralising antibody(ies) |
| PHEIC | Public Health Emergency of International Concern |
| PI | Product information |
| PIP | Paediatric Investigation Plan |
| PPIS-Neg | Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status |
| PT | Preferred term |
| RMP | Risk management plan |
| RTI | Respiratory tract infection |
| S | Spike (protein) |
| S-2P | Spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS | Severe acute respiratory syndrome |

| | |
|---|---|
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SARS-CoV-2 rS | SARS-CoV-2 recombinant spike protein nanoparticle vaccine |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| SOC | System organ class |
| SRR | Seroresponse rate |
| TEAE | Treatment-emergent adverse event |
| UK | United Kingdom |
| US | United States of America |
| WHO | World Health Organisation |
| WHO-UMC | WHO Uppsala Monitoring Centre |

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 8th February 2023 an application for a group of variations.

The following variations were requested in the group:

| **Variations requested** | **Type** | **Annexes affected** |
|---|---|---|
| C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | Type II | I |
| C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | Type II | I and IIIB |
| C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Grouped variation:
- C.I.6.a (Type II): Extension of indication to include a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran) in children aged 6 through 11 years of age; as a consequence, sections 2, 4.1, 4.2, 4.4, and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 6.5 of the RMP has also been submitted.
- C.I.z (Type II): Update of sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.1 SmPC to add median follow-up period and D91 persistence data, based on Parts F and G (mRNA- 1273.214) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines. The Package Leaflet is updated accordingly.
- C.I.z (Type II): To update sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.4-5 SmPC to add ADR details and clinical data, based on Part H (mRNA- 1273.222) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines.
In addition, the Marketing authorisation holder took the opportunity to implement a number of editorial changes to the product information.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0256/2022 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0256/2022 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

| Timetable | Actual dates |
|---|---|
| Submission date | 8 February 2023 |
| Start of procedure | 26 February 2023 |
| CHMP Rapporteur Assessment Report | 28 March 2023 |
| PRAC Rapporteur Assessment Report | 31 March 2023 |
| PRAC members comments | 04 April 2023 |
| Updated PRAC Rapporteur Assessment Report | 5 April 2023 |
| PRAC Outcome | 14 April 2023 |
| CHMP members comments | 17 April 2023 |
| Updated CHMP Rapporteur Assessment Report | 20 April 2023 |
| Opinion | 26 April 2023 |

# 2. Scientific discussion

## *2.1. Introduction*

Currently, Spikevax bivalent Original/Omicron BA.4-5 (mRNA-1273.222) booster vaccination is authorised in individuals 12 years of age and older for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. The purpose of this submission is to request the extension of the indication to authorise booster vaccination in individuals 6 through 11 years of age. The proposed dosing regimen is a single 25 µg dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran).

On 15th December 2022, the use of a 25 µg dose Spikevax bivalent Original/Omicron BA.1 (mRNA-1273.214, 12.5 µg elasomeran /12.5 µg imelasomeran) was authorised as a booster dose in children 6 through 11 years of age.

To support this application, the MAH submitted additional clinical data from Study mRNA-1273-P205 Part G (mRNA-1273.214; Spikevax bivalent Original/Omicron BA.1 as a 2nd booster dose) compared with the data from Part F Cohort 2 (mRNA-1273; Spikevax original as a 2nd booster dose), including the data previously assessed during procedures EMEA/H/C/005791/II/75/G and EMEA/H/C/005791/II/84/G.

Supportive data from Study P205 Part H (mRNA-1273.222; Spikevax bivalent Original/Omicron BA.4-5 as 2nd booster dose) administered in an adult population (with a follow-up duration time of 37 days) was previously assessed during procedure EMEA/H/C/005791/077.

The data from Study mRNA-1273-P204 Booster Dose Phase is also supportive based on the safety and reactogenicity profile after administration of 25 µg of mRNA-1273 as a booster dose in children 6 through 11 years of age, as previously evaluated during procedure EMEA/H/C/005791/II/83/G.

### 2.1.1. Problem statement

#### *Disease or condition*

Coronaviruses are a large family of viruses that cause illnesses ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV. Coronaviruses are also zoonotic, with different species causing disease in other mammals, such as bats and cats.

An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally (WHO 2020). This virus is not known to have previously caused disease in humans. The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) on 30th January 2020 and a pandemic on 11th March 2020.

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in 3 principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by contact with fomites (CDC 2021).

Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission (Johansson et al 2021).

Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and the distinctive symptoms of loss of taste or smell.

During the COVID-19 pandemic, the sequence of SARS-CoV-2 is constantly changing over time. After the onset of the Omicron wave, the demographics of hospitalised patients with COVID-19 shifted to younger age groups (UK Health Security Agency 2021; Abdullah et al 2022; Goga et al 2021).

#### *Claimed therapeutic indication*

Currently, Spikevax bivalent Original/Omicron BA.4-5 booster vaccination is authorised for individuals 12 years of age and older. The purpose of this submission is to request an age extension to the current Spikevax bivalent Original/Omicron BA.4-5 indication to support the use of a booster in individuals 6 through 11 years of age for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

The intended indication is the following: Spikevax bivalent Original/Omicron BA.4-5 is indicated 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.

### 2.1.2. About the product

The MAH is using its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability.

Prior to the emergence of the novel SARS-CoV-2 coronavirus, the MAH had developed an understanding of mRNA vaccine approaches against coronavirus based on prior experience in the development of mRNA vaccines against MERS-CoV. This preclinical effort led to the evaluation of several mRNA vaccine designs against MERS-CoV, the most effective of which were spike (S) protein designs. Of these, a full-length spike protein modified to introduce 2 proline residues to stabilise the spike protein into a prefusion conformation (S-2P) showed improved performance versus the wild-type spike protein. These improvements included better expression of protein, stabilisation of the spike protein in the prefusion conformation, and improved immunogenicity in murine studies.

The coronavirus spike protein mediates attachment and entry of the virus into host cells by attachment followed by membrane fusion, making it a primary target for neutralising antibodies (Corti et al 2015; Wang L 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilised SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the pre-fusion conformation (Wrapp et al 2020).

The mRNA-1273 vaccines are delivered via IM injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilises the cell's translational machinery to produce the SARS-CoV-2 spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.

mRNA-1273 stimulates innate immune responses, resulting in the production of proinflammatory cytokines and type 1 interferon (Nelson et al 2020). This process activates B-cell and T-cell responses from the adaptive immune system. mRNA-1273 directly activates B-cells, including memory B-cells, resulting in the secretion of antibodies that bind and neutralise SARS-CoV-2 viruses. mRNA-1273 also directly activates T-cells, which eliminate infected cells and support B-cell responses. mRNA-1273 induces Th1-biased CD4 T-cell responses (Jackson et al 2020) and antigen-specific CD8 T-cells in humans (Zhang et al 2022).

To respond to emerging SARS-CoV-2 variants the MAH is developing modified mRNA COVID-19 booster vaccines. The variant-matched bivalent COVID-19 mRNA vaccines contain equal amounts of two mRNAs that encode for the Spike protein of the original SARS-CoV-2 (Wuhan-Hu-1) and antigenically divergent variants of concern, each encapsulated into individual LNPs, and co-formulated into a single drug product. After delivery, both mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers (mixed protomers from the original spike and the variant spike) are formed.

The inclusion of both the original and the variant spikes in the vaccine is intended to broaden immunity as significantly as possible. To that end, inclusion of the original spike allows reactivation and boosting of memory immune cell populations, increasing immunity that was previously present. In addition, inclusion of the variant spike, which has novel functional epitopes present primarily on the receptor-binding domain and the N-terminal domain, allows new naïve immune populations to be engaged and new memory responses to be elicited. This likely broadens immunity not only to the spike antigens delivered but likely also against a broader diversity of spike proteins.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek Scientific advice at the CHMP. According to the MAH, the Study P204 protocol and SAP have been designed in accordance with both US FDA general guidance on COVID-19 vaccine development (Department of Health and Human Services (DHHS), Food and Drug Administration, and Center for Biologics Evaluation and Research (US) 2020, 2021) and product-specific guidance. Study P204 protocol development, paediatric study plan, and paediatric investigation plan were discussed with EMA, Health Canada, and other agencies as part of the authorisation pathway developed to expedite regulatory approval in each country.

### 2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

## *2.2. Non-clinical aspects*

No new non-clinical data was submitted in this application, which is considered acceptable by the CHMP.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Overview of relevant clinical studies:

**Study mRNA-1273-P205**

Study mRNA-1273-P205 is an ongoing open-label Phase 2/3 study with multiple, sequentially enrolled cohorts to evaluate the immunogenicity and safety of variant-targeting booster candidate vaccines. mRNA-1273.222 is the bivalent Original/Omicron BA.4-5 booster vaccine that contains 25 µg Original SARS-CoV-2 Spike mRNA and 25 µg Omicron BA.4-5 Spike mRNA. The study consists of 7 parts: A, (1, 2), B, C, D, E, F, G, and H.

Part F - (Cohort 2)- 50 µg of the mRNA-1273 administered as a second booster dose to adult participants

who previously received 2 doses of 100 µg mRNA-1273 as a primary series and 1 booster dose of 50 µg mRNA-1273.

Part G - Second booster dose 50 µg mRNA-1273.214: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273.

Part H - Second booster dose 50 µg mRNA-1273.222: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273.

**Study mRNA-1273 P204**

Study mRNA-1273 P204 is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety,

reactogenicity, and immunogenicity of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 years through 11 years, 2 years to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age groups in P204 has been previously submitted and primary series of 50 µg is currently authorised for use in children from 6 through 11 years. In a subsequent amendment, the protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group. Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a booster dose of 25 µg mRNA-1273 to all children enrolled in the 6 through 11 years age group, which could be administered starting 6 months post-dose 2 of the primary series.

## *2.4. Clinical efficacy*

## *Results*

The MAH submitted a second interim analysis CSR with Day 91 immunogenicity results from study mRNA-1273-P205 part F (second booster dose with mRNA-1273) and part G (second booster dose with mRNA-1273.214 (Original/Omicron BA.1). Immunogenicity results until Day 29 have been assessed in the variations EMEA/H/C/005791/II/0075/G and EMEA/H/C/005791/II/84/G.

The MAH provided an Executive Summary on the new content:

**Intended Use**

Study mRNA-1273-P205 (Part G) demonstrated the safety, reactogenicity, and immunogenicity of mRNA 1273.214 (Spikevax bivalent Original/Omicron BA.1) 1 month after administration of a 50 µg booster dose in participants 18 years of age and older. Building upon these data, the purpose of this document is to summarise 3-month antibody persistence data for mRNA-1273.214 when administered as a 50 µg booster dose for the prevention of COVID-19 caused by SARS-CoV-2.

**Unmet Medical Need**

Over the course of the pandemic, SARS-CoV-2 variants have emerged and are likely to continue to emerge, some of which have some level of escape from immunity associated with previous infection or vaccination.

In November 2021, the SARS-CoV-2 Omicron variant (BA.1) emerged with significant antigenic change and a growth advantage. After the emergence of the BA.1 sublineage, other Omicron sublineages (such as BA.2, BA.4, and BA.5) with additional antibody escape mutations have been detected in multiple geographies.

The evolving antigenic variation of SARS-CoV-2 underscores the urgent need for vaccination strategies that induce broader protection, specifically against variants of concern with attendant risk of viral escape. To address the need for vaccination strategies that induce broader protection against variants of concern, Omicron-containing bivalent booster vaccines were authorised or approved globally for immunisation in the autumn of 2022. Based on the experience of mRNA-1273 and leveraging the flexible nature of the mRNA technology, the MAH evaluated multiple mRNA variant-targeting booster vaccines, including mRNA-1273.214 in study mRNA-1273-P205, to address emerging variants.

**Summary of the Clinical Development Program**

The MAH has developed a portfolio of modified, bivalent booster vaccines, which contain equal amounts of the mRNA sequence for the spike protein of the original SARS-CoV-2 and of a variant of concern. This includes mRNA-1273.214 50 µg (also referred to as ".214"), which contains 25 µg of mRNA-1273 and 25 µg of the Omicron BA.1 spike mRNA sequence, and was evaluated in Study mRNA 1273-P205 Part G.

In this open-label study, the safety and immunogenicity of an Omicron-containing bivalent vaccine (mRNA-1273.214) administered as a fourth dose (second booster after mRNA-1273 primary series and booster) was evaluated in comparison to mRNA-1273 booster 50 µg administered as a fourth dose (second booster after mRNA-1273 primary series and booster). All 437 and 376 participants in the mRNA 1273.214 and mRNA-1273 groups, respectively, received the booster, and as of a data cut-off of 6$^{th}$ July 2022, the follow-up time from the booster was ≥ 3 months for most participants (98.6%, 99.5%, respectively). The median follow-up time from the booster was 113 days in the mRNA-1273.214 group (134.32 person-years) and 127 days in the mRNA-1273 group (131.28 person-years) (Day 91 Interim Analysis Clinical Study Report [Part F [Cohort 2] and Part G Immunogenicity and Safety]).

**Benefit-Risk Conclusion**

*Immunogenicity*

A second 50 µg booster dose of the bivalent Omicron BA.1-containing mRNA-1273.214 met all pre-specified endpoints at Day 29 and Day 91 post-booster including superior neutralising antibody response against Omicron BA.1 and non-inferior response against SARS-CoV-2 (D614G) (the original strain) when compared to the prototype mRNA-1273 vaccine 1 month after administration.

In participants without prior SARS-CoV-2 infection:

- mRNA-1273.214 elicited Omicron BA.1 neutralising antibody titres (observed GMT [95% CI]) that were significantly higher (964.4 [834.4, 1114.7]) than those of mRNA- 1273 (624.2 [533.1, 730.9]) and similar between boosters against original SARS-CoV-2 at 3 months.
- The Omicron BA.1 GMR (mRNA-1273.214/mRNA-1273) was 1.740 (97.5% CI: 1.489, 2.035) and 1.655 (97.5% CI: 1.380, 1.985) at Day 29 and Day 91, respectively, in the Per-Protocol Immunogenicity Set without SARS-CoV-2 infection prior to the booster dose (PPIS-Neg).
- The seroresponse rate difference (97.5% CI) based on pre-dose 1 baseline was 1.5% (-1.1, 4.1) and 2.1% (-1.6, 5.8) at Day 29 and Day 91, respectively.

*For further comparison, see Table 1 below.*

***Table 1 - Pseudovirus Neutralizing Antibody Against Omicron BA.1 Variant: Comparison of Day 29 and Day 91 nAb Levels and Seroresponse Rates (PsVNA ID50) between mRNA-1273.214***

***Second Booster (P205G) and mRNA-1273 Second Booster (P205F) (PPIS-Neg [Participants without SARS-CoV-2 Infection Pre-booster])***

| | Omicron BA.1 Variant | |
|---|---|---|
| | Part G | Part F |
| | mRNA-1273.214 | mRNA-1273 |
| **Antibody: BA.1 Neutralizing Antibody (LLOQ: 19.85, ULOQ: 15502.7)** | **50 µg (N=335)** | **50 µg (N=259)** |
| **Pre-vaccination (pre-dose 1), n** [a] | 334 | 257 |
| Observed GMT (95% CI) [b] | 9.9 (NE, NE) | 9.9 (NE, NE) |
| **Pre-booster, n** [a] | 335 | 259 |
| Observed GMT (95% CI) [b] | 297.6 (258.4, 342.8) | 329.5 (280.0, 387.9) |
| **Day 29, n** [a] | 335 | 259 |
| Observed GMT (95% CI) [b] | 2366.6 (2066.2, 2710.7) | 1468.7 (1266.2, 1703.6) |
| Observed GMFR (pre-booster baseline), N1 | 335 | 259 |
| Observed GMFR (95% CI) | 8.0 (7.2, 8.8) | 4.5 (4.0, 5.0) |
| GLSM [Estimated GMT] (95% CI) [c] | 2469.7 (2255.5, 2704.3) | 1419.1 (1280.8, 1572.3) |
| **GMR (mRNA-1273.214 vs. mRNA-1273) (97.5% CI)** [c] | 1.740 (1.489, 2.035) | |
| **Seroresponse rate (pre-dose 1 baseline)** [c]**, N1** [d] | 334 | 257 |
| Seroresponse rate (95% CI) [e] | 100% (98.9, 100) | 99.2% (97.2, 99.9) |
| Difference in seroresponse rates (97.5% CI) [f] | 1.5% (-1.1, 4.1) | |
| **Seroresponse rate (pre-booster baseline)** [c]**, N1** [d] | 335 | 259 |
| Seroresponse rate (95% CI) [e] | 74.9% (69.9, 79.5) | 53.3% (47.0, 59.5) |
| Difference in seroresponse rates (97.5% CI) [f] | 21.5% (12.8, 30.2) | |
| **Day 91, n** [a] | 324 | 243 |
| Observed GMT (95% CI) [b] | 964.4 (834.4, 1114.7) | 624.2 (533.1, 730.9) |
| Observed GMFR (pre-booster baseline), N1 | 324 | 243 |
| Observed GMFR (95% CI) [b] | 3.2 (2.8, 3.6) | 1.9 (1.7, 2.1) |
| GLSM [Estimated] (95% CI) [c] | 997.5 (898.4, 1107.4) | 602.7 (534.7, 679.4) |
| **GMR (mRNA-1273.214 vs. mRNA-1273) (97.5% CI)** [c] | 1.655 (1.380, 1.985) | |
| **Seroresponse rate (pre-dose 1 baseline)** [c]**, N1** [d] | 323 | 241 |

| | Omicron BA.1 Variant | |
|---|---|---|
| | Part G | Part F |
| | mRNA-1273.214 | mRNA-1273 |
| **Antibody: BA.1 Neutralizing Antibody (LLOQ: 19.85, ULOQ: 15502.7)** | **50 µg (N=335)** | **50 µg (N=259)** |
| Seroresponse rate (95% CI) [e] | 98.5% (96.4, 99.5) | 96.3% (93.0, 98.3) |
| Difference in seroresponse rates (97.5% CI) [f] | 2.1 (-1.6, 5.8) | |
| **Seroresponse rate (pre-booster baseline) [c], N1 [d]** | 324 | 243 |
| Seroresponse rate (95% CI) [e] | 38.0% (32.7, 43.5) | 17.7% (13.1, 23.1) |
| Difference in seroresponse rates (97.5% CI) [f] | 19.9% (11.7, 28.1) | |

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; GLSM = geometric least squares mean; GM = geometric mean; GMFR = geometric mean fold rise; GMR geometric mean ratio; GMT = geometric mean titer; $ID_{50}$ = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; NE = not estimable; PPIS-neg = per protocol immunogenicity SARS-CoV-2 negative; PsVNA = pseudotyped neutralization assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.

Participants' immune response data was censored at the last date of study participation (study discontinuation, study completion, or death), non-study COVID-19 vaccination date, or data cutoff/extraction date, whichever was the earliest.

N1 = number of participants with non-missing data at baseline (pre-dose 1 or pre-booster) and the corresponding timepoint.

[a] Number of participants 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.

[c] The log-transformed antibody levels were analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, >=65 years) and pre-booster antibody titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose. The resulted LS means, difference of LS means, and confidence intervals were back transformed to the original scale for presentation.

[d] Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline (pre-dose 1/pre-booster) was equal to or above the LLOQ. Seroresponse (using pre-dose 1 as baseline), for participants without pre-dose 1 antibody titer information who had a corresponding Day 29 post-boost assessment, seroresponse was defined as >= 4*LLOQ for participants with negative SARS-CoV-2 status at their pre-dose 1 of the primary series, and these participants' antibody titers were imputed as <LLOQ at pre-dose 1 of the primary series. For participants who were without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status was used to impute their SARS-CoV-2 status at their pre-dose 1 of the primary series.

[e] The 95% CI is calculated using the Clopper-Pearson method.

[f] Common risk difference and confidence interval is calculated using the stratified Miettinen-Nurminen method to adjust for age group (<65, >=65 years). When both groups have response rate equal to 100%, common risk difference and confidence interval cannot be calculated.

**Safety**

The safety profile of mRNA-1273.214 (median follow-up period of 113 days) was favourable and similar to the safety profile of mRNA-1273 (median follow-up period of 127 days).

**Conclusion**

Based on review of the effectiveness (immunogenicity) and safety data of the BA.1-containing bivalent booster vaccine mRNA-1273.214 50 µg, the benefit-risk profile of mRNA-1273.214 is favourable to support use of a bivalent booster vaccine against COVID-19 after completion of a primary series and/or previous booster dose with mRNA-1273 or another authorised or approved COVID-19 vaccine.

Superiority in eliciting nAb response against Omicron BA.1 after booster vaccination with mRNA-1273.214 is maintained on Day 91. Although waning is observed, GMT values on Day 91 remain above pre-booster

GMT values. The CHMP considered the addition of these results to the SmPC to be appropriate.

**Extension of indication for mRNA-1273.222 (Original/Omicron BA.4-5) to children 6 through 11 years of age**

No new clinical study results on efficacy or immunogenicity are provided by the MAH in the current application for approval of mRNA-1273.222 (bivalent Original/Omicron BA.4-5) as a booster vaccine.

## *Summary of main study*

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

***Table 2 - Summary of Efficacy for trial P205***

<table>
<tr><td colspan="4">Title: A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants</td></tr>
<tr><td>Study identifier</td><td colspan="3">mRNA-1273-P205</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">This is an open-label, Phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of variant-targeting vaccines. This report evaluates the Day 91 interim immunogenicity, safety, and reactogenicity of 50 µg of the Omicron BA.1-containing bivalent vaccine mRNA-1273.214 when administered as a second booster dose to adults who previously received 2 doses of 100 µg mRNA-1273 as a primary series. A single booster dose of 50 µg mRNA-1273. Part F (Cohort 2) (mRNA-1273) serves as the within study, non-contemporaneous comparator group. The study was not designed to evaluate vaccine effectiveness but active surveillance for COVID-19 and SARS-CoV-2 infection was performed.</td></tr>
<tr><td colspan="2">Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase:</td><td>ongoing<br>not applicable<br>not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Part F (Cohort 2)</td><td>mRNA-1273, 50 µg</td></tr>
<tr><td colspan="2">Part G</td><td>mRNA-1273.214, 50 µg</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td></td><td>• GMT ratio of Omicron-specific GMT of mRNA-1273.214 over the Omicron specific GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91<br>• SRR difference between mRNA-1273.214 against the Omicron variant and mRNA-1273 against the Omicron variant at Day 29 and Day 91<br>• GMT ratio of original SARS-CoV-2 GMT of mRNA-1273.214 over original SARS-CoV-2 GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 or Day 91</td></tr>
</table>

| | | | |
|---|---|---|---|
| | Key Secondary endpoint | | • Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination<br>• Unsolicited AEs during the 28-day follow-up period after vaccination<br>• SAEs, MAAEs, AEs leading to withdrawal and AESIs from Day 1 to EoS |
| Database lock | 8th September 2022, 2nd interim CSR based on protocol amendment 8, current version protocol amendment 9. | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Interim Analysis** | | |
| Analysis population and time point description | Per-Protocol Immunogenicity Set – Negative (PPIS-Neg) | | |
| Descriptive statistics and estimate variability | Treatment group | Part F (Cohort 2) (mRNA-1273) | Part G (mRNA-1273.214) |
| | Number of subjects | 259 | 335 |
| | GMT pre-booster | 329.5 | 297.6 |
| | 95% CI | 280.0, 387.9 | 258.4, 342.8 |
| | GMT Day 29 | 1468.7 | 2366.6 |
| | 95% CI | 1266.2, 1703.6 | 2066.2, 2710.7 |
| | GMT Day 91 | 624.2 | 964.4 |
| | 95% CI | 533.1, 730.9 | 834.4, 1114.7 |
| Notes | Not applicable | | |
| **Analysis description** | **Interim analysis Day 91 immunogenicity** | | |

## 2.4.1. Discussion on clinical efficacy

The MAH submitted a second interim analysis CSR including Day 91 immunogenicity results from study

mRNA-1273-P205 part F Cohort 2 (second booster dose with mRNA-1273) and part G (second booster dose with mRNA-1273.214 (Original/Omicron BA.1). Immunogenicity results until Day 29 have been assessed in variation EMEA/H/C/005791/II/0075/G.

The CHMP endorsed the addition of these results to the SmPC.

**Extension of indication for mRNA-1273.222 (Original/Omicron BA.4-5) to children 6 through 11 years of age**

No new clinical study results on efficacy or immunogenicity are provided by the MAH in the current application for approval of mRNA-1273.222 (bivalent Original/Omicron BA.4-5) as a booster vaccine.

Efficacy of mRNA-1273 as a primary series and as a booster vaccination has initially been demonstrated in clinical efficacy studies. Bivalent Original/Omicron BA.1 mRNA-1273.214 has been approved as a booster vaccination in adolescent and adults from 12 years of age and older based on immunogenicity results that support effectiveness of this bivalent vaccine. Bivalent Original/Omicron BA.1 mRNA-1273.214 could demonstrate superiority as a second booster against SARS-CoV-2 Omicron BA.1 and non-inferiority against the original SARS-CoV-2 strain based on nAB GMTs, compared to booster vaccination with mRNA-1273 (Original).

Bivalent Original/Omicron BA.1 mRNA-1273.214 was thereafter approved as a booster vaccination for children 6 through 11 years of age based on:

- immunogenicity results in children 6 through 11 years of age after vaccination with mRNA-1273 (studies P203 and P204),
- considering that immunogenicity results against SARS-CoV-2 Omicron BA.1 could demonstrate superiority of a booster dose with mRNA-1273.214 as compared to mRNA-1273 based on GMRs in study P205 (EMEA/H/C/005791/II/0083/G).

Non-clinical studies in K18-hACE2 mice demonstrated that nABs against SARS-CoV-2 Omicron BA.4-5 are elicited after booster vaccination with mRNA-1273.222 (EMEA/H/C/005791/II/0084/G). Based on immunogenicity results in children 6 through 11 years of age after vaccination with mRNA-1273 (studies P203 and P204, EMEA/H/C/005791/II/0083/G) and supported by non-clinical studies, it is reasonably likely that bivalent Original/Omicron BA.4-5 mRNA-1273.222 will elicit a superior neutralising antibody response against SARS-CoV-2 Omicron BA.4-5 and a non-inferior neutralising antibody response against the original SARS-CoV-2 strain in children 6 through 11 years of age.

## 2.4.2. Conclusions on the clinical efficacy

The addition of results from the second interim analysis CSR with Day 91 immunogenicity results from study mRNA-1273-P205 part F (second booster dose with mRNA-1273) and part G (second booster dose with mRNA-1273.214 (Original/Omicron BA.1) is endorsed.

No new clinical study results on efficacy or immunogenicity are provided by the MAH in the current application for approval of mRNA-1273.222 (bivalent Original/Omicron BA.4-5) as a booster vaccine.

Based on immunogenicity results in children 6 through 11 years of age after vaccination with mRNA-1273 (studies P203 and P204, EMEA/H/C/005791/II/0083/G) and supported by non-clinical studies it is reasonably likely that bivalent Original/Omicron BA.4-5 mRNA-1273.222 will elicit a superior neutralising antibody response against SARS-CoV-2 Omicron BA.4-5 and a non-inferior neutralising antibody response against the original SARS-CoV-2 strain in children 6 through 11 years of age. Therefore, the CHMP considered that the extension of the indication for mRNA-1273.222 as booster in children 6 through 11 years of age is endorsed.

## *2.5. Clinical safety*

### Introduction

Currently, Spikevax bivalent Original/Omicron BA.4-5 booster vaccination is authorised for individuals 12 years of age and older. The purpose of this submission is to request an age extension to the current Spikevax bivalent Original/Omicron BA.4-5 indication to support the use of a booster in individuals 6 through 11 years of age for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. The proposed dosing regimen is a single 25 µg dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran).

To support this application, the MAH submitted safety data from the following studies:

1. **Study mRNA-1273-P205 Part G and Part F**. This includes safety data from participants who received mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1) as a second booster dose compared to safety data from participants who received mRNA-1273 as a second booster dose. These data was used to support the marketing authorisation of both Spikevax bivalent Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.1 BA.4-5) in adults and adolescents (EMEA/H/C/005791/II/75/G and EMEA/H/C/005791/II/84/G).
2. **Study P205 Part H (mRNA- 1273.222)**, with safety data for the bivalent 50 µg mRNA-1273.222 vaccine given as a second booster dose in adults (EMEA/H/C/005791/REC/077).
3. **Study mRNA-1273-P204**, the same safety data used to support the marketing authorisation of Spikevax bivalent Original/Omicron BA.1 in individuals 6 through 11 years of age (EMEA/H/C/005791/II/83/G).

#### 1. Study mRNA-1273-P205 Part G and Part F

#### Participant exposure and follow-up

In part G, there were 437 participants who received mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1) and the median duration of follow-up after booster dose was 113 days.

In part F (Cohort 2), there were 376 participants who received mRNA-1273 and the median duration of follow-up after second booster dose was 127 days.

The CHMP noted that during procedure EMEA/H/C/005791/II/75/G, the safety data submitted for Study P205, part G had a median follow-up of 43 days and for the Part F (Cohort 2) was 57 days. As it is described above, there is a longer median follow-up time in this submission, respectively 113 days and 127 days including the unsolicited AEs, MAAEs, SAEs and fatal events. None of these parts studies include children aged 6 through 11 years of age.

### Adverse events

Safety assessment included the monitoring of:

- Solicited local and systemic ARs collected during the 7-day follow-up period after the second booster dose, recorded daily using an eDiary.
- Unsolicited AEs collected during the 28-day follow-up period after the second booster dose.

- SAEs, MAAEs, AEs leading to discontinuation from study, AESIs, and pregnancies collected throughout this interim analysis period.

## Summary of Solicited Adverse Reactions

**Part G** (**mRNA-1273.214**): Solicited ARs were reported for 87% of participants after booster dose. Solicited local ARs were reported for 79.4% participants and the most common reported were: injection site pain (77.3%), followed by axillary swelling or tenderness (17.4%), and injection site erythema and injection site swelling were each reported in less than 7% of participants (each 6.9%). Most solicited local ARs were Grade 1 (66.6%), Grade 2 (9.4%), and none were Grade 4. Grade 3 were reported by 3.4% participants with the most common reported: injection site erythema (2.1%), followed by injection site swelling (1.1%).

Solicited systemic ARs were reported for 70.3% participants, with the most common reported: fatigue (54.9%), followed by headache (43.9%), myalgia (39.8%) and arthralgia (31.1%). Most systemic ARs were Grade 1 (38.2%), followed by Grade 2 (26.5%) and none were Grade 4. Grade 3 were reported by 5.5% participants with the most common reported: fatigue (3.4%) followed by myalgia (2.3%).

**Part F Cohort 2 (mRNA-1273)**: Solicited ARs were reported for 85.7% participants after the booster dose. Solicited local ARs were reported for 79.4% participants and the most common reported were: injection site pain (76.6%), followed by axillary swelling or tenderness (15.1%) and injection site erythema and injection site swelling were each reported in less than 7% of participants (respectively 3.7% and 6.3%). Most solicited local ARs were Grade 1 (68.3%) followed by Grade 2 (7.7%), and none were Grade 4. Grade 3 local ARs were reported for 3.4 % participants and the most commonly reported were: injection site swelling (1.4%) followed by axillary swelling or tenderness (1.1%) and injection site pain (1.1%).

Solicited systemic ARs were reported in 66.0% participants and the most reported were: fatigue (51.3%) followed by headache (41.0%), myalgia (38.4%), and arthralgia (31.5%). Most solicited systemic ARs were Grade 1 (35.4%) followed by Grade 2 (26.0%) and none were Grade 4. Grade 3 systemic ARs were reported for 4.6% participants, with the most reported: myalgia (3.7%) followed by fatigue (3.2%).

The CHMP noted that solicited local and systemic adverse events in the mRNA-1273.214 50 µg booster dose group (Part G) and the mRNA-1273 50 µg booster dose group (Part F) respectively have been assessed and discussed in details in two previous procedures, respectively during the assessment process on booster indication of bivalent vaccines in individuals 12 years of age and older (EMEA/H/C/005791/II/0075/G and EMEA/H/C/005791/II/0084/G respectively).

It has been concluded that slightly higher incidences of local and systemic adverse events were observed, when comparing mRNA-1273.214 50 µg administered as second booster to mRNA-1273 50 µg given as a booster dose. However, these differences were not clinically meaningful and were not considered to have a significant impact on the safety profile of mRNA-1273.214 when compared to that of mRNA-1273.

### Solicited AEs by Day of Onset

Most solicited ARs were reported with onset from Days 1-3 after the booster dose.

**mRNA-1273.214**: Among local ARs, the most frequently reported was pain, mostly with onset on Day 2, reported by 68.2% participants followed by axillary swelling or tenderness (onset on Day 2), reported by 9.4% participants. Among systemic ARs was fatigue (44.4%) followed by headache (31.4%). The most common solicited local and systemic ARs reported within 30 minutes were: pain (6.6%), fatigue and

headache (2.1% each); axillary swelling or tenderness (1.6%); myalgia and arthralgia (0.9% each); nausea/vomiting and chills (0.5% each); and injection site erythema (0.2%).

**mRNA-1273 (Part F Cohort 2)**: Among local ARs, the most frequently reported was pain, mostly with onset on Day 2, reported by 66.9 % participants followed by axillary swelling or tenderness (8.3%). Among systemic ARs was fatigue (39.5%) followed by myalgia (30.4%) and headache (29.5%). The most common solicited local and systemic ARs reported within 30 mins were: pain (7.1%); headache (2.9%); fatigue (2.6%) and axillary swelling or tenderness (2.0%).

**Solicited AEs by Duration**

**mRNA-1273.214:** The median duration of local and systemic ARs was 2.0 days. The most reported of solicited local AR was pain with median duration of 2 days, followed by swelling or tenderness (1 day). Among solicited systemic AR the most frequently reported were fatigue and headache with the median duration 2.0 and 1.0 days. The maximum duration was reported for fatigue with 21 days.

**mRNA-1273 (Part F Cohort 2):** The median duration of local and systemic ARs was 2.0 days. The most reported of solicited local AR was pain (2 days), followed by swelling or tenderness (1 day). Among solicited systemic AR the most frequently reported were fatigue and headache with the median duration 2.0 and 1.0 days. The maximum duration was reported for fatigue with 13 days.

## Subgroup Analyses

Baseline SARS-CoV-2 Status

*mRNA-1273.214 (Part G):* In the solicited Safety Set there were 22% participants had a positive pre booster status; 77.8% had a negative status and 1 participant had missing status. The frequency of solicited local ARs was comparable between the two groups, respectively positive vs negative status (77.1% vs 80.0%). The same applies for the solicited systemic ARs between the two groups (66.5% vs 71.8%).

*mRNA-1273 (Part F Cohort 2):* There were 26.2% participants with positive pre booster SARS-CoV-2 status; 71.2% had a negative status and for 8 participants the status was missing. The frequency of solicited local ARs was comparable between the two groups, respectively positive vs negative status (78.3% vs 80%). The same applies for the solicited systemic ARs between the two groups (60.9% vs 68.4%).

Solicited AEs by Age Group

*mRNA-1273.214 (Part G):* Higher frequency of solicited local ARs in participants ≥ 18 to < 65 years of age (89.4%) compared to the age group ≥ 65 years (64.4%). Similarity applies for the solicited systemic ARs, respectively (74.9 % vs 63.2%).

*mRNA-1273 (Part F Cohort 2):* Higher frequency of solicited local ARs in participants ≥ 18 to < 65 years of age (85.2%) compared to the age group ≥ 65 years (70.7%). Similarity applies for the solicited systemic ARs, respectively (70.5% vs 59.3%).

More details are provided in the Table 3 below, comparing the subgroups and the two respective parts:

***Table 3 - Summary of Participants with Solicited Adverse Reactions Within 7 Days After the Injection by Age Group and Grade – Second Booster Dose: mRNA- 1273.214, mRNA-1273 (Solicited Safety Set)***

| | Part G mRNA-1273.214 50 µg | | Part F Cohort 2 mRNA-1273 50 µg | |
|---|---|---|---|---|
| | Age Group (Years) | | Age Group (Years) | |
| Solicited Adverse Reaction Category Grade | ≥18 and <65 (N=263) n (%) | ≥65 (N=174) n (%) | ≥18 and <65 (N=210) n (%) | ≥65 (N=140) n (%) |
| Solicited adverse reactions - N1 | 263 | 174 | 210 | 140 |
| Any solicited adverse reactions | 244 (92.8) | 136 (78.2) | 186 (88.6) | 114 (81.4) |
| 95% CI | 88.9, 95.6 | 71.3, 84.1 | 83.5, 92.5 | 74.0, 87.5 |
| Grade 1 | 135 (51.3) | 85 (48.9) | 103 (49.0) | 81 (57.9) |
| Grade 2 | 85 (32.3) | 40 (23.0) | 65 (31.0) | 23 (16.4) |
| Grade 3 | 24 (9.1) | 11 (6.3) | 18 (8.6) | 10 (7.1) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Solicited local adverse reactions - N1 | 263 | 174 | 210 | 140 |
| Any solicited local adverse reactions | 235 (89.4) | 112 (64.4) | 179 (85.2) | 99 (70.7) |
| 95% CI | 85.0, 92.8 | 56.8, 71.5 | 79.7, 89.7 | 62.4, 78.1 |
| Grade 1 | 193 (73.4) | 98 (56.3) | 150 (71.4) | 89 (63.6) |
| Grade 2 | 32 (12.2) | 9 (5.2) | 20 (9.5) | 7 (5.0) |
| Grade 3 | 10 (3.8) | 5 (2.9) | 9 (4.3) | 3 (2.1) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Pain - N1 | 263 | 174 | 210 | 140 |
| Any | 231 (87.8) | 107 (61.5) | 174 (82.9) | 94 (67.1) |
| Grade 1 | 202 (76.8) | 101 (58.0) | 151 (71.9) | 89 (63.6) |
| Grade 2 | 27 (10.3) | 4 (2.3) | 19 (9.0) | 5 (3.6) |
| Grade 3 | 2 (0.8) | 2 (1.1) | 4 (1.9) | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Erythema (redness) - N1 | 263 | 174 | 210 | 140 |
| Any | 20 (7.6) | 10 (5.7) | 10 (4.8) | 3 (2.1) |
| Grade 1 | 10 (3.8) | 5 (2.9) | 5 (2.4) | 0 |
| Grade 2 | 3 (1.1) | 3 (1.7) | 4 (1.9) | 2 (1.4) |
| Grade 3 | 7 (2.7) | 2 (1.1) | 1 (0.5) | 1 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Swelling (hardness) - N1 | 263 | 174 | 210 | 140 |
| Any | 22 (8.4) | 8 (4.6) | 14 (6.7) | 8 (5.7) |
| Grade 1 | 12 (4.6) | 5 (2.9) | 9 (4.3) | 4 (2.9) |
| Grade 2 | 6 (2.3) | 2 (1.1) | 3 (1.4) | 1 (0.7) |
| Grade 3 | 4 (1.5) | 1 (0.6) | 2 (1.0) | 3 (2.1) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Axillary swelling or tenderness - N1 | 263 | 174 | 210 | 140 |
| Any | 56 (21.3) | 20 (11.5) | 38 (18.1) | 15 (10.7) |
| Grade 1 | 53 (20.2) | 18 (10.3) | 31 (14.8) | 14 (10.0) |
| Grade 2 | 3 (1.1) | 1 (0.6) | 3 (1.4) | 1 (0.7) |
| Grade 3 | 0 | 1 (0.6) | 4 (1.9) | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Solicited systemic adverse reactions - N1 | 263 | 174 | 210 | 140 |
| Any solicited systemic adverse reactions | 197 (74.9) | 110 (63.2) | 148 (70.5) | 83 (59.3) |
| 95% CI | 69.2, 80.0 | 55.6, 70.4 | 63.8, 76.6 | 50.7, 67.5 |
| Grade 1 | 102 (38.8) | 65 (37.4) | 70 (33.3) | 54 (38.6) |
| Grade 2 | 78 (29.7) | 38 (21.8) | 69 (32.9) | 22 (15.7) |
| Grade 3 | 17 (6.5) | 7 (4.0) | 9 (4.3) | 7 (5.0) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Fever - N1 | 262 | 174 | 210 | 140 |
| Any | 9 (3.4) | 8 (4.6) | 9 (4.3) | 2 (1.4) |
| Grade 1 | 6 (2.3) | 6 (3.4) | 7 (3.3) | 1 (0.7) |
| Grade 2 | 2 (0.8) | 2 (1.1) | 2 (1.0) | 1 (0.7) |
| Grade 3 | 1 (0.4) | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Headache - N1 | 263 | 174 | 210 | 139 |
| Any | 129 (49.0) | 63 (36.2) | 99 (47.1) | 44 (31.7) |
| Grade 1 | 96 (36.5) | 54 (31.0) | 77 (36.7) | 34 (24.5) |
| Grade 2 | 29 (11.0) | 8 (4.6) | 21 (10.0) | 9 (6.5) |
| Grade 3 | 4 (1.5) | 1 (0.6) | 1 (0.5) | 1 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Fatigue - N1 | 263 | 174 | 210 | 139 |
| Any | 154 (58.6) | 86 (49.4) | 114 (54.3) | 65 (46.8) |
| Grade 1 | 75 (28.5) | 50 (28.7) | 53 (25.2) | 41 (29.5) |
| Grade 2 | 69 (26.2) | 31 (17.8) | 54 (25.7) | 20 (14.4) |
| Grade 3 | 10 (3.8) | 5 (2.9) | 7 (3.3) | 4 (2.9) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Myalgia - N1 | 263 | 174 | 210 | 139 |
| Any | 114 (43.3) | 60 (34.5) | 89 (42.4) | 45 (32.4) |
| Grade 1 | 64 (24.3) | 38 (21.8) | 43 (20.5) | 25 (18.0) |
| Grade 2 | 41 (15.6) | 21 (12.1) | 38 (18.1) | 15 (10.8) |
| Grade 3 | 9 (3.4) | 1 (0.6) | 8 (3.8) | 5 (3.6) |
| Grade 4 | 0 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Arthralgia - N1 | 263 | 174 | 210 | 139 |
| Any | 87 (33.1) | 49 (28.2) | 68 (32.4) | 42 (30.2) |
| Grade 1 | 56 (21.3) | 37 (21.3) | 39 (18.6) | 30 (21.6) |
| Grade 2 | 28 (10.6) | 11 (6.3) | 27 (12.9) | 11 (7.9) |
| Grade 3 | 3 (1.1) | 1 (0.6) | 2 (1.0) | 1 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Nausea/vomiting - N1 | 263 | 174 | 210 | 139 |
| Any | 35 (13.3) | 10 (5.7) | 27 (12.9) | 8 (5.8) |
| Grade 1 | 31 (11.8) | 8 (4.6) | 22 (10.5) | 5 (3.6) |
| Grade 2 | 4 (1.5) | 1 (0.6) | 5 (2.4) | 3 (2.2) |
| Grade 3 | 0 | 1 (0.6) | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Chills - N1 | 263 | 174 | 210 | 139 |
| Any | 64 (24.3) | 40 (23.0) | 54 (25.7) | 20 (14.4) |
| Grade 1 | 38 (14.4) | 27 (15.5) | 33 (15.7) | 13 (9.4) |
| Grade 2 | 25 (9.5) | 13 (7.5) | 21 (10.0) | 6 (4.3) |
| Grade 3 | 1 (0.4) | 0 | 0 | 1 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 |

Abbreviations: C = Celsius; CI = confidence intervals; N1 = number of exposed participants who submitted any data for the event
"any" = Grade 1 or higher.
Percentages were based on the number of exposed participants who submitted any data for the event (N1).
95% CI was calculated using the Clopper-Pearson method.
Toxicity grade for erythema (Redness) was defined as: G1 = 25 – 50 mm; G2 = 51 – 100 mm; G3 = > 100 mm.
Toxicity grade for fever was defined as: G1 = 38 – 38.4 C; G2 = 38.5 – 38.9 C; G3 = 39 – 40 C; G4 = > 40 C.
The data cutoff date for safety and SARS-CoV-2 infection was 06 Jul 2022.
Source: Table 14.3.1.1.2.8

The CHMP noted that no clinically meaningful imbalances were seen in subgroup analyses with regards to the frequencies when stratifying according to, SARS-CoV -2- status and age group. No new safety concerns were identified by SARS-CoV-2 status after vaccination with mRNA-1273.214 or mRNA-1273 given as a second booster. However higher reactogenicity was observed among participants ≥ 18 to < 65 years of age than among those ≥ 65 years of age for both booster groups (i.e. after mRNA-1273.214 or mRNA-1273 given as a second booster).

### Medication Use for AEs of Pain and Fever

The table below summarises the use of medication for pain and fever accordingly by groups.

***Table 4 - Summary of Medications for Pain/Fever After the Injection Overall and by Age Group – Second Booster Dose: mRNA-1273.214, mRNA-1273 (Solicited Safety Set)***

| | Part G | Part F Cohort 2 |
|---|---|---|
| | mRNA-1273.214 50 ug n(%) | mRNA-1273 50 ug n(%) |
| **Age Group: >=18 and <65 Years** | **N=263** | **N=210** |
| Medication taken for pain or fever | 104 (39.5) | 67 (31.9) |
| Prevent pain or fever | 25 (9.5) | 21 (10.0) |
| Treat pain or fever | 95 (36.1) | 61 (29.0) |
| **Age Group: >=65 Years** | **N=174** | **N=140** |
| Medication taken for pain or fever | 46 (26.4) | 40 (28.6) |
| Prevent pain or fever | 7 (4.0) | 14 (10.0) |
| Treat pain or fever | 42 (24.1) | 37 (26.4) |

Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: medications were collected on eDiary.
The data cutoff date for safety and SARS-CoV-2 infection was 06 Jul 2022.
Sources: Table 14.1.5.4.8

**The CHMP noted that** in both parts, approximately one- third of participants reported use of medication for pain and fever, as reported in the eDiary. In the table above, describing the incidence of participants taking these medications and by age group classification, it is observed that in the age group >=18 and <65 Years, the incidence is slightly higher in the mRNA-1273.214 group compared to the

mRNA-1273 group, respectively (36.1% vs 29.1%). The opposite applies for the age group >=65 Years (26.4% vs 28.6%). The CHMP did not consider these minor differences to be clinically meaningful.

### Unsolicited Adverse Events

**mRNA-1273.214 (Part G):** Within 28 days, unsolicited TEAEs were reported for 19.2% participants, of these 4.8% were reported to be related to study vaccine. Up to the data cut-off, there were reported 47.8% TEAEs and no additional TEAEs were considered to be related to study vaccine.

**mRNA-1273 (Part F Cohort 2):** Within 28 days, unsolicited TEAEs were reported for 21.3% participants and of those for 5.6% participants were considered by the investigator to be vaccine related. Up to the data cut-off, there were reported 52.1% TEAEs and no additional TEAEs were considered to be related to study vaccine.

The table below is a summary of the TEAEs regardless of relationship to study vaccination and those considered related to study vaccination.

***Table 5 - Summary of Unsolicited TEAEs up to 28 Days After the Injection — Second Booster Dose: mRNA-1273.214, mRNA-1273 (Safety Set)***

| | Part G | Part F Cohort 2 |
|---|---|---|
| | mRNA-1273.214 50 ug (N=437) n(%) | mRNA-1273 50 ug (N=376) n(%) |
| Unsolicited TEAEs regardless of relationship to study vaccination | | |
| All | 84 (19.2) | 80 (21.3) |
| Serious | 2 (0.5) | 1 (0.3) |
| Fatal | 0 | 0 |
| Medically-attended | 51 (11.7) | 57 (15.2) |
| Leading to discontinuation from participation in the study | 0 | 0 |
| Grade 3 or higher | 4 (0.9) | 3 (0.8) |
| Non-serious [a] | 82 (18.8) | 79 (21.0) |
| Grade 3 or higher | 3 (0.7) | 2 (0.5) |
| At least 1 non-serious event [b] | 82 (18.8) | 80 (21.3) |
| Grade 3 or higher | 3 (0.7) | 2 (0.5) |
| Unsolicited TEAEs related to study vaccination | | |
| All | 21 (4.8) | 21 (5.6) |
| Serious | 0 | 0 |
| Fatal | 0 | 0 |
| Medically-attended | 2 (0.5) | 2 (0.5) |
| Leading to discontinuation from participation in the study | 0 | 0 |
| Grade 3 or higher | 1 (0.2) | 2 (0.5) |
| Non-serious [a] | 21 (4.8) | 21 (5.6) |
| Grade 3 or higher | 1 (0.2) | 2 (0.5) |
| At least 1 non-serious event [b] | 21 (4.8) | 21 (5.6) |
| Grade 3 or higher | 1 (0.2) | 2 (0.5) |

Abbreviations: SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment emergent adverse event.
A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Percentages were based on the number of participants in the Safety Set.
a. Participants without any SAE and with any non-serious TEAE.
b. Participants with at least one non-serious TEAE regardless of reporting any SAE or not.
The data cutoff date for safety and SARS-CoV-2 infection was 06 Jul 2022.
Sources: Table 14.3.1.7.1.8

The CHMP noted that the incidences of unsolicited TEAEs regardless of relationship to study vaccination and those related to study vaccination were comparable between the two parts after the booster dose. Also, no clinical meaningful differences were noted between the age groups in the two parts as follows: *>=18 and <65 Years*: In part G (after booster dose mRNA-1273.214) unsolicited TEAEs related to study vaccine were 5.7% vs 4.9% in part F (after booster dose mRNA-1273); age group *>=65 Years*, respectively 3.4% vs 6.7%.

### Unsolicited AEs by SOC and PT

**mRNA-1273.214 (Part G):** Up to 28 days after booster the most frequently reported unsolicited TEAEs by PT regardless of causality were fatigue (2.5%), arthralgia (1.6%), followed by headache (1.4%) and at least COVID-19 infection (1.1%). By SOC the most frequently reported were: Infections and infestations (6.6%), followed by general disorders and administration site conditions (4.1%) and musculoskeletal and connective tissue disorders (3%).

**mRNA-1273 (Part F Cohort 2):** Up to 28 days after booster the most frequently reported unsolicited TEAEs by PT regardless of causality were: fatigue (2.9%), upper RTI (2.4%), arthralgia and coronavirus infection (2.1% each); myalgia (1.6%); and headache (1.1%). By SOC the most frequently reported were: Infections and infestations (9.0%), followed by general disorders and administration site conditions (4.3%) and musculoskeletal and connective tissue disorders (3.5%).

### Unsolicited AEs reported as severe

**mRNA-1273.214 (Part G):** Up to 28 days after the booster, severe TEAEs were reported for 0.9% participants; 1 participant had fatigue with duration (Day 1-14) as vaccine related. The other 3 TEAEs were considered not related to study IP were:

- cataract (bilateral; onset on Day 5, resolved on Day 73 for the right eye and ongoing at data cut-off for the left eye)
- Barrett's esophagus (onset Day 23 and ongoing as of data cut-off)
- traumatic fracture (Day 14 to 113)

**mRNA-1273 (Part F Cohort 2):** Up to 28 days after the booster, severe TEAEs were reported for 0.8% participants. The events reported were:

- related event of fatigue with duration from Days 2- 8.
- related event of myalgia from Day 7- 8.
- unrelated event of spinal osteoarthritis from Days 9-49.

The CHMP noted that there were no imbalances reported after the booster dose for both parts with regards to the severe TEAEs, with comparable incidences (0.9% vs 0.8%). Fatigue is a known adverse drug reaction and is included in the section 4.8 of the SmPC, therefore no additional clinical information is requested with regards to the severe event of fatigue with duration from Day 1-14 in the mRNA-1273.214 booster group.

### Unsolicited AEs considered vaccine related

**mRNA-1273.214 (Part G):** Unsolicited TEAEs considered vaccine related were reported for 4.8% participants. By preferred PTs the frequently reported were: injection site erythema, injection site lymphadenopathy, urticaria, and dermatitis (each in one participant). The solicited ARs persisted beyond Day 7 and considered related to study vaccine were: fatigue (n=9), arthralgia (n=6), headache (n=5), myalgia (n=3) and injection site pain (n=3). Most events were mild or moderate in severity. The event of severe fatigue is described at the section of the severe events.

**mRNA-1273 (Part F Cohort 2):** Unsolicited TEAEs considered vaccine related considered vaccine related were reported for 5.6% participants. Events PTs reported were: injection site lymphadenopathy (n=1), induration (n=1), injection site bruising and nodule (occurring in the same participant), and urticaria (n =1). The solicited ARs beyond Day 7 considered vaccine related were: fatigue (n=10), arthralgia (n=6), myalgia (n=6), headache (n=3) and injection site pain (n=1). The events of fatigue; myalgia and hypertension are described in the respective sections.

The CHMP noted that there were slight differences with regards to the TEAEs considered vaccine related between the two parts, with a slightly lower incidence in the mRNA-1273.214 booster dose group compared to the mRNA-1273 group, respectively 4.8% vs 5.6%. The AEs persisted beyond Day 7 are related with the known reactogenicity of mRNA-1273 and all the events considered as vaccine related are already included as ADRs at the Section 4.8 of the SmPC.

## Deaths

There were three fatal events reported in total up to data cut-off as follows:

**mRNA-1273.214 (Part G)**: There are two deaths reported after the data cut-off.

- **Death** (verbatim term: death unknown causes): A 60-69 year old female participant with a medical history of Raynaud's syndrome, COPD, depression, and iron deficiency died due to unknown causes on Day 148 after the booster dose (mRNA-1273.214). According to the safety database, the study site was unable to reach the family despite multiple attempts and medical records could not be obtained. It is unknown if an autopsy was performed. One other unsolicited AE, fatigue, was reported for this participant. The event was assessed as unrelated to vaccine by the investigator and MAH due to the long latency, but the lack of additional information limits the final assessment.

The CHMP noted that the participant received a second booster dose of 50 µg mRNA-1273.214. The participant's pre-booster SARS-CoV-2 status was positive. The medical history included these diagnoses: depression, post-menopausal, intermittent headaches, chronic obstructive pulmonary disease (COPD), iron deficiency and Raynaud's syndrome. Ongoing medications reported 30 days prior to the fatal event were acetaminophen and albuterol. After 147 days, the participant died due to unknown causes. As stated above, the event was considered not to be related to the study vaccine by the investigator and the MAH. However, due to the lack of any clinical information and not any autopsy results, reasonably likely causality cannot be inferred.

- **Atherosclerotic cardiovascular disease**: A 60-69 year old male participant with morbid obesity, hypertension, and chronic peripheral oedema (water retention –in legs and feet) called EMS because of shortness of breath approximately 4.5 months after the booster dose, having experienced a cardiac arrest with secondary diagnosis of acidosis, respiratory arrest, and septic shock. After defibrillation, CPR was initiated. The participant was transported to the hospital, where return of circulation was achieved but was unable to be maintained despite continuing CPR, pressors and bicarbonate drip. A fatal myocardial infarction was diagnosed. An autopsy was performed, and the cause of death was reported as atherosclerotic cardiovascular disease, with obesity as a significant contributing factor. The fatal event was considered unrelated to the study vaccine by the investigator and MAH and was attributed to underlying disease.

The CHMP noted that the participant received 50 µg mRNA-1273.214 as a second booster dose. Pre-booster SARS-CoV-2 status was negative. Medical history included: tibia fracture and tibia reconstruction; vasectomy; hand injury and hand crush amputation; hypertension; hypothyroidism; water retention (legs and feet) due to side effect of lisinopril and sensory neuropathy in hands. There is a list of many medications including as most relevant: lisinopril, levothyroxine, hydrocodone APAP, morphine sulfate, hydralazine HCl, famotidine, heparin (2000 units/1000 mL normal saline) etc. A SAE of nephrolithiasis

(kidney stones) occurred on Study Day 44, a CT scan of the abdomen and pelvis showed a stone in the ureter and one stone in the kidney. The participant was hospitalised, underwent a left retrograde pyelogram but attempts to extract the kidney stone were unsuccessful. Antibiotics were given for kidney infection and the participant was discharged. After that, the participant returned to the hospital due to worsening flank pain, urinary tract infection (UTI) was confirmed, elevated blood pressure (183/102 mmHg) as likely secondary to pain was reported. Treatment included: ketorolac tromethamine IM; ceftriaxone IV and hydralazine IV and the catheter was replaced with an internal ureteral stent. The laboratory tests showed alteration in blood tests parameters such as increase of granulocyte, decrease of lymphocytes, low haematocrit, BUN 48 mg/dl, creatine 5.6 mg/dL, low GFR (37 mL/min/1.73 m2) and elevated transaminases. The participant was discharged again, while on (Study Day 131) reported shortening of breath, emergent department performed defibrillation and intubation to the participant, EKG showed ST abnormality, likely myocardial infarction; B-type natriuretic peptide was high at 233 pg/mL (15-100). Dead was announced, but the event was announced after the database lock, therefore was not included in the clinical database. Autopsy results reported as cause of death atherosclerotic cardiovascular disease, with obesity as a secondary contributing factor. The CHMP supported the conclusion that the event was not related to the study vaccine but more likely due to underlying disease.

**mRNA-1273 (Part F Cohort 2):** One death was reported as of data cut-off date, as follows:

- **Hypotension**: A ≥70 year old female participant with known coronary artery disease, hypertension, and hypercholesterolemia and a history of palpitations presented with sepsis and hypotension on Day 64 following an elective diagnostic catheterisation procedure conducted on Day 59 after the booster dose (mRNA-1273). The participant died on Day 64, reportedly due to these events. The participant had an asymptomatic SARS-CoV-2 infection on Day 29 after the booster dose. No autopsy was performed. No death certificate or medical records could be obtained at the time of this report. The investigator and MAH considered the event to be unrelated to the study vaccine.

The CHMP noted that the participant received the 50 µg mRNA-1273 booster dose. Pre-booster SARS-CoV-2 status was positive. The participant had a medical history as mentioned above and ongoing medications (aspirin, amlodipine, atorvastatin, nitroglycerin, and lisinopril). Unsolicited AEs of asymptomatic COVID-19 was reported 28 days after the dose was received. Less than two months after the booster dose the participant experienced chest pain and palpitations, was admitted to the hospital and underwent to catheterisation procedure which might have led to the SAE of Sepsis. After 5 days the participant experienced hypotension and reportedly died due to the events of sepsis and hypotension. As mentioned above there was no autopsy performed. The CHMP supported the conclusion to consider these events as not related to the study IP (sepsis likely due to the diagnostic procedure) and considering the atherosclerotic diseases as an underlying risk condition.

## Other Serious adverse events (SAEs)

SAEs were reported in less than 3% participants in both groups, and they were considered not to be related to the study vaccine as follows:

**mRNA-1273.214 (Part G)**: Serious TEAEs were reported for 8/437 participants (1.8%) up to data cut-off, of them there were two participants who had SAEs within 28 days (prostate cancer and traumatic fracture). These two events were considered not to be related to study vaccine.

The CHMP was of the opinion that the two SAEs of prostate cancer/ prostate cancer metastatic and the event of traumatic fracture are considered not related to the study IP, by considering these diagnoses and the medical history of the participants.

**SAEs captured in SMQs** included one case of ischemic cerebral infarction and one case of coronary artery disease described as follows:

**Ischemic cerebral infarction:** A ≥70 year old male participant received the booster dose of 50 µg mRNA-1273.214. A relevant medical history included hyperlipidemia and hypertension and ongoing medications with anti-hypertensive medications, anti-allergic and antibiotics. On Study Day 76 developed peripheral vision loss, headache, and light headedness. Participant was hospitalised and based on the findings of CT and MRI of the head it was diagnosed with Ischemic cerebral infarction (ischemic infarct right occipital). The event was ongoing at the time of data cut-off but was subsequently reported as resolved with sequelae of residual left visual field deficit. The event was reported as an AESI and was considered by the investigator and MAH to be unrelated to the study vaccine and more likely due to underlying disease.

The investigator and the MAH judged the event not to be related to the study IP, considering also the fact that the participant was on treatment with celecoxib at the time of the event, which has a known association with thromboembolic disease. This is agreed by the CHMP.

**Coronary artery disease**: A ≥70 year old male participant with history of tobacco use and a medical history of COPD, hypothyroidism, and hypercholesterolemia underwent cardiac catheterisation and was diagnosed with coronary artery disease on Day 78 after the booster. The participant underwent a coronary artery bypass graft, and the event was reported as resolved with sequelae (continuing medication) on Day 118. The event was considered by the investigator and MAH to be unrelated to the study vaccine, most likely due to underlying atherosclerotic disease. This is agreed by the CHMP.

**mRNA-1273 (Part F Cohort 2):** SAEs were reported for 10/376 participants (2.7%) up to data cut-off.

- One unrelated event of spinal osteoarthritis within 28 days.

**SAEs captured in SMQs** included two SAEs as follows:

- **Atrial fibrillation** (SMQ: cardiac arrhythmia) A 60-69 year old female participant with medical history including morbid obesity, hypertension, hypercholesterolemia, hyperthyroidism, and obstructive sleep apnea, asthma, and atrial fibrillation experienced atrial fibrillation (worsening atrial fibrillation) on Day 97 that resolved on Day 121. The event was considered by the investigator and MAH to be unrelated to the study vaccine. This is agreed by the CHMP, the event is likely due to the underlying diseases including participant's past medical history of atrial fibrillation.
- **Syncope** (SMQ: cardiomyopathy): A ≥70 year old male participant with medical history of hypercholesterolemia, hypertension, osteoarthritis, benign prostatic hyperplasia, and erectile dysfunction who was taking lisinopril, sildenafil, finasteride, ezetimibe/simvastatin, and diclofenac gel experienced syncope on Day 95 and was hospitalised after a head strike. Results of CT, MRI, and ultrasound were normal. The participant was discharged to home after 2 days, and the event resolved on Day 97. No final diagnosis was provided; the participant received no treatment. The event was considered by the investigator and MAH to be unrelated to the study vaccine. This is agreed by the CHMP, considering the medical history and ongoing treatment such as lisinopril and sildenafil which may interact due to vasodilation and could be confounders for the syncope event.

**Analyses of Adverse Events of Special Interest (AESI)**

A priority list of AESIs that may be related to COVID-19 was developed by the Brighton Collaboration (Law 2020) has been used for the study. In addition to other AESIs, investigators were to report all suspected cases of probable and confirmed myocarditis, pericarditis, or myopericarditis regardless of whether they met the CDC case definition (Gargano et al 2021). An independent CEAC was available to

assess any relevant events to determine whether they met the CDC criteria of "probable" or "confirmed" myocarditis, pericarditis, or myopericarditis.

**mRNA-1273.214 (Part G)**: AESIs were reported for 1.6% participants up to data cut-off and none within 28 days. The events considered all unrelated were as follows: ageusia (n=4), anosmia (n=3) and cerebral small vessel, ischemic disease, ischemic cerebral infarction, and atrial fibrillation (in one participant each).

**mRNA-1273 (Part F Cohort 2):** AESIs were reported for 0.8 % participants up to data cut-off. The events were: augesia and anosmia (in a single participant), supraventricular tachycardia (n=1, within 28 days) and tachycardia (n=1).

**Anaphylaxis/ Hypersensitivity**

No events of anaphylaxis were reported within 28 days after the booster for both groups.

**mRNA-1273.214 (Part G):** Two events considered related to the study vaccine; A 60-69 year old male participant experienced urticaria on Study Day 2 reported as resolved without treatment nearly on month later. An event of dermatitis (unspecified type) in a 50-59 year old female participant on Day 7 and resolved within 2 weeks and treatment included dimenhydrinate and diphenhydramine hydrochloride.

**mRNA-1273 (Part F Cohort 2):** An event of urticaria (bilateral upper arms hives) in a 50-59 year old female participant, on Day 1 and resolved within the same day, treatment included diphenhydramine hydrochloride and the event was considered as not related; a related urticaria event (generalised urticaria) started and resolved among Days 18-22. The CHMP noted that urticaria is included in section 4.8 of the SmPC. The event of dermatitis was reported as unspecified type and reported resolved within 2 weeks. The event of dermatitis could be considered covered by the broad term of 'Rash' and due to the fact that it was considered as unspecified type, follow-up information is not required at this point.

**Myocarditis and Pericarditis**

No events of myocarditis or pericarditis were reported in both booster dose groups. The additional review done for the unrecognised cases did not reveal any new cases.

**CNS Vascular Disorders**: No events of deep vein thrombosis, pulmonary embolism, or transient ischemic attack were reported for both groups. The SAE of ischemic cerebral infarction is described in the SAEs section. One non SAE of cerebral small vessel reported in a 60-69 year old female participant in the mRNA-1273.214 booster group (medical history included: obesity, hypertension, and tobacco use), considered as unrelated to the study IP.

**Arthritis**

**mRNA-1273.214 (Part G):** There were mostly arthralgia events, considered to be related to the study vaccine and occurred within 28 days. Others included: joint swelling, osteoarthritis, and rheumatoid arthritis (bilateral hands, onset on Day 27), none considered related to the study IP.

**mRNA-1273 (Part F Cohort 2):** Apart the arthralgia events there was one event of worsening lumbar osteoarthritis, and considered as unrelated by the investigator.

The CHMP noted that arthralgia is a known ADR of the original Spikevax and the bivalent Original/Omicron BA.1 vaccine applied as booster dose and is already included in the section 4.8 of the SmPC.

**Hearing and Vestibular Disorders:** No new safety concerns in both groups.

**Neurologic SMQs**: No safety concerns in both groups.

**Ageusia and Anosmia:**

**mRNA-1273.214 (Part G**): Up to data cut-off there were reported (0.9%) Ageusia and (0.7%) Anosmia, considered unrelated to study vaccine by the investigator.

**mRNA-1273 (Part F Cohort 2):** Up to data cut-off there were reported (0.3%) for ageusia and anosmia, considered as unrelated to study vaccine.

The CHMP did not identify any concerns between the two parts with regards to the ageusia and anosmia events, the participants had concurrent COVID-19.

**Hematopoietic Cytopenias:** No new safety concerns in both groups.

## Medically Attended Adverse Events (MAAEs)

**mRNA-1273.214 (Part G):** Within 28 days after second booster dose, MAAEs were reported for (11.7%) participants, and MAAEs that were considered by the investigator to be related to study vaccine were reported for 2 participants (0.5%) as follows:

- dermatitis (described in the Hypersensitivity section).
- fatigue, solicited AR, with onset on Day 2 and resolved on Day 13.

Up to data cut-off MAAEs were reported for 39.1% participants with the most commonly reported: COVID-19 (9.0%), upper RTI (3.9%) and rhinovirus infection (2.3%), considered as unrelated to the study vaccine.

**mRNA-1273 (Part F Cohort 2):** Within 28 days after second booster dose, MAAES were reported for 15.2% participants and the one considered related to the study IP were reported for 2 participants (0.5%): Hypertension and urticaria (the events are described in the respective section of the AR). Up to data cut-off, MAAEs were reported for 47.9% participants, with the most common reported: COVID-19 (9.0%), upper RTI (5.6%), coronavirus infection (3.7%), hypertension (2.7%), rhinovirus infection (2.4%), and urinary tract infection (2.1%). The most commonly reported were in the infections and infestations SOC (29.0%). No MAAEs that occurred beyond 28 days were considered by the investigator to be related to study vaccine.

More details with regards to the MAAEs for the two parts are summarised in the Table 6 below:

***Table 6 - Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cut-off Date — 2nd Booster Dose: mRNA-1273.214, mRNA-1273 Safety Set***

| System Organ Class<br>Preferred Term | Part G<br>mRNA-1273.214<br>50 ug<br>(N=437)<br>n (%)<br>Any | Related | Part F Cohort 2<br>mRNA-1273<br>50 ug<br>(N=376)<br>n (%)<br>Any | Related |
|---|---|---|---|---|
| Number of Subjects Reporting<br>Medically-Attended TEAEs | 171 (39.1) | 2 (0.5) | 180 (47.9) | 2 (0.5) |
| Number of Medically-Attended TEAEs | 268 | 2 | 292 | 2 |
| Infections and infestations | 104 (23.8) | 0 | 109 (29.0) | 0 |
| COVID-19 | 49 (11.2) | 0 | 34 (9.0) | 0 |
| Upper respiratory tract infection | 17 (3.9) | 0 | 21 (5.6) | 0 |
| Rhinovirus infection | 10 (2.3) | 0 | 9 (2.4) | 0 |
| Coronavirus infection | 7 (1.6) | 0 | 14 (3.7) | 0 |
| Urinary tract infection | 7 (1.6) | 0 | 8 (2.1) | 0 |
| Sinusitis | 5 (1.1) | 0 | 5 (1.3) | 0 |
| Viral upper respiratory tract infection | 5 (1.1) | 0 | 2 (0.5) | 0 |
| Cellulitis | 3 (0.7) | 0 | 0 | 0 |
| Influenza | 2 (0.5) | 0 | 2 (0.5) | 0 |
| Parainfluenzae virus infection | 2 (0.5) | 0 | 5 (1.3) | 0 |
| Pharyngitis | 2 (0.5) | 0 | 0 | 0 |
| Postoperative wound infection | 2 (0.5) | 0 | 0 | 0 |
| Sinusitis bacterial | 2 (0.5) | 0 | 0 | 0 |
| Infections and infestations (Cont.) | | | | |
| Alveolar osteitis | 1 (0.2) | 0 | 0 | 0 |
| Laryngitis | 1 (0.2) | 0 | 0 | 0 |
| Otitis media acute | 1 (0.2) | 0 | 0 | 0 |
| Periorbital cellulitis | 1 (0.2) | 0 | 0 | 0 |
| Pharyngitis streptococcal | 1 (0.2) | 0 | 1 (0.3) | 0 |
| Respiratory tract infection viral | 1 (0.2) | 0 | 4 (1.1) | 0 |
| Staphylococcal skin infection | 1 (0.2) | 0 | 0 | 0 |
| Suspected COVID-19 | 1 (0.2) | 0 | 1 (0.3) | 0 |
| Tooth abscess | 1 (0.2) | 0 | 0 | 0 |
| Viral infection | 1 (0.2) | 0 | 2 (0.5) | 0 |
| Abscess limb | 0 | 0 | 1 (0.3) | 0 |
| Acute sinusitis | 0 | 0 | 1 (0.3) | 0 |
| Asymptomatic COVID-19 | 0 | 0 | 2 (0.5) | 0 |
| Bronchitis | 0 | 0 | 4 (1.1) | 0 |
| Conjunctivitis | 0 | 0 | 1 (0.3) | 0 |
| Corneal infection | 0 | 0 | 1 (0.3) | 0 |
| Ear infection | 0 | 0 | 3 (0.8) | 0 |
| Erythema migrans | 0 | 0 | 1 (0.3) | 0 |
| Infections and infestations (Cont.) | | | | |
| Gastroenteritis | 0 | 0 | 1 (0.3) | 0 |
| Gastroenteritis viral | 0 | 0 | 1 (0.3) | 0 |
| Localised infection | 0 | 0 | 1 (0.3) | 0 |
| Nasopharyngitis | 0 | 0 | 2 (0.5) | 0 |
| Otitis media | 0 | 0 | 2 (0.5) | 0 |
| Pneumonia | 0 | 0 | 3 (0.8) | 0 |
| Tonsillitis | 0 | 0 | 1 (0.3) | 0 |
| Tooth infection | 0 | 0 | 2 (0.5) | 0 |
| Ureaplasma infection | 0 | 0 | 1 (0.3) | 0 |
| Vulvovaginal mycotic infection | 0 | 0 | 2 (0.5) | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 9 (2.1) | 0 | 2 (0.5) | 0 |
| Prostate cancer | 2 (0.5) | 0 | 0 | 0 |
| Basal cell carcinoma | 1 (0.2) | 0 | 1 (0.3) | 0 |
| Benign lung neoplasm | 1 (0.2) | 0 | 0 | 0 |
| Invasive ductal breast carcinoma | 1 (0.2) | 0 | 0 | 0 |
| Malignant melanoma | 1 (0.2) | 0 | 0 | 0 |

The CHMP noted that with regards to the MAAEs (related and unrelated to vaccination), there were no safety signals identified for both two parts. The incidence of MAAEs after the second booster dose of mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1) was lower compared to the incidence of MAAEs after the second booster dose with the original Spikevax (mRNA-1273), respectively 39.1% vs 47.9%. The same applies for the SOCs accordingly 23.8% vs 29.0%, and no significant imbalances were observed for the PT events between the two groups.

## Laboratory findings

No laboratory evaluation has been performed in the trial. No clinical concerns arose from review of vital signs data.

### Safety in special populations

No special population has been included in the trial.

### Pregnancies

No pregnancies were reported at the time of the data cut-off.

## Safety related to drug-drug interactions and other interactions

Drug-drug interactions and other interactions are not part of the scope of this trial.

## Discontinuation due to adverse events

There were no unsolicited AEs leading to discontinuation from study vaccine or study participation within 28 days or up to the data cut-off date, in both parts of the study.

## 2. Study P205 Part H (mRNA- 1273.222)

In the part H, Study P205, have been enrolled 511 participants, the median interval between the first booster dose of 50 µg mRNA-1273 and the 50 µg mRNA 1273.222 dose was 289 days and the median follow-up duration after the mRNA-1273.222 booster dose was 37 days. Participants age group was 18 years of age and older. The Table 7 below summarises the solicited local and systemic ARs:

***Table 7 - Summary of Participants with Solicited Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.222 (Solicited Safety Set)***

| | P205 Part H |
|---|---|
| **Solicited Adverse Reaction Category Grade** | **mRNA-1273.222 50 µg (N=508) n (%)** |
| Solicited adverse reactions - N1 | 508 |
| Any solicited adverse reactions | 443 (87.2) |
| 95% CI | 84.0, 90.0 |
| Grade 1 | 219 (43.1) |

| | |
|---|---|
| Grade 2 | 165 (32.5) |
| Grade 3 | 59 (11.6) |
| Grade 4 | 0 |
| Solicited local adverse reactions - N1 | 507 |
| Any solicited local adverse reactions | 420 (82.8) |
| 95% CI | 79.3, 86.0 |
| Grade 1 | 329 (64.9) |
| Grade 2 | 63 (12.4) |
| Grade 3 | 28 (5.5) |
| Grade 4 | 0 |
| Pain - N1 | 507 |
| Any | 418 (82.4) |
| Grade 1 | 344 (67.9) |
| Grade 2 | 54 (10.7) |
| Grade 3 | 20 (3.9) |
| Grade 4 | 0 |
| Erythema (redness)[a] - N1 | 507 |
| Any | 23 (4.5) |
| Grade 1 | 10 (2.0) |
| Grade 2 | 8 (1.6) |
| Grade 3 | 5 (1.0) |
| Grade 4 | 0 |
| Swelling (hardness)- N1 | 507 |
| Any | 40 (7.9) |
| Grade 1 | 22 (4.3) |
| Grade 2 | 13 (2.6) |
| Grade 3 | 5 (1.0) |
| Grade 4 | 0 |
| Axillary swelling or tenderness - N1 | 507 |
| Any | 106 (20.9) |
| Grade 1 | 86 (17.0) |
| Grade 2 | 19 (3.7) |
| Grade 3 | 1 (0.2) |
| Grade 4 | 0 |
| Solicited systemic adverse reactions - N1 | 508 |
| Any solicited systemic adverse reactions | 372 (73.2) |
| 95% CI | 69.2, 77.0 |
| Grade 1 | 172 (33.9) |
| Grade 2 | 165 (32.5) |
| Grade 3 | 35 (6.9) |
| Grade 4 | 0 |
| Fever[b] - N1 | 507 |
| Any | 20 (3.9) |
| Grade 1 | 12 (2.4) |
| Grade 2 | 7 (1.4) |
| Grade 3 | 1 (0.2) |
| Grade 4 | 0 |
| Headache - N1 | 507 |
| Any | 249 (49.1) |

| | P205 Part H |
|---|---|
| Solicited Adverse Reaction<br>Category<br>Grade | mRNA-1273.222<br>50 µg<br>(N=508)<br>n (%) |
| Grade 1 | 164 (32.3) |
| Grade 2 | 73 (14.4) |
| Grade 3 | 12 (2.4) |
| Grade 4 | 0 |
| Fatigue - N1 | 508 |
| Any | 304 (59.8) |
| Grade 1 | 161 (31.7) |
| Grade 2 | 126 (24.8) |
| Grade 3 | 17 (3.3) |
| Grade 4 | 0 |
| Myalgia - N1 | 507 |
| Any | 235 (46.4) |
| Grade 1 | 127 (25.0) |
| Grade 2 | 88 (17.4) |
| Grade 3 | 20 (3.9) |
| Grade 4 | 0 |
| Arthralgia - N1 | 507 |
| Any | 177 (34.9) |
| Grade 1 | 108 (21.3) |
| Grade 2 | 60 (11.8) |
| Grade 3 | 9 (1.8) |
| Grade 4 | 0 |
| Nausea/vomiting - N1 | 507 |
| Any | 71 (14.0) |
| Grade 1 | 56 (11.0) |
| Grade 2 | 14 (2.8) |
| Grade 3 | 1 (0.2) |
| Grade 4 | 0 |
| Chills - N1 | 507 |
| Any | 112 (22.1) |
| Grade 1 | 60 (11.8) |
| Grade 2 | 48 (9.5) |
| Grade 3 | 4 (0.8) |
| Grade 4 | 0 |

Abbreviations: CI = confidence interval.

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method.

[a] Toxicity grade for erythema (redness) is defined as: Grade 1 = 25 – 50 mm; Grade 2 = 51 – 100 mm; Grade 3 = greater than 100 mm.

[b] Toxicity grade for fever is defined as: Grade 1 = 38 – 38.4 °C; Grade 2 = 38.5 – 38.9 °C; Grade 3 = 39 – 40 °C; Grade 4 = greater than 40 °C.

Source: Appendix D, Table 14.3.1.1.1.9.

The CHMP noted that the safety data was evaluated during EMEA/H/C/005791/077 and a summary is provided as follows: after the 2nd booster dose of 50 µg mRNA 1273.222 the following was reported: any solicited adverse reactions by 87.2% participants; local ARs (82.8%) with pain as most common (82.4%); systemic ARs (73.2%) with fatigue as most common (59.8%). No clinically meaningful

imbalances were seen in subgroup analyses with regards to the frequencies when stratifying according to the age group: Solicited ARs were more reported in the ≥18 to <65 years age group (89.8%) compared to the ≥65 years age group with (77.1%). Mostly of the events were Grade 1 or Grade 2 and Grade 3 accordingly (12.2% versus 9.5%). No grade 4 were reported. Unsolicited AEs considered vaccine related were reported by 7.8% participants, MAAEs reported by 13.7 % participants and none considered to be related to the Study IP. There was one death: Subarachnoid haemorrhage reported in a ≥70 year old male participant, assessed as not related to the vaccine due to the participants underlying disease and medications. There were four SAEs reported in 3 participants: the fatal event of Subarachnoid haemorrhage; events of anginal equivalent and syncope and one event of anaemia, considered as unrelated to the vaccination.

No events of potential myocarditis or pericarditis were identified with the CMQ for participants in the mRNA-1273.222 50 µg (Part H). From the post-marketing experience there was one reported case of 'unassessable' pericarditis due to important missing information.

Overall, the CHMP considered that the review of the clinical safety data of mRNA-1273.222 showed that the benefit-risk profile of Spikevax bivalent Original/Omicron BA.4-5 booster vaccine is favourable for individuals 12 years of age and older.

### Post-marketing experience

Spikevax Bivalent .222 (Original/BA.4/5) received an emergency use authorisation in the US for use as a booster dose in individuals 18 years of age and older on 31st August 2022. In Europe, Spikevax bivalent Original/Omicron BA.4-5 received CHMP authorisation to be administered as a booster dose for adults and children from 12 years of age who have already had a primary vaccination course against COVID-19 on 19th October 2022. During procedure EMEA/H/C/005791/077, the following post-marketing experience with Spikevax bivalent Original/Omicron BA.4-5 was provided: Cumulatively as of 18th October 2022, 677 cases (1,922 events) were reported to the MAH, of those 376 cases were medically confirmed, 37 cases (69 events) were serious, and 2 cases were reported with a fatal outcome. The mean age was 60.3 years and the most of the cases were reported in females (43.6%) compared to males (27.0%), and (29.4%) cases had missing sex information. The majority of cases were non-serious (94.5%). Cumulatively, the most frequently reported clinical events associated with mRNA-1273.222 booster included pyrexia (2.7%), fatigue (2.3%), vaccination site pain (2.3%), chills (2.2%), and pain in extremity (2.2%). Events coded as "No adverse event" (18.0%) were often associated with events involving product administration errors (eg, accidental underdose (9.4%), wrong product administered (2.2%), etc. The 2 events (0.1%) with a reported fatal outcome, were one case of unknown death cause in a female participant and the second fatal case was reported in a male participant with underlying diseases including blood clot problems. With regards to myocarditis and pericarditis cases there was one reported pericarditis case concerning a male of unknown age who had a family history of atrial fibrillation and heart rate increased. According to the WHO-UMC standardised case causality assessment (WHO 2013), this case was assessed as "unassessable" due to important missing information including exposure information, time to onset, laboratory values, medical history and clinical course.

## 3. Study mRNA-1273-P204

The safety data used to support the marketing authorisation of Spikevax bivalent Original/Omicron BA.1 in individuals 6 through 11 years of age has been assessed during EMEA/H/C/005791/II/83/G and are not repeated here. However, in response to request for supplementary information during this procedure, the MAH submitted the following information:

- Booster safety data from P203 12-17yo with 6 months of safety follow-up on at least 1000 boosted participants can be provided in the form of a CSR in May 2023.
- Longer term safety data for a booster dose in 6 through 11 years of age (6 months of safety follow-up on at least 1000 boosted participants) is anticipated to be available at the end of 2023. As participants in P204 are still being boosted currently, the proposed timing is tentative.

**Solicited Local Adverse Reactions (ARs)**

The incidences of any local solicited ARs were similar across all of the age groups, from 87.3% to 92.1%. Most of the events were Grade 1 and Grade 2; the 6 through 11 years of age group tended to have more Grade 2 events than the other groups. Grade 3 events occurred less frequently, and more frequently after a 100 µg booster dose than a 50 µg booster dose; no trends were identified across the age ranges. There were no Grade 4 solicited local ARs. The most commonly reported solicited local AR was pain, with a similar incidence across age ranges (86.1% to 91.7%). This was followed by axillary swelling or tenderness (21.3% to 28.0%), which tended to occur more commonly in the two younger age groups, including Grade 3 events which were not reported in the adult groups. Overall, no major differences in local reactogenicity were noted across the age groups.

***Table 8 – Frequency of solicited local adverse reactions***

**Frequency of Solicited Local Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ≥6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose**

| Event | Study P204 | Study P203 | P201 (B) | P205 (G) |
|---|---|---|---|---|
| | ≥6 to <12 years mRNA-1273 50 µg Primary Series – 25 µg Booster (N=1280) n (%) | 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) |
| Solicited Local Adverse Reaction | N1=1279 | N1=1312 | N1=79 | N1=263 |
| Any solicited local adverse reactions | 1165 (91.1) | 1208 (92.1) | 69 (87.3) | 235 (89.4) |
| Grade 1 | 722 (56.5) | 835 (63.6) | 48 (60.8) | 193 (73.4) |
| Grade 2 | 410 (32.1) | 316 (24.1) | 17 (21.5) | 32 (12.2) |
| Grade 3 | 33 (2.6) | 57 (4.3) | 4 (5.1) | 10 (3.8) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Pain | N1=1279 | N1=1312 | N1=79 | N1=263 |
| Any | 1152 (90.1) | 1196 (91.2) | 68 (86.1) | 231 (87.8) |
| Grade 1 | 778 (60.8) | 900 (68.6) | 50 (63.3) | 202 (76.8) |
| Grade 2 | 350 (27.4) | 257 (19.6) | 15 (19.0) | 27 (10.3) |
| Grade 3 | 24 (1.9) | 39 (3.0) | 3 (3.8) | 2 (0.8) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Erythema (redness) | N1= 1279 | N1=1311 | N1=79 | N1=263 |
| Any | 137 (10.7) | 120 (9.2) | 5 (6.3) | 20 (7.6) |
| Grade 1 | 67 (5.2) | 59 (4.4) | 2 (2.5) | 10 (3.8) |
| Grade 2 | 66 (5.2) | 53 (4.0) | 2 (2.5) | 3 (1.1) |
| Grade 3 | 4 (0.3) | 9 (0.7) | 1 (1.3) | 7 (2.7) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Swelling (hardness) | N1= 1279 | 1311 | N1=79 | N1=263 |
| Any | 139 (10.9) | 176 (13.4) | 5 (6.3) | 22 (8.4) |
| Grade 1 | 83 (6.5) | 98 (7.5) | 3 (3.8) | 12 (4.6) |
| Grade 2 | 52 (4.1) | 69 (5.3) | 2 (2.5) | 6 (2.3) |
| Grade 3 | 4 (0.3) | 9 (0.7) | 0 | 4 (1.5) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Axillary (or groin) swelling or tenderness | N1= 1279 | N1=1311 | N1=79 | N1=263 |
| Any | 355 (27.8) | 367 (28.0) | 22 (27.8) | 56 (21.3) |
| Grade 1 | 245 (19.2) | 310 (23.6) | 18 (22.8) | 53 (20.2) |
| Grade 2 | 106 (8.3) | 53 (4.0) | 3 (3.8) | 3 (1.1) |
| Grade 3 | 4 (0.3) | 4 (0.3) | 1 (1.3) | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1=Number of exposed participants who submitted any data for the event.

Note: Any=Grade 1 or higher. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Percentages are based on the number of exposed participants who submitted any data for the event (N1). Pain is injection site pain or tenderness. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 2=51-100 mm; Grade 3=>100 mm; Grade 4=necrosis or exfoliative dermatitis. Toxicity grade for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization. The Solicited Safety Set consists of all

**Solicited Systemic Adverse Reactions**

The incidence of solicited systemic ARs was similar across the 3 older age groups (74.7% to

76.6%) in contrast to children (6 through 11 years of age group) in which the overall rate was 64.3%. Rates of solicited systemic ARs were the lowest in all categories in the 6 through 11 years of age group except for fever where children had the highest rate (8.5%), including one Grade 4 event. Fever was least common in the mRNA-1273.214 group (3.4%). Children (6 through 11 years of age group) generally experienced lower incidence rates than the older 3 age groups for the solicited systemic ARs of

headache, fatigue, myalgia, arthralgia, and chills with absolute differences of 10 to 20%. Systemic reactogenicity tended to be lower in the mRNA-1273.214 group compared to the adolescent and adult mRNA-1273 groups in the events of fever, headache, nausea/vomiting, and chills.

Across the groups the incidence of Grade 3 systemic ARs ranged from 6.0% to 8.2%, with children (6 through 11 years of age group) having the lowest overall incidence and adolescents having the highest.

As reporting rates were low for individual event terms, differences across the groups were not notable. The largest difference was for myalgia, where children (6 through 11 years of age) had Grade 3 ARs in 1.9% whereas the other age groups had Grade 3 events in 3.4% to 3.8% of participants.

Overall, while children (6 through 11 years of age group) tended to demonstrate less systemic reactogenicity than older age groups with the exception of fever, there were no findings concerning for overall tolerability in any of the treatment groups.

***Table 9 – Frequency of solicited systemic adverse reactions***

**Frequency of Solicited Systemic Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ≥6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose**

| Solicited Adverse reaction Category Grade | P204<br>≥6 to <12 years<br>mRNA-1273<br>50 µg Primary Series–<br>25 µg Booster<br>N=1280<br>n (%) | P203<br>12 to <18 Years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>(N=1312)<br>n (%) | P201 (B)<br>≥18 to <55 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>N=79<br>N (%) | P205 (G)<br>≥18 to <65 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster -<br>mRNA-1273.214<br>50 µg Booster<br>N=263<br>n (%) |
|---|---|---|---|---|
| Solicited adverse reaction | N1=1280 | N1=1311 | N1=79 | N1=263 |
| Any Solicited Systemic Adverse Reactions | 823 (64.3) | 1004 (76.6) | 59 (74.7) | 197 (74.9) |
| Grade 1 | 414 (32.3) | 463 (35.3) | 23 (29.1) | 102 (38.8) |
| Grade 2 | 331 (25.9) | 433 (33.0) | 29 (36.7) | 78 (29.7) |
| Grade 3 | 77 (6.0) | 108 (8.2) | 6 (7.6) | 17 (6.5) |
| Grade 4 | 1 (<0.1) | 0 | 0 | 0 |

| Solicited Adverse reaction Category Grade | P204<br>≥6 to <12 years<br>mRNA-1273<br>50 µg Primary Series–<br>25 µg Booster<br>N=1280<br>n (%) | P203<br>12 to <18 Years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>(N=1312)<br>n (%) | P201 (B)<br>≥18 to <55 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>N=79<br>N (%) | P205 (G)<br>≥18 to <65 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster -<br>mRNA-1273.214<br>50 µg Booster<br>N=263<br>n (%) |
|---|---|---|---|---|
| Fever | N1=1276 | N1=1297 | N1=79 | N1=262 |
| Any | 108 (8.5) | 79 (6.1) | 6 (7.6) | 9 (3.4) |
| Grade 1 | 59 (4.6) | 45 (3.5) | 4 (5.1) | 6 (2.3) |
| Grade 2 | 32 (2.5) | 26 (2.0) | 1 (1.3) | 2 (0.8) |
| Grade 3 | 16 (1.3) | 8 (0.6) | 1 (1.3) | 1 (0.4) |
| Grade 4 | 1 (<0.1) | 0 | 00 | 0 |
| Headache | N1=1280 | N1=1311 | N1=79 | N1=263 |
| Any | 489 (38.2) | 748 (57.1) | 45 (57.0) | 129 (49.0) |
| Grade 1 | 275 (21.5) | 492 (37.5) | 28 (35.4) | 96 (36.5) |
| Grade 2 | 192 (15.0) | 228 (17.4) | 16 (20.3) | 29 (11.0) |
| Grade 3 | 22 (1.7) | 28 (2.1) | 1 (1.3) | 4 (1.5) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Fatigue | N1=1279 | N1=1311 | N1=79 | N1=263 |
| Any | 625 (48.9) | 769 (58.7) | 46 (58.2) | 154 (58.6) |
| Grade 1 | 340 (26.6) | 364 (27.8) | 18 (22.8) | 75 (28.5) |
| Grade 2 | 238 (18.6) | 352 (26.8) | 25 (31.6) | 69 (26.2) |
| Grade 3 | 47 (3.7) | 53 (4.0) | 3 (3.8) | 10 (3.8) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Myalgia | N1=1280 | N1=1311 | N1=79 | N1=263 |
| Any | 269 (21.0) | 529 (40.4) | 37 (46.8) | 114 (43.3) |
| Grade 1 | 147 (11.5) | 274 (20.9) | 19 (24.1) | 64 (24.3) |
| Grade 2 | 103 (8.0) | 208 (15.9) | 15 (19.0) | 41 (15.6) |
| Grade 3 | 19 (1.5) | 47 (3.6) | 3 (3.8) | 9 (3.4) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Arthralgia | N1=1279 | N1=1311 | N1=79 | N1=263 |
| Any | 160 (12.5) | 316 (24.1) | 34 (43.0) | 87 (33.1) |
| Grade 1 | 102 (8.0) | 184 (14.0) | 20 (25.3) | 56 (21.3) |
| Grade 2 | 46 (3.6) | 115 (8.8) | 12 (15.2) | 28 (10.6) |
| Grade 3 | 12 (0.9) | 17 (1.3) | 2 (2.5) | 3(1.1) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Nausea/vomiting | N1=1279 | N1=1311 | N1=79 | N1=263 |
| Any | 168 (13.1) | 234 (17.8) | 12 (15.2) | 35 (13.3) |
| Grade 1 | 126 (9.9) | 180 (13.7) | 12 (15.2) | 31 (11.8) |
| Grade 2 | 36 (2.8) | 52 (4.0) | 0 | 4 (1.5) |
| Grade 3 | 6 (0.5) | 2 (0.2) | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |
| Chills | N1=1279 | N1=1311 | N1=79 | N1=263 |
| Any | 179 (14.0) | 399 (30.4) | 30 (38.0) | 64 (24.3) |

| Solicited Adverse reaction Category Grade | P204<br>≥6 to <12 years<br>mRNA-1273<br>50 µg Primary Series–<br>25 µg Booster<br>N=1280<br>n (%) | P203<br>12 to <18 Years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>(N=1312)<br>n (%) | P201 (B)<br>≥18 to <55 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster<br>N=79<br>N (%) | P205 (G)<br>≥18 to <65 years<br>mRNA-1273<br>100 µg Primary Series –<br>50 µg Booster -<br>mRNA-1273.214<br>50 µg Booster<br>N=263<br>n (%) |
|---|---|---|---|---|
| Grade 1 | 118 (9.2) | 251 (19.1) | 20 (25.3) | 38 (14.4) |
| Grade 2 | 57 (4.5) | 141 (10.8) | 10 (12.7) | 25 (9.5) |
| Grade 3 | 4 (0.3) | 7 (0.5) | 0 | 1 (0.4) |
| Grade 4 | 0 | 0 | 0 | 0 |

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1 = Number of exposed participants who submitted any data for the event.

Study P204 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Pain for participant age 37 months to <12 years is injection site pain. Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participant age 37 months to < 12 years is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm; G4 = Necrosis or exfoliative dermatitis. Toxicity grade for Axillary swelling or tenderness for participant age 37 months to < 12 years is defined as: G1 = No interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization. Toxicity grade for Fever for participant age 37 months to < 12 years is defined as: G1 = 38 — 38.4 °C; G2 = 38.5 — 38.9 °C; G3 = 39 — 40 °C; G4 = > 40 °C.

Study P203 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who received BD in Part C, and contribute any solicited AR data (ie, had at least 1 post-booster solicited safety assessment in Part C).

[a] Toxicity grade for erythema (redness) is defined as: G1 = 25 - 50 mm; G2 = 51 - 100 mm; G3 = > 100 mm.

Study P205 Notes: Toxicity grade for Erythema (Redness) is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm. Toxicity grade for Fever is defined as: G1 = 38 — 38.4 C; G2 = 38.5 — 38.9 C; G3 = 39 — 40 C; G4 = > 40 C. This interim analysis includes Part F Cohort 2 mRNA-1273 and Part G subjects immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27APR2022.

Source: P204: Table 14.3.1.3.7.1.2, Table 14.1.8.3.2; P203: Table 14.3.1.1.1.5.1, Table 14.1.5.3.5; P201: Table 14.3.1.1.4.1; P205: Table 14.3.1.1.1.8

**Unsolicited Adverse Events**

Common unsolicited events (occurring in ≥1% in any group) are presented in the table below. In study P205, subgroup analysis was not performed for unsolicited AEs, therefore the data is comprised of all adults in the cohort.

The incidences of unsolicited AEs were similar across age groups with the exception of the P201 group where event rates were lower than the other 3 groups (7.3% vs. 13.1% to 18.5%).

The size of the treatment group for P201 was also notably smaller than the other groups. Most of the events reported within 28 days after booster dose injection were respiratory-related infections and reactogenicity-related events. These events occurred with similar rates across groups. There were very few severe events and the findings are typical for the safety profile of mRNA-1273 across clinical trials.

***Table 10 - Frequency of unsolicited TEAEs***

**Frequency of Unsolicited TEAEs with Occurrence in ≥ 1% of Participants in Any Treatment Group up to 28 Days After Injection Classified by MedDRA System Organ Class and Preferred Term (Safety Set)**

| System Organ Class<br>Preferred Term | P204 | | P203 | | P201 | | P205 (G) | |
|---|---|---|---|---|---|---|---|---|
| | mRNA-1273 50 µg Primary Series – 25 µg Booster N=1294 n (%) | | 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1346) n (%) | | ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=82) n (%) | | ≥18 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=437 n (%) | |
| | Any | Severe | Any | Severe | Any | Severe | Any | Severe |
| **Number of participants reporting unsolicited adverse events** | 169 (13.1) | 7 (0.5) | 191 (14.2) | 3 (0.2) | 6 (7.3) | 0 | 81 (18.5) | 4 (0.9) |
| **Number of unsolicited adverse events** | 238 | 13 | 263 | 3 | 8 | 0 | 114 | 5 |
| **Infections and infestations** | 80 (6.2) | 0 | 102 (7.6) | 0 | 2 (2.4) | 0 | 29 (6.6) | 0 |
| COVID-19 | 25 (1.9) | 0 | 41 (3.0) | 0 | 2 (2.4) | 0 | 5 (1.1) | 0 |
| Asymptomatic COVID-19 | 6 (0.5) | 0 | 17 (1.3) | 0 | 0 | 0 | 2 (0.5) | 0 |
| Upper respiratory tract infection | 17 (1.3) | 0 | 16 (1.2) | 0 | 0 | 0 | 5 (1.1) | 0 |
| Urinary tract infection | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 1 (0.2) | 0 |
| **Immune System Disorder** | 5 (0.4) | 0 | 1 (<0.1) | 1 (<0.1) | 1 (1.2) | 0 | 0 | 0 |
| Allergy to arthropod bite | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 0 | 0 |
| **Psychiatric disorders** | 3 (0.2) | 0 | 6 (0.4) | 0 | 1 (1.2) | 0 | 0 | 0 |
| Anxiety | 0 | 0 | 2 (0.1) | 0 | 1 (1.2) | 0 | 0 | 0 |
| **Nervous system disorders** | 15 (1.2) | 1 (<0.1) | 26 (1.9) | 0 | 2 (2.4) | 0 | 8 (1.8) | 0 |
| Headache | 15 (1.2) | 1 (<0.1) | 26 (1.9) | 0 | 2 (2.4) | 0 | 7 (1.6) | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | 23 (1.8) | 0 | 11 (0.8) | 0 | 0 | 0 | 5 (1.1) | 0 |
| **Skin and subcutaneous tissue disorders** | 13 (1.0) | 0 | 12 (0.9) | 0 | 0 | 0 | 4 (0.9) | 0 |
| **Musculoskeletal and connective tissue disorders** | 9 (0.7) | 2 (0.2) | 13 (1.0) | 0 | 0 | 0 | 14 (3.2) | 0 |
| Myalgia | 3 (0.2) | 2 (0.2) | 7 (0.5) | 0 | 0 | 0 | 5 (1.1) | 0 |
| Arthralgia | 4 (0.3) | 0 | 5 (0.4) | 0 | 0 | 0 | 7 (1.6) | 0 |
| **General disorders and administration site conditions** | 34 (2.6) | 5 (0.4) | 43 (3.2) | 1 (<0.1) | 1 (1.2) | 0 | 21 (4.8) | 1 (0.2) |
| Fatigue | 13 (1.0) | 3 (0.2) | 23 (1.7) | 1 (<0.1) | 1 (1.2) | 0 | 11 (2.5) | 1 (0.2) |
| **Injury, poisoning and procedural complications** | 8 (0.6) | 0 | 14 (1.0) | 0 | 0 | 0 | 9 (2.1) | 1 (0.2) |

Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of exposed participants who reported the event on any day within 28 days of the booster dose; TEAE=treatment-emergent adverse event.

Note: Data from P204 includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants (N) in booster dose analysis.

Note: Data from P203 includes mRNA-1273-booster group. Percentages are based on the number of safety participants in Part C.

Note: Data from P301 is the Total of mRNA-1273-booster + placebo-mRNA-1273-booster. Percentages are based on the number of Part C safety subjects between 18-25 years of age.

Note: Data from P205 Part G interim analysis includes immunogenicity data up to Day 29 visit.

Source: P204: Table 14.3.1.10.3.2, P203: Table 14.3.1.8.5.1.1; P201: Table 14.3.1.8.3.1, Table 14.3.1.16.3.1; P205: Table 14.3.1.8.1.8, Table 14.3.1.15.1.8

The CHMP noted that the intended approach is to support the administration of a 25 µg booster dose of mRNA-1273.222 based on the safety and reactogenicity profile after administration of 25 µg of mRNA-1273 as a booster dose to children 6 through 11 years of age, and to extrapolate from the known safety profile of a booster dose of mRNA-1273.214 and of the safety profile of a booster dose mRNA-1273.222 (with a short follow-up duration of 37 days) given to adults.

To support the indication extension of mRNA-1273.222 to children 6 through 11 years of age without safety data for the mRNA-1273.222 variant vaccine in this age group, the MAH was requested to submit a comparative table summarising the reactogenicity profile of a booster dose of mRNA-1273 in three age groups (children 6 through 11 years of age; adolescent 12-<17 years and in young adults 18-25 years of age) and the solicited ARs after a booster dose of mRNA-1273.214 in adults 18-25 and the solicited ARs after a booster dose of mRNA-1273.222 in the same age group (young adults 18-25 years). A similar table for unsolicited AEs (unrelated and considered being vaccine related) was also requested. The MAH was also requested to provide a discussion of the robustness of the extrapolation of the safety data across these groups (i.e. from children to adolescents and to adults, particularly focusing on the safety profile of a booster dose of the mRNA-1273.222 in adults.

The comparative tables with regards to the solicited ARs and unsolicited ARs across vaccine groups were provided as follows:

***Table 11 – Frequency of Solicited Local Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ⩾6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose***

| Event | Study P204 | Study P203 | P201 (B) | P205 (G) | P205 Part H |
|---|---|---|---|---|---|
| | ≥6 to <12 years mRNA-1273 50 µg Primary Series – 25 µg Booster (N=1280) n (%) | 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster (N=403) n (%) |
| Solicited Local Adverse Reaction | N1=1279 | N1=1312 | N1=79 | N1=263 | N=402 |
| Any solicited local adverse reactions | 1165 (91.1) | 1208 (92.1) | 69 (87.3) | 235 (89.4) | 347 (86.3) |
| Grade 1 | 722 (56.5) | 835 (63.6) | 48 (60.8) | 193 (73.4) | 267 (66.4) |
| Grade 2 | 410 (32.1) | 316 (24.1) | 17 (21.5) | 32 (12.2) | 57 (14.2) |
| Grade 3 | 33 (2.6) | 57 (4.3) | 4 (5.1) | 10 (3.8) | 23 (5.7) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Pain | N1=1279 | N1=1312 | N1=79 | N1=263 | N=402 |
| Any | 1152 (90.1) | 1196 (91.2) | 68 (86.1) | 231 (87.8) | 347 (86.3) |
| Grade 1 | 778 (60.8) | 900 (68.6) | 50 (63.3) | 202 (76.8) | 279 (69.4) |
| Grade 2 | 350 (27.4) | 257 (19.6) | 15 (19.0) | 27 (10.3) | 49 (12.2) |
| Grade 3 | 24 (1.9) | 39 (3.0) | 3 (3.8) | 2 (0.8) | 19 (4.7) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Erythema (redness) | N1= 1279 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 137 (10.7) | 120 (9.2) | 5 (6.3) | 20 (7.6) | 17 (4.2) |
| Grade 1 | 67 (5.2) | 59 (4.4) | 2 (2.5) | 10 (3.8) | 9 (2.2) |
| Grade 2 | 66 (5.2) | 53 (4.0) | 2 (2.5) | 3 (1.1) | 5 (1.2) |
| Grade 3 | 4 (0.3) | 9 (0.7) | 1 (1.3) | 7 (2.7) | 3 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Swelling (hardness) | N1= 1279 | 1311 | N1=79 | N1=263 | N=402 |
| Any | 139 (10.9) | 176 (13.4) | 5 (6.3) | 22 (8.4) | 32 (8.0) |
| Grade 1 | 83 (6.5) | 98 (7.5) | 3 (3.8) | 12 (4.6) | 19 (4.7) |
| Grade 2 | 52 (4.1) | 69 (5.3) | 2 (2.5) | 6 (2.3) | 11 (2.7) |
| Grade 3 | 4 (0.3) | 9 (0.7) | 0 | 4 (1.5) | 2 (0.5) |

| Event | Study P204 | Study P203 | P201 (B) | P205 (G) | P205 Part H |
|---|---|---|---|---|---|
| | ≥6 to <12 years mRNA-1273 50 µg Primary Series – 25 µg Booster (N=1280) n (%) | 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster (N=403) n (%) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Axillary (or groin) swelling or tenderness | N1= 1279 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 355 (27.8) | 367 (28.0) | 22 (27.8) | 56 (21.3) | 91 (22.6) |
| Grade 1 | 245 (19.2) | 310 (23.6) | 18 (22.8) | 53 (20.2) | 72 (17.9) |
| Grade 2 | 106 (8.3) | 53 (4.0) | 3 (3.8) | 3 (1.1) | 18 (4.5) |
| Grade 3 | 4 (0.3) | 4 (0.3) | 1 (1.3) | 0 | 1 (0.2) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1=Number of exposed participants who submitted any data for the event.

Note: Any=Grade 1 or higher. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Percentages are based on the number of exposed participants who submitted any data for the event (N1). Pain is injection site pain or tenderness. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 2=51-100 mm; Grade 3=>100 mm; Grade 4=necrosis or exfoliative dermatitis. Toxicity grade for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment).

Source: P204: Table 14.3.1.3.7.1.2; P203: Table 14.3.1.1.1.5.1; P201: Table 14.3.1.1.4.1; P205 (G): Table 14.3.1.1.1.8: P205 (H): Table 14.3.1.1.2.9

***Table 12 – Frequency of Solicited Systemic Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ⩾6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose***

| Solicited Adverse reaction Category Grade | P204 | P203 | P201 (B) | P205 (G) | P205 Part H |
|---|---|---|---|---|---|
| | ≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%) | 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) | ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster (N=403) n (%) |
| Solicited adverse reaction | N1=1280 | N1=1311 | N1=79 | N1=263 | N=403 |

| Solicited Adverse reaction Category Grade | P204<br>≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%) | P203<br>12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | P201 (B)<br>≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%) | P205 (G)<br>≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) | P205 Part H<br>≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster (N=403) n (%) |
|---|---|---|---|---|---|
| Any Solicited Systemic Adverse Reactions | 823 (64.3) | 1004 (76.6) | 59 (74.7) | 197 (74.9) | 307 (76.2) |
| Grade 1 | 414 (32.3) | 463 (35.3) | 23 (29.1) | 102 (38.8) | 135 (33.5) |
| Grade 2 | 331 (25.9) | 433 (33.0) | 29 (36.7) | 78 (29.7) | 142 (35.2) |
| Grade 3 | 77 (6.0) | 108 (8.2) | 6 (7.6) | 17 (6.5) | 30 (7.4) |
| Grade 4 | 1 (<0.1) | 0 | 0 | 0 | 0 |
| Fever | N1=1276 | N1=1297 | N1=79 | N1=262 | N=402 |
| Any | 108 (8.5) | 79 (6.1) | 6 (7.6) | 9 (3.4) | 16 (4.0) |
| Grade 1 | 59 (4.6) | 45 (3.5) | 4 (5.1) | 6 (2.3) | 9 (2.2) |
| Grade 2 | 32 (2.5) | 26 (2.0) | 1 (1.3) | 2 (0.8) | 6 (1.5) |
| Grade 3 | 16 (1.3) | 8 (0.6) | 1 (1.3) | 1 (0.4) | 1 (0.2) |
| Grade 4 | 1 (<0.1) | 0 | 00 | 0 | 0 |
| Headache | N1=1280 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 489 (38.2) | 748 (57.1) | 45 (57.0) | 129 (49.0) | 210 (52.2) |
| Grade 1 | 275 (21.5) | 492 (37.5) | 28 (35.4) | 96 (36.5) | 135 (33.6) |
| Grade 2 | 192 (15.0) | 228 (17.4) | 16 (20.3) | 29 (11.0) | 64 (15.9) |
| Grade 3 | 22 (1.7) | 28 (2.1) | 1 (1.3) | 4 (1.5) | 11 (2.7) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Fatigue | N1=1279 | N1=1311 | N1=79 | N1=263 | N=403 |
| Any | 625 (48.9) | 769 (58.7) | 46 (58.2) | 154 (58.6) | 243 (60.3) |
| Grade 1 | 340 (26.6) | 364 (27.8) | 18 (22.8) | 75 (28.5) | 119 (29.5) |
| Grade 2 | 238 (18.6) | 352 (26.8) | 25 (31.6) | 69 (26.2) | 110 (27.3) |
| Grade 3 | 47 (3.7) | 53 (4.0) | 3 (3.8) | 10 (3.8) | 14 (3.5) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Myalgia | N1=1280 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 269 (21.0) | 529 (40.4) | 37 (46.8) | 114 (43.3) | 197 (49.0) |
| Grade 1 | 147 (11.5) | 274 (20.9) | 19 (24.1) | 64 (24.3) | 103 (25.6) |
| Grade 2 | 103 (8.0) | 208 (15.9) | 15 (19.0) | 41 (15.6) | 77 (19.2) |
| Grade 3 | 19 (1.5) | 47 (3.6) | 3 (3.8) | 9 (3.4) | 17 (4.2) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Arthralgia | N1=1279 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 160 (12.5) | 316 (24.1) | 34 (43.0) | 87 (33.1) | 145 (36.1) |

| Solicited Adverse reaction Category Grade | P204<br>≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%) | P203<br>12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%) | P201 (B)<br>≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%) | P205 (G)<br>≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%) | P205 Part H<br>≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster (N=403) n (%) |
|---|---|---|---|---|---|
| Grade 1 | 102 (8.0) | 184 (14.0) | 20 (25.3) | 56 (21.3) | 84 (20.9) |
| Grade 2 | 46 (3.6) | 115 (8.8) | 12 (15.2) | 28 (10.6) | 52 (12.9) |
| Grade 3 | 12 (0.9) | 17 (1.3) | 2 (2.5) | 3(1.1) | 9 (2.2) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Nausea/vomiting | N1=1279 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 168 (13.1) | 234 (17.8) | 12 (15.2) | 35 (13.3) | 67 (16.7) |
| Grade 1 | 126 (9.9) | 180 (13.7) | 12 (15.2) | 31 (11.8) | 54 (13.4) |
| Grade 2 | 36 (2.8) | 52 (4.0) | 0 | 4 (1.5) | 12 (3.0) |
| Grade 3 | 6 (0.5) | 2 (0.2) | 0 | 0 | 1 (0.2) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Chills | N1=1279 | N1=1311 | N1=79 | N1=263 | N=402 |
| Any | 179 (14.0) | 399 (30.4) | 30 (38.0) | 64 (24.3) | 96 (23.9) |
| Grade 1 | 118 (9.2) | 251 (19.1) | 20 (25.3) | 38 (14.4) | 51 (12.7) |
| Grade 2 | 57 (4.5) | 141 (10.8) | 10 (12.7) | 25 (9.5) | 42 (10.4) |
| Grade 3 | 4 (0.3) | 7 (0.5) | 0 | 1 (0.4) | 3 (0.7) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1 = Number of exposed participants who submitted any data for the event.

Study P204 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Pain for participant age 37 months to <12 years is injection site pain. Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participant age 37 months to < 12 years is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm; G4 = Necrosis or exfoliative dermatitis. Toxicity grade for Axillary swelling or tenderness for participant age 37 months to < 12 years is defined as: G1 = No interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization. Toxicity grade for Fever for participant age 37 months to < 12 years is defined as: G1 = 38 — 38.4 °C; G2 = 38.5 — 38.9 °C; G3 = 39 — 40 °C; G4 = > 40 °C.

Study P203 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who received BD in Part C, and contribute any solicited AR data (ie, had at least 1 post-booster solicited safety assessment in Part C).

[a] Toxicity grade for erythema (redness) is defined as: G1 = 25 - 50 mm; G2 = 51 - 100 mm; G3 = > 100 mm.

Study P205 Notes: Toxicity grade for Erythema (Redness) is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm. Toxicity grade for Fever is defined as: G1 = 38 — 38.4 C; G2 = 38.5 — 38.9 C; G3 = 39 — 40 C; G4 = > 40 C. This interim analysis includes Part F Cohort 2 mRNA-1273 and Part G subjects immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27APR2022.

Source: P204: Table 14.3.1.3.7.1.2, Table 14.1.8.3.2; P203: Table 14.3.1.1.1.5.1, Table 14.1.5.3.5; P201: Table 14.3.1.1.4.1; P205 (G): Table 14.3.1.1.1.8; P205 (H): Table 14.3.1.1.2.9

***Table 13 – Frequency of Unsolicited TEAEs with Occurrence in ⩾ 1% of Participants in Any Treatment Group up to 28 Days After Injection Classified by MedDRA System Organ Class and Preferred Term (Safety Set)***

| System Organ Class<br>Preferred Term | P204<br>6-11 years<br>mRNA-1273 50 µg Primary Series – 25 µg Booster<br>N=1294<br>n (%) | | P203<br>12 to <18 Years<br>mRNA-1273<br>100 µg Primary Series – 50 µg Booster<br>(N=1346)<br>n (%) | | P301<br>18 to <25 year<br>mRNA-1273<br>100 µg Primary Series – 50 µg Booster<br>(N=954)<br>n (%) | | P205 (G)<br>≥18 years<br>mRNA-1273<br>100 µg Primary Series – 50 µg Booster - mRNA-1273.214<br>50 µg Booster<br>N=437<br>n (%) | | P205 (H)<br>≥18 years<br>mRNA-1273<br>100 µg Primary Series – 50 µg Booster - mRNA-1273.222<br>50 µg Booster<br>N=511<br>n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any | Related | Any | Related | Any | Related* | Any | Related | Any | Related |
| **Number of participants reporting unsolicited adverse events** | 169 (13.1) | 52 (4.0) | 191 (14.2) | 55 (4.1) | 316 (33.1) | - | 84 (19.2) | 21 (4.8%) | 116 (22.7) | 40 (7.8) |
| **Number of unsolicited adverse events** | 238 | 75 | 263 | 79 | 647 | - | 117 | 30 | 176 | 57 |
| **Infections and infestations** | 80 (6.2) | 4 (0.3) | 102 (7.6) | 1 (<0.1) | 57 (6.0) | - | 29 (6.6) | 0 | 56 (11.0) | 0 |
| COVID-19 | 25 (1.9) | 4 (0.3) | 41 (3.0) | 0 | 18 (1.9) | - | 5 (1.1) | 0 | 11 (2.2) | 0 |
| Asymptomatic COVID-19 | 6 (0.5) | 0 | 17 (1.3) | 0 | 1 (0.1) | - | 2 (0.5) | 0 | 4 (0.8) | 0 |
| Upper respiratory tract infection | 17 (1.3) | 0 | 16 (1.2) | 0 | 11 (1.2) | - | 4 (0.9) | 0 | 7 (1.4) | 0 |
| Rhinovirus infection | 1 (<0.1) | 0 | 1 (<0.1) | 0 | 6 (0.6) | - | 1 (0.2) | 0 | 7 (1.4) | 0 |
| Urinary tract infection | 0 | 0 | 0 | 0 | 4 (0.4) | - | 1 (0.2) | 0 | 5 (1.0) | 0 |
| **Blood and lymphatic system** | 1 (<0.1) | 0 | 2 (0.1) | 1 (<0.1) | 13 (1.4) | - | 0 | 0 | 2 (0.4) | 0 |
| Lymphadenopathy | 1 (<0.1) | 0 | 1 (<0.1) | 1 (<0.1) | 10 (1.0) | - | 0 | 0 | 1 (0.2) | 0 |
| **Nervous system disorders** | 15 (1.2) | 12 (0.9) | 26 (1.9) | 22 (1.6) | 74 (7.8) | - | 7 (1.6) | 5 (1.1) | 22 (4.3) | 13 (2.5) |
| Headache | 15 (1.2) | 12 (0.9) | 26 (1.9) | 22 (1.6) | 61 (6.4) | - | 6 (1.4) | 5 (1.1) | 15 (2.9) | 12 (2.3) |
| **Vascular Disorders** | 0 | 0 | 0 | 0 | 1 (0.1) | - | 3 (0.7) | 0 | 5 (1.0) | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | 23 (1.8) | 1 (<0.1) | 11 (0.8) | 1 (<0.1) | 27 (2.8) | - | 6 (1.4) | 0 | 2 (0.4) | 0 |
| Oropharyngeal pain | 6 (0.5) | 0 | 2 (0.1) | 0 | 13 (1.4) | - | 2 (0.5) | 0 | 0 | 0 |
| **Gastrointestinal Disorders** | 12 (0.9) | 7 (0.5) | 10 (0.7) | 4 (0.3) | 28 (2.9) | - | 6 (1.4) | 0 | 7 (1.4) | 1 (0.2) |
| Nausea | 1 (<0.1) | 0 | 0 | 0 | 13 (1.4) | - | 0 | 0 | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | 13 (1.0) | 2 (0.2) | 12 (0.9) | 2 (0.1) | 14 (1.5) | - | 4 (0.9) | 2 (0.5) | 2 (0.4) | 0 |
| **Musculoskeletal and connective tissue disorders** | 9 (0.7) | 4 (0.3) | 13 (1.0) | 4 (0.3) | 49 (5.1) | - | 13 (3.0) | 7 (1.6) | 9 (1.8) | 7 (1.4) |

| System Organ Class<br>Preferred Term | P204<br>6-11 years mRNA-1273 50 µg Primary Series – 25 µg Booster N=1294 n (%) | | P203<br>12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1346) n (%) | | P301<br>18 to <25 year mRNA-1273 100 µg Primary Series – 50 µg Booster (N=954) n (%) | | P205 (G)<br>≥18 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=437 n (%) | | P205 (H)<br>≥18 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.222 50 µg Booster N=511 n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any | Related | Any | Related | Any | Related* | Any | Related | Any | Related |
| Myalgia | 3 (0.2) | 3 (0.2) | 7 (0.5) | 4 (0.3) | 29 (3.0) | - | 4 (0.9) | 3 (0.7) | 5 (1.0) | 5 (1.0) |
| Arthralgia | 4 (0.3) | 1 (<0.1) | 5 (0.4) | 3 (0.2) | 5 (0.5) | - | 7 (1.6) | 6 (1.4) | 5 (1.0) | 5 (1.0) |
| **General disorders and administration site conditions** | 34 (2.6) | 30 (2.3) | 43 (3.2) | 33 (2.5) | 202 (21.2) | - | 18 (4.1) | 13 (3.0) | 31 (6.1) | 30 (5.9) |
| Fatigue | 13 (1.0) | 13 (1.0) | 23 (1.7) | 20 (1.5) | 61 (6.4) | - | 11 (2.5) | 9 (2.1) | 22 (4.3) | 22 (4.3) |
| Injection site pain | 5 (0.4) | 5 (0.4) | 9 (0.7) | 8 (0.6) | 137 (14.4) | - | 3 (0.7) | 3 (0.7) | 2 (0.4) | 2 (0.4) |
| Pain | 0 | 0 | 2 (0.1) | 0 | 33 (3.5) | - | 0 | 0 | 1 (0.2) | 0 |
| Chills | 2 (0.2) | 2 (0.2) | 3 (0.2) | 3 (0.2) | 28 (2.9) | - | 0 | 0 | 2 (0.4) | 1 (0.2) |
| Pyrexia | 10 (0.8) | 5 (0.4) | 5 (0.4) | 2 (0.1) | 29 (3.0) | - | 0 | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | 8 (0.6) | 1 (<0.1) | 14 (1.0) | 0 | 5 (0.5) | - | 10 (2.3) | 0 | 5 (1.0) | 0 |

Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of exposed participants who reported the event on any day within 28 days of the booster dose; TEAE=treatment-emergent adverse event. Related= TEAEs assessed as related to vaccine by investigators

Note: Data from P204 6-11years includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants (N) in booster dose analysis. Data cutoff 23 May2022

Note: Data from P203 includes mRNA-1273-booster group. Percentages are based on the number of safety participants in Part C. Data cutoff 16 May 2022

Note: Data from P301 is the Total of mRNA-1273-booster + placebo-mRNA-1273-booster. Percentages are based on the number of Part C safety subjects between 18-25 years of age. Data cutoff 17 May 2022.

*Treatment-related data not available for 18-25y age group currently

Note: Data from P205 Part G interim analysis includes immunogenicity data up to Day 91 visit – Data cutoff 06 Jul 2022. Data from P205 Part H interim analysis includes immunogenicity data up to Day 29 visit – Data cutoff 23 Sep 2022.

The MAH submitted the requested additional safety data in the adult population who received a second booster dose of 50 µg mRNA-1273.222. No clear pattern was noted which may suggest clinical meaningful differences when comparisons are done between a booster dose of mRNA-1273 applied in children, adolescent and adults; a booster dose of mRNA-1273.214 in adults and a booster dose of mRNA-1273.222 administered in adults. There were observed only minor differences with regards to reactogenicity across the vaccine groups and age related as presented in the submitted tables: The incidence of any solicited local adverse reaction in the mRNA-1273 vaccine group ranged from 91.1% in the age group 6 through 11 years of age; to 92.1% in the age group 12 to below 18 and to 87.3% in the adult population; in the mRNA-1273.214 booster vaccine group 89.4% in adults and in the mRNA-1273.222 booster vaccine group 86.3% in adult population. There were no Grade 4 local ARs reported in any of the group and the incidences of the Grade 3 solicited local ARs were comparable (respectively in the adult population (≥18 to <55 years) there were 5.1 % Grade 3 events in the mRNA-1273 group; 3.8% in the of mRNA-1273.214 vaccine group in adults ≥18 to below 65 years of age and 5.7% in the mRNA-1273.222 vaccine group in adults mRNA-1273.222, with 'Pain' as most common reported local ARs for all the groups.

The incidence of any solicited systemic adverse reaction in the mRNA-1273 vaccine group ranged from 64.3 % in the age group 6 through 11 years of age; to 76.6 % in the age group 12 to below 18 and to 74.7% in the adult population; in the mRNA-1273.214 booster vaccine group 74.9% in adults and in the

mRNA-1273.222 booster vaccine group 76.2% in adult population. Grade 4 solicited systemic adverse events were reported only for fever (any fever < 0.1%) in the Study P204, mRNA-1273 vaccine group, in children 6 through 11 years of age. In more details fever was reported as following: in the mRNA-1273 group 8.5% in children; 6.1% in adolescents and 7.6% in adults; in the mRNA-1273.214 booster vaccine group 3.4% in adults and in the mRNA-1273.222 booster vaccine group 4.0% in adults. It is observed that lower incidences of fever are reported in the adults in the bivalent vaccine's groups compare to the Spikevax original so there are not awaited significant clinical differences in the paediatric population between the vaccine groups.

The incidences of any unsolicited ARs/ treatment related were comparable between the vaccine groups as following: in the mRNA-1273 vaccine group ranged from (Any: 13.1 %/ Treatment related 4.0% in children; Any TEAEs 14.2% / Treatment related TEAEs 4.1% in adolescents; Any 33.1%/ treatment-related TEAEs data not available for 18-25y age group currently (young adults); in the mRNA-1273.214 booster vaccine group Any 19.2%/ treatment related TEAEs 4.8% in adults and in the mRNA-1273.222 booster vaccine group Any 22.7%/ treatment related TEAEs 7.8 % in adult population.

Overall, based on the comparative analysis from the clinical trials safety data, the CHMP considered that there are no clear trends or patterns that might lead in clinical meaningful differences with regards to the safety and reactogenicity between a booster dose of mRNA-1273 administered in children, adolescents and adults, compared with the bivalent vaccines; mRNA-1273.214 given as a booster dose in adults and the mRNA-1273.222 when given as a booster dose in adults. There the differences with regards to the sample size across the treatment groups, the timing of trials related to emerging SARS-CoV-2 variants and the treatments related adverse reactions, including the expected variability of TEAEs age related (respectively children, adolescents and adults) are acknowledged. The MAH will continue to monitor the safety profile of mRNA-1273.222 and the prevalence of the rare events in paediatric population, which can be detected through post-marketing experience.

## 2.5.1. Discussion on clinical safety

Currently, Spikevax bivalent Original/Omicron BA.4-5 (mRNA-1273.222) booster vaccination is authorised in individuals 12 years of age and older for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. No clinical data was provided for the sought indication of a booster dose with mRNA-1273.222 in children 6 through 11 years of age and the safety profile is intended to be extrapolated from the available safety data from mRNA-1273.222 available from the adult population and from the safety and reactogenicity of a 25 µg booster dose of mRNA-1273 Original vaccine given to children 6 through 11 years of age.

On 15$^{th}$ December 2022, authorisation was given for the use of mRNA-1273.214 25 µg dose (Original/Omicron BA.1) as a booster vaccine for children 6 through 11 years of age. Upon request, the MAH confirmed that there are 181 participants in Study P204, aged 6 through 11 years of age, who received a mRNA-1273.214 booster vaccine. Data collected included only safety data (respectively SAEs, AESIs, MAAEs and AEs leading to discontinuation from study) and will become available in the final CSR, due in March 2024.

To support the current inclusion of children aged 6 through 11 years of age to receive a booster dose (dose 4) of the bivalent vaccine mRNA-1273.222 (Original/Omicron BA.4-5), the MAH has submitted safety data from the Study mRNA-1273-P205 Part G (mRNA-1273.214; Spikevax bivalent Original/Omicron BA.1 as a 2$^{nd}$ booster dose and Part F Cohort 2 (mRNA-1273; Spikevax original as a 2$^{nd}$ booster dose). Regarding the reactogenicity these data have been assessed during the procedures EMEA/H/C/005791/II/75/G and EMEA/H/C/005791/II/84/G. However, in this submission there is a longer median follow-up time, respectively 113 days and 127 days and the reported unsolicited AEs, MAAEs,

SAEs and fatal events have been included. None of these study parts include children aged 6 through 11 years of age.

Part G (mRNA-1273.214): Solicited ARs were reported for 87% of participants after booster dose. Solicited local ARs were reported for 79.4% participants and the most common reported were: injection site pain (77.3%), followed by axillary swelling or tenderness (17.4%). Solicited systemic ARs were reported for 70.3% participants, with the most common reported: fatigue (54.9%), followed by headache (43.9%). Most local and systemic ARs were Grade 1 and Grade and none were Grade 4.

Part F Cohort 2 (mRNA-1273): Solicited ARs were reported for 85.7% participants after the booster dose. Solicited local ARs were reported for 79.4% participants and the most common reported were: injection site pain (76.6%), followed by axillary swelling or tenderness (15.1%). Solicited systemic ARs were reported in 66.0% participants and the most reported were: fatigue (51.3%) followed by headache (41.0%). Most solicited systemic ARs were Grade 1 and Grade 2 and none were Grade 4. Most solicited ARs were reported with onset from Days 1-3 after the booster dose, and the median duration was 2.0 days.

Slightly higher incidences of local and systemic adverse events were observed, when comparing mRNA-1273.214 50 µg administered as second booster to mRNA-1273 50 µg given as booster dose. However, these differences were not clinically significant and are not considered to have a significant impact on the safety profile of mRNA-1273.214 when compared to that of mRNA-1273. No clinically meaningful imbalances were seen in subgroup analyses with regards to the frequencies when stratifying according to SARS-CoV-2- status and age group.

The incidences of unsolicited TEAEs regardless of relationship to study vaccination and those related to study vaccination were comparable between the two parts after the booster dose. There were no imbalances reported after the booster dose for both parts with regards to the severe TEAEs, with comparable incidences (0.9% vs 0.8%). Fatigue is a known adverse drug reaction and it is included in the section 4.8 of the SmPC, therefore no additional clinical information is requested with regards to the severe event of fatigue with duration from Day 1-14 in the mRNA-1273.214 booster group.

With regards to the TEAEs considered vaccine related observed in the two parts, had a slightly lower incidence in the mRNA-1273.214 booster dose group compared to the mRNA-1273 group, respectively 4.8% vs 5.6%. The AEs persisting beyond Day 7 are related to the known reactogenicity of mRNA-1273 and all the events considered as vaccine related are already included as ADRs at the Section 4.8 of the SmPC. There were three fatal events reported up to data cut-off. Two deaths were reported in the mRNA-1273.214 booster group; one death of unknown case and one other fatal event of atherosclerotic cardiovascular disease. One fatal event of hypotension was reported in the mRNA-1273 booster group. All three events were considered not to be related to the study vaccine by the investigator and the CHMP supported this conclusion. SAEs were reported for 1.8 % participants in part G (prostate cancer and traumatic fracture) up to data cut-off both considered not to be related to study vaccine. In Part F Cohort 2, the SAEs were reported 2.7% participants (2.7%), with one unrelated event of spinal osteoarthritis within 28 days. MAAEs (related and unrelated to vaccination) did not reveal any safety signals for both two parts, with lower incidence of MAAEs after the second booster dose with the original Spikevax (mRNA-1273), respectively 39.1% vs 47.9%. The same applies for the SOCs accordingly 23.8% vs 29.0%, and no significant imbalances were observed for the PT events between the two groups. No events of myocarditis or pericarditis were reported in both booster dose groups. The additional review done for the unrecognised cases did not reveal any new cases.

Study mRNA-1273-P205 Part H (mRNA-1273.222; Spikevax bivalent Original/Omicron BA.4-5 as 2nd booster vaccine): This part of the study includes 511 participants with a median follow-up duration of 37 days after 50 µg mRNA-1273.222 booster dose.

The safety data was evaluated during EMEA/H/C/005791/077 and showed the following: any solicited adverse reactions reported by 87.2% participants; local ARs (82.8%) with pain as most common (82.4%); systemic ARs (73.2%) with fatigue as most common (59.8%). No clinically meaningful imbalances were seen in subgroup analyses with regards to the frequencies when stratifying according to the age group: Solicited ARs were more reported in the ≥18 to <65 years age group (89.8%) compared to the ≥65 years age group with (77.1%). Mostly of the events were Grade 1 or Grade 2 and Grade 3 accordingly (12.2% versus 9.5%). No grade 4 were reported. Unsolicited AEs considered vaccine related were reported by 7.8% participants, MAAEs reported by 13.7 % participants and none considered to be related to the study IP. There was one death Subarachnoid haemorrhage reported in a ≥70 year old male participant, assessed as not related to the vaccine due to the participants underlying disease and medications. There were four SAEs reported in 3 participants: the fatal event of subarachnoid haemorrhage; events of anginal equivalent and syncope and one event of anaemia, considered as unrelated to the vaccination.

No events of potential myocarditis or pericarditis were identified with the CMQ for participants in the mRNA-1273.222 50 µg (Part H). From the post-marketing experience there was one reported case of 'unassessable' pericarditis due to important missing information.

Overall, the CHMP considered that the review of the clinical safety data of mRNA-1273.222 showed that the benefit-risk profile of Spikevax bivalent Original/Omicron BA.4-5 booster vaccine was favourable for individuals 12 years of age and older.

Study mRNA-1273-P204

The safety data used to support the marketing authorisation of Spikevax bivalent Original/Omicron BA.1 in individuals 6 through 11 years of age has been assessed during EMEA/H/C/005791/II/83/G. The MAH indicated that longer term safety data for a booster dose in children 6 through 11 years of age (6 months of safety follow-up on at least 1000 boosted participants) is anticipated to be available at the end of 2023. As participants in P204 are still being boosted currently, the proposed timing is tentative. The MAH also provided comparative tables summarising the solicited local and systemic ARs, concluding that the incidences of any local solicited ARs were similar across all of the age groups, from 87.3% to 92.1%. Most of the events were Grade 1 and Grade 2; the 6 through 11 years of age group tended to have more Grade 2 events than the other groups. Grade 3 events occurred less frequently, and more frequently after a 100 µg booster dose than a 50 µg booster dose; no trends were identified across the age ranges. There were no Grade 4 solicited local ARs. The most commonly reported solicited local AR was pain, with a similar incidence across age ranges (86.1% to 91.7%). This was followed by axillary swelling or tenderness (21.3% to 28.0%), which tended to occur more commonly in the two younger age groups, including Grade 3 events which were not reported in the adult groups.

The incidence of solicited systemic ARs was similar across the 3 older age groups (74.7% to 76.6%) in contrast to children (6 through 11 years of age) in which the overall rate was 64.3%. Rates of solicited systemic ARs were the lowest in all categories in the 6 through 11 years of age group except for fever where children had the highest rate (8.5%), including one Grade 4 event. Fever was least common in the mRNA-1273.214 group (3.4%). Children (6 through 11 years of age) generally experienced lower incidence rates than the older 3 age groups for the solicited systemic ARs of headache, fatigue, myalgia, arthralgia, and chills with absolute differences of 10 to 20%. Systemic reactogenicity tended to be lower in the mRNA-1273.214 group compared to the adolescent and adult mRNA-1273 groups in the events of fever, headache, nausea/vomiting, and chills. Across the groups the incidence of Grade 3 systemic ARs ranged from 6.0% to 8.2%, with children (6 through 11 years of age) having the lowest overall incidence and adolescents having the highest. As reporting rates were low for individual event terms, differences across the groups were not notable. The largest difference was for myalgia, where children (6 through 11

years of age) had Grade 3 ARs in 1.9% whereas the other age groups had Grade 3 events in 3.4% to 3.8% of participants.

Overall, while children (6 through 11 years of age) tended to demonstrate less systemic reactogenicity than older age groups with the exception of fever, there were no findings concerning for overall tolerability in any of the treatment groups.

The intended approach is to support the administration of a 25 µg booster dose of mRNA-1273.222 based on the safety and reactogenicity profile after administration of 25 µg of mRNA-1273 as a booster dose to children 6 through 11 years of age, and to extrapolate from the known safety profile of a booster dose of mRNA-1273.214 and of the safety profile of a booster dose mRNA-1273.222 (with a follow-up duration time of 37 days) given to adults.

To support the indication extension of mRNA-1273.222 to children 6 through 11 years of age without safety data for the mRNA-1273.222 variant vaccine in this age group, the MAH was requested to provide a summary of the reactogenicity profile of a booster dose of mRNA-1273 in three age groups (children 6 through 11 years of age; adolescent 12-<17 years and in young adults 18-25 years of age) and the solicited ARs after a booster dose of mRNA-1273.214 in adults 18-25 and the solicited ARs after a booster dose of mRNA-1273.222 in the same age group (young adults 18-25 years).

Overall, based on the comparative analysis from the clinical trials safety data, no clear trend or pattern was observed that might lead in clinical meaningful differences with regards to the safety and reactogenicity between a booster dose of mRNA-1273 administered in children, adolescents and adults, compared with the bivalent vaccines; mRNA-1273.214 given as a booster dose in adults and the mRNA-1273.222 when given as a booster dose in adults. The differences with regards to the sample size across the treatment groups, the timing of trials related to emerging SARS-CoV-2 variants and the treatments related adverse reactions, including the expected variability of TEAEs age related (respectively children, adolescents and adults) are acknowledged. Post-marketing surveillance activities will continue to monitor the safety profile of mRNA-1273.222 and the prevalence of the rare events in paediatric population, which can be detected through post-marketing experience.

## 2.5.2. Conclusions on clinical safety

No clinical data was provided to support the sought indication of a booster dose with mRNA-1273.222 in children 6 through 11 years of age and the safety profile is intended to be extrapolated from the safety data from mRNA-1273.222 available from the adult population and from the safety and reactogenicity of a 25 µg booster dose of mRNA-1273 Original vaccine given to children 6 through 11 years of age.

Additional supportive data was provided on the use of mRNA-1273.214 as a second booster, compared to data on mRNA-1273 administered as a second booster dose in the adult population. The review of all the submitted safety data did not show any clear trend or pattern of clinical meaningful differences with regards to the safety and reactogenicity between a booster dose of mRNA-1273 administered in children, adolescents and adults, compared with the bivalent vaccine mRNA-1273.214 given as a booster dose in adults and the bivalent vaccine mRNA-1273.222 when given as a booster dose in adults. Post-marketing surveillance activities will continue to monitor the safety profile of mRNA-1273.222 and the prevalence of the rare events in paediatric population, which can be detected through post-marketing experience.

The current interval for the booster dose in the posology section of the SmPC is currently 3 months after primary series.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version 6.5 with data lock point of 17th September 2022 and final sign-off date of 7th February 2023 with this application. The (main) proposed RMP changes were the following:

- To update the indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older
- To update the qualitative and quantitative composition for Spikevax bivalent Original/Omicron BA.4-5
- To update the products overview table in Module SI in line with the current SmPC
- To update the indication in the Epidemiology for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 years of age and older
- To update Module SVII.2 to state no changes to the safety concerns
- To update the indication in the Summary of the Risk Management Plan for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 years of age and older

Part I – Product overview

The information provided in Part I is considered sufficient and is acceptable. Few editorial comments for the next RMP update are made below.

Part II module SI – Epidemiology of the indication and the target population

The indication has been updated in this module, which is acceptable. The wording of the indication included in this section will also have to be aligned at the next RMP update.

Part II module SVII.2 – New safety concerns and reclassification with a submission of an updated RMP

The module has been updated to state that there are no changes in safety concerns. This is acceptable.

Part VI: Summary of the Risk Management Plan

The indication has been updated in this module, which is acceptable.

The PRAC considered that the risk management plan version 6.5 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

1. In the section 'Indication(s) in the EEA' in the RMP, a paragraph break may be inserted between 'Proposed:' and 'Spikevax […]' to increase readability, as outlined below:

   *Current:*
   *[…] Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.*

***Proposed: Spikevax*** *bivalent Original/Omicron BA.4-5 is indicated 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.*

2. In the section 'Dosage in the EEA' in the RMP, '**Proposed**' and 'Current' should have a similar font, i.e. non-bold. Moreover, the specification 'Individuals' and 'Children' 12 and 6 years of age and older, respectively, should be used consistently, i.e. both for Spikevax bivalent Original/Omicron BA.1 and BA.4-5.
3. In Part II module SI, the wording of the indication should be brought up in line with the PI:

   *Spikevax bivalent Original/Omicron BA.4-5 is indicated 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~~, after primary COVID-19 immunisation~~.*

## *2.7. Changes to the Product information*

As a result of this group of variations, sections 2, 4.1, 4.2, 4.4, and 6.6 of the SmPC are updated to reflect the use of a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran) in children aged 6 through 11 years of age. The Package Leaflet and Labelling are updated in accordance. Sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.4-5 SmPC are further updated to add additional ADR details and clinical data.

In addition, sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.1 SmPC are also updated, to add median follow-up period and D91 persistence data. The Package Leaflet is updated accordingly.

Finally, the MAH took the opportunity to implement a number of editorial changes to the product information, including the update of section 5.1 of the SmPC for all Spikevax products, to reflect the correct VE values based on the P301 case definition for children 2 through 5 years of age and 6 through 23 months of age.

Please refer to Attachment 1.

### 2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV. Coronaviruses are also zoonotic, with different species causing disease in other mammals, such as bats and cats.

An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally (WHO 2020). This virus is not

known to have previously caused disease in humans. The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) on 30th January 2020 and declared COVID-19 a pandemic on 11th March 2020.

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in 3 principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by contact with fomites (CDC 2021).

Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission (Johansson et al 2021).

Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and the distinctive symptoms of loss of taste or smell.

During the COVID-19 pandemic, the sequence of SARS-CoV-2 has been constantly changing over time. After the onset of the Omicron wave, the demographics of hospitalised patients with COVID-19 shifted to younger age groups (UK Health Security Agency 2021; Abdullah et al 2022; Goga et al 2021).

## 3.1.2. Available therapies and unmet medical need

While the efficacy of COVID-19 vaccine encoding the original strain is maintained against severe disease, the efficacy against COVID-19 of any severity wanes over time. Moreover, SARS-CoV-2 epidemiology has changed rapidly over time and new SARS-CoV-2 strains have emerged. The Spikevax bivalent variant mRNA vaccine containing the original strain together with the Omicron BA.1 strain has been approved for individuals 12 years of age and older, subsequently followed by the approval of Spikevax Original/Omicron BA.4-5 in the same age group. In the adult clinical development program, two doses of 100 µg mRNA-1273 demonstrated 93.2% (95% CI: 91.0%, 94.8%; $p < 0.0001$) efficacy against COVID-19 in more than 30,000 participants over a median observation period of over 5.3 months. Effectiveness against Omicron-related COVID-19 declined after time, but could be enhanced after a 50 µg booster dose. Successful immunobridging of booster responses between children 6 through 11 years of age and young adults post-primary series from Study mRNA-1273-P301 provides confidence that the booster benefit afforded to adults will also be afforded to children.

## 3.1.3. Main clinical studies

**Study mRNA-1273-P205**

Study mRNA-1273-P205 is an ongoing open-label Phase 2/3 study with multiple, sequentially enrolled cohorts to evaluate the immunogenicity and safety of variant-targeting booster candidate vaccines. mRNA-1273.222 is the bivalent Original/Omicron BA.4-5 booster vaccine that contains 25 µg Original SARS-CoV-2 Spike mRNA and 25 µg Omicron BA.4-5 Spike mRNA. The study consists of 7 parts: A, (1, 2), B, C, D, E, F, G, and H.

**Part F (Cohort 2)**- 50 µg of the mRNA-1273 administered as a second booster dose to adult participants

who previously received 2 doses of 100 µg mRNA-1273 as a primary series and 1 booster dose of 50 µg mRNA-1273.

**Part G**- Second booster dose 50 µg mRNA-1273.214: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273.

**Part H** - Second booster dose 50 µg mRNA-1273.222: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273.

**Study mRNA-1273 P204**

Study mRNA-1273 P204 is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 through 11 years of age, 2 years to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age groups in P204 has been previously submitted and primary series of 50 µg is currently authorised for use in children from 6 through 11 years of age. In a subsequent amendment, the protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group. Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a booster dose of 25 µg mRNA-1273 to all children enrolled in the 6 through 11 years age group, which could be administered starting 6 months post-dose 2 of the primary series.

## *3.2. Favourable effects*

It is reasonably likely that Spikevax bivalent Original/Omicron BA.4-5 will elicit a superior neutralising antibody response against SARS-CoV-2 Omicron BA.4-5 and a non-inferior neutralising antibody response against the Original SARS-CoV-2 strain in children 6 through 11 years of age.

## *3.3. Uncertainties and limitations about favourable effects*

No clinical results have been provided for the sought indication of a booster dose with mRNA-1273.222 in children 6 through 11 years of age.

## *3.4. Unfavourable effects*

After receipt of a 25 µg booster dose of mRNA-1273 at least 6 months after the primary vaccination, 93.2% of children 6 through 11 years of age reported any solicited AR. Any solicited local AR was reported by 91.1% of participants. Pain was the most reported solicited local AR (90.1% of participants), followed by Axillary (or Groin) Swelling or Tenderness (27.8%) and erythema (10.7%) and swelling/hardness (10.9%). Any systemic solicited AR was reported by 64.3% of participants. The most frequently reported systemic solicited AR was fatigue (48.9%), followed by headache (38.2%) and myalgia (21.0%). Chills, nausea, and arthralgia were reported by comparable proportions of subjects, i.e. by 14.0%, 13.1%, and 12.5%, respectively. Fever was reported by 8.5% of subjects.

Solicited ARs had a median onset within 1 day after vaccination and a median duration of 3 days. Solicited local ARs persisting beyond 7 days after booster dose administration were reported in 1.3% of participants. The most common events were axillary (or groin) swelling or tenderness (0.7%) and pain (0.5%). Solicited systemic ARs persisting beyond 7 days after booster vaccination were reported in 2.0% of participants. The most common events were fatigue (1.3%) and headache (1.0%).

## *3.5. Effects Table*

***Table 14 - Effects Table for mRNA-1273; mRNA-1273.222***

| Effect | Treatment | Control |
|---|---|---|
| | 6 through 11 years of age **mRNA-1273** 50 µg Primary Series - 25 µg Booster (**Study P204)** | Adults ≥18 yo after 50 µg mRNA-1273.222 2nd Booster **(P205 Part H)** |
| Any solicited local ARs<br><br>Grade 3 | 1165/1279 (91.1%)<br><br>33 /1279 (2.6%) | 420/507 (82.8%)<br><br>28 /508 (5.5%) |
| Any solicited systemic ARs<br><br>Grade 3 | 823/ 1280 (64.3%)<br><br>77/ 1280 (6.0%) | 372/508 (73.2%)<br><br>35/508 (6.9%) |
| Any unsolicited ARs | 169/1294 (13.1%) | 116/511 (22.7%) |

## *3.6. Benefit-risk assessment and discussion*

### 3.6.1. Balance of benefits and risks

Even though the course of COVID-19 in children is generally milder than in the older population, there are individuals that suffer considerably from the direct consequences of the infection. It is therefore important to have access to COVID-19 variant vaccines for this population.

### 3.6.2. Additional considerations on the benefit-risk balance

The benefit-risk of the administration of a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 in children 6 through 11 years of age is considered positive.

## *3.7. Conclusions*

The overall benefit-risk of Spikevax bivalent Original/Omicron BA.4-5 as a booster dose in children 6 through 11 years of age is considered positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

| Variations accepted | | Type | Annexes affected |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | Type II | I and IIIB |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | Type II | I |

Grouped variation:
- C.I.6.a (Type II): Extension of indication to include a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran) in children aged 6 through 11 years of age; as a consequence, sections 2, 4.1, 4.2, 4.4, and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. A revised RMP version 6.5 has been approved.
- C.I.z (Type II): Update of sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.1 SmPC to add median follow-up period and D91 persistence data, based on Parts F and G (mRNA- 1273.214) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines. The Package Leaflet is updated accordingly.
- C.I.z (Type II): To update sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.4-5 SmPC to add ADR details and clinical data, based on Part H (mRNA- 1273.222) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines.
In addition, the Marketing authorisation holder took the opportunity to implement a number of editorial changes to the product information.

The group of variations leads to amendments to the Summary of Product Characteristics, the Labelling and the Package Leaflet and to the Risk Management Plan (RMP).

### *Amendments to the marketing authorisation*

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0256/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Spikevax-H-C-005791-II-97-G'

# Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 26th April 2023