EMA/571969/2021
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMEA/H/C/005791/R/0025

Invented name: Spikevax

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

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 and personal data anonymised.

| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 19 Jul 2021 | 19 Jul 2021 |
| ☐ | CHMP and PRAC Rapporteurs Joint Assessment Report | 24 Aug 2021 | 24 Aug 2021 |
| ☐ | CHMP and PRAC members comments | 27 Aug 2021 | 27 Aug 2021 |
| ☐ | Updated CHMP and PRAC Rapporteurs Joint Assessment Report | 30 Aug 2021 | 14 Sep 2021 |
| ☐ | PRAC endorsed relevant sections of the assessment report | 03 Sep 2021 | 03 Sep 2021 |
| ☒ | Opinion | 16 Sep 2021 | 16 Sep 2021 |

| Procedure resources | |
|---|---|
| CHMP Rapporteur | Jan Mueller-Berghaus |
| PRAC Rapporteur | Hans Christian Siersted |

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# 1. Background information on the annual renewal

The European Commission issued on 6 January 2021, a conditional marketing authorisation (cMA) for Spikevax (also known as mRNA-1273). This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the marketing authorisation, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the cMA.

A cMA is valid for one year and may be renewed annually upon request by the marketing authorisation holder (MAH). Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Moderna Biotech Spain, S.L., submitted to the Agency on 1 July 2021 an application for renewal of the cMA for Spikevax. The expiry date of the cMA is 6 January 2022.

The period covered by this annual renewal is 6 January 2021 to 5 June 2021.

# 2. Specific Obligations

## *2.1. Specific Obligations adopted by the CHMP at time of initial marketing authorisation*

| Number | Description | Due date |
|---|---|---|
| SOB 001 | In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data. | January 2021 |
| SOB 002 | In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data. | April 2021<br>Interim reports will be provided monthly prior to this date. |
| SOB 003 | In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. | June 2021 |
| SOB 010 | In order to confirm the efficacy and safety of COVID-19 Vaccine Moderna, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301. | December 2022 |

Since the granting of the cMA, several aspects of all three quality SOBs were covered, however all SOBs are only partially fulfilled at the time point of the present assessment report. The clinical SOB pertaining to study 1273-P301 remains outstanding as per the official due date. The following report provides a detailed update on the status of the fulfilment of specific obligations and a discussion on any other data received during the reporting period with a potential impact on the benefit risk balance.

## *2.2. Outstanding Specific Obligations – Status report for period covered*

During the reporting period, the quality specific obligations were modified, as some aspects were fulfilled, whilst variations introducing new supply chains led to the addition of additional requirements. The existing clinical obligation, to provide the final clinical study report (CSR) from the pivotal study mRNA-1273-P301 remains unchanged. A new clinical specific obligation was introduced during the reporting period in the context of the extension of indication in adolescents aged 12 or older, namely providing the final CSR for the clinical trial mRNA-1273-P203, which initial results supported this extension. The following table provides a full overview of the status of fulfilment for all specific obligations.

**Table 1. Status of the Specific Obligations**

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| Specific Obligation 1 (SO1) | In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data. | 31-07-2021 | | | | |
| SO1 (i) | A tabulated summary of FMEA performed for the CX-024414 (mRNA) active substance including the conclusions drawn and appropriate justifications for criticality assignment and (de)prioritization of characterization studies should be provided no later than 15.01.2021 | 15-01-2021 | 12-02-2021 | 22-04-2021 | Fulfilled | |
| SO1 (ii) | Tabulated summaries of the actual settings of the investigated parameters, analytical results, and the prediction profiles should be provided for all process characterization studies of CX-024414 (mRNA) active substance no later than 15.01.2021 | 15-01-2021 | 12-02-2021 | 22-04/2021 | Fulfilled | |
| SO1 (iii) | The applicant should provide the updated SM-102 LNP and mRNA-1273 LNP intermediate and finished product appearance testing description including the characterization test of potentially occurring particles no later than 01.02.2021 | 31-07-2021 | 30-07-2021 | | On-going | The deadline of this SO was extended to 31-07-2021 with variation IB/02. |
| SO1 (iv) | A summary of the process risk assessment that forms the basis for process characterisation and the control strategy for the finished product should be submitted as committed by the applicant by 15.01.2021 | 15-01-2021 | 12-02-2021 | 22-04-2021 | Fulfilled | |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| Specific Obligation 2 (SO2) | In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data. Interim reports will be provided monthly prior to and quarterly after this date | 15-11-2021 | | | | Additional data falling within this SO has been requested as part of several variation applications (II/07-G, II-11-G, II-18-G, II-26-G and II-29-G). The latest due date being 15-11-2021. |
| SO2 (v) | The applicant should provide additional data to confirm that the initial Scale B CX-024414 (mRNA) active substance and the initial Scale B for SM-102 LNP and mRNA-1273 LNP intermediate processes are properly validated at Lonza Visp. | 30-04-2021 | 12-05-2021 | 24-06-2021 | Fulfilled | |
| SO2 (vi) | Process and batch data from at least 3 representative batches should be provided for the CX-024414 (mRNA) 20 l scale (initial Scale B) process at Lonza Visp. The final PPQ report for initial Scale B will be submitted no later than 30.04.2021. Batch data will be submitted monthly before final PPQ | 30-04-2021 | 12-05-2021 | 24-06-2021 | Fulfilled | |
| SO2 (vii) | The applicant should provide comprehensive comparability data on CX-024414 (mRNA) active substance, SM-102 LNP and mRNA-1273 LNP intermediate from initial Scale B process at Lonza Visp demonstrating that the commercial product manufactured at the Lonza Visp site is representative of the material used in the clinical trials no later than 30.04.2021 | 30-04-2021 | 12-05-2021 | 24-06-2021 | Fulfilled | |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| SO2 (viii) | The applicant should provide additional data to confirm finished product process validation. Process and batch data from at least 3 representative finished product batches should be provided for the final scale B process at Rovi, Spain. A justification of the hold times, from a microbiological perspective should be included. A process validation data summary report will be submitted no later than 01.02.2021. | 01-02-2021 | 12-02-2021 | 22-04-2021 | Fulfilled | |
| SO2 (ix) | The applicant should provide comprehensive comparability data demonstrating that the commercial finished product manufactured at the Rovi site is representative of the material used in the clinical trials. A final validation report including an assessment of comparability will be provided no later than 01.02.2021. | 01-02-2021 | 12-02-2021 | 22-04/2021 | Fulfilled | |
| SO2 (x) | The applicant should submit the description of the CCI test used as part of stability testing and its validation by 31.03.2021 | 31-03-2021 | 31-03-2021 | 20-04 /2021 | Fulfilled | Fulfilled with variation IB/08 |
| SO2 (xv) | The applicant is requested to commit to provide the PPQ and comparability report of Kit 4 for the active substance as soon as available, latest June 2021. | 30-06-2021 | 30-06-2021 | 16-09-2021 | Fulfilled | This SO is a consequence of KIT 4 variation (EMEA/H/C/005791 /II/0007/G). |
| SO2(xvi) | The applicant is requested to provide the final PPQ and comparability report including data of Kit 5 and 6 for the active substance as soon as available, latest July 2021. | 31-07-2021 | 02-08-2021 | NA | Ongoing | This SO is a consequence of KIT 4 variation (EMEA/H/C/005791 /II/0007/G). |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| SO2 (xvii) | The MAH should commit to provide a validation report and comparability report covering the finished product intermediates PPQ batches of the 4800 g batch size of SM-102 LNP and 200 g batch size of mRNA-1273 LNP of Kit 4 as soon as available, latest June 2021. | 30-06-2021 | 30-06-2021 | 16-09-2021 | Fulfilled | This SO is a consequence of KIT 4 variation (EMEA/H/C/005791/II/0007/G). |
| SO2 (xviii) | The MAH should commit to provide a validation report and comparability report covering the finished product intermediates PPQ batches of the 4800 g batch size of SM-102 LNP and 200 g batch size of mRNA-1273 LNP of Kit 5 and 6 as soon as available, latest July 2021. | 31-07-2021 | 02-08-2021 | NA | Ongoing | This SO is a consequence of KIT 4 variation (EMEA/H/C/005791/II/0007/G). |
| SO2 (xix) | The applicant is requested to provide the submit the final PPQ report for the Dara filling line at Rovi, San Sebastian de los Reyes upon completion of the validation exercise PPQ report as soon as available | 30-07-2021 | 29-07-2021 | NA | Ongoing | This SO is a consequence of DARA line variation (EMEA/H/C/005791/II/0011/G). |
| SO2 (xx) | The applicant is requested to provide the final outcome of the completed comparability assessment as described in the master comparability protocol when results from all three PPQ lots are available | 30-07-2021 | 29-07-2021 | NA | Ongoing | This SO is a consequence of DARA line variation (EMEA/H/C/005791/II/0011/G) |
| SO2 (xxi) | The applicant is requested to submit the final process validation and comparability report for the Recipharm site including data from three PPQ lots. | 31-08-2021 | 01-09-2021 | NA | Ongoing | This SO is a consequence of Recipharm variation (EMEA/H/C/005791/II/0018/G). |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| SO2 (xxii) | After completion of the process validation, batch release data for all PPQ lots from Recipharm and from ROVI (Dara line) should be included in the dossier. | 31-08-2021 | 01-09-2021 | NA | Ongoing | This SO is a consequence of Recipharm variation (EMEA/H/C/005791/II/0018/G). |
| SO2 (xxiii) | The applicant commits to provide the updated process validation documentation for Moderna Norwood after PPQ (75L IVT scale) no later than end of October 2021 | 31-10-2021 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/005791/II/26/G) |
| SO2 (xxiv) | The applicant commits to provide the final in process hold qualification performed for the 75L scale at Moderna Norwood no later than end of October 2021 | 31-10-2021 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/005791/II/26/G) |
| SO2 (xxv) | The applicant commits to include at least 2 more batches in the comparability analysis (Moderna Norwood) no later than end of October 2021 | 31-10-2021 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/005791/II/26/G) |
| SO2 (xxvi) | The applicant commits to provide the updated process validation documentation for Lonza Portsmouth after PPQ (75L IVT scale) no later than end of October 2021 | 31-10-2021 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/005791/II/26/G) |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| SO2 (xxvii) | The applicant commits to provide at least 3 more batches in the comparability analysis (Lonza Portsmouth) no later than end of October 2021 | 31-10-2021 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/00579 1/II/26/G) |
| SO2 (xxviii) | The applicant commits to provide the purity data for LNP and Drug Product derived from the batch 996648 when the lot is used to manufacture LNP and Drug Product by 30 November 2021 | 30-11-2022 | NA | NA | Unfulfilled | This SO is consequence of 75 L variation<br><br>(EMEA/H/C/00579 1/II/26/G) |
| SO2 (xxix) | The applicant is asked to commit to provide the final PPQ reports for all three filling lines from Catalent Indiana as soon as possible | 15-11-2021 | NA | NA | Unfulfilled | This SO is consequence of the Catalent variation<br><br>(EMEA/H/C/00579 1/II/29/G) |
| SO2 (xxx). | The applicant is asked to commit to provide a full comparability report for all three filling lines from Catalent Indiana as soon as possible | 15-11-2021 | NA | NA | Unfulfilled | This SO is consequence of the Catalent variation<br><br>(EMEA/H/C/00579 1/II/29/G) |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| Specific Obligation 3 (SO3) | In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. no later than 30.06.2021 | 15-07-2021 | | | | |
| SO3 (xi) | An update on all ongoing stability studies on CX-024414 (mRNA) acitve substance should be provided when data through 3 months is available from the three PPQ batches (initial Scale B CX-024414) manufactured at Lonza Visp in Mobius bags no later than 31.05.2021 | 15-07-2021 | 23-07-2021 | NA | On-going | The deadline of this SO was extended to 15-07-2021 with variation IB/17 |
| SO3 (xii) | The applicant should review the specifications for CX-024414 (mRNA) active substance: appearance, purity, product related impurities, % 5'capped, % PolyA tailed RNA, residual DNA template. LNP: appearance, lipid impurities, purity, product related impurities, % RNA encapsulation, particle size, polydispersity, osmolality no later than 30.06.2021 | 30-06-2021 | 30-06-2021 | NA | Ongoing | |
| SO3 (xiii) | The MAH should review the specifications for the finished product: appearance, RNA content, purity, product related impurities % RNA encapsulation, in vitro translation, lipid content, lipid impurities, particle size, polydispersity, osmolality no later than 30.06.2021 | 30-06-2021 | 30-06-2021 | NA | Ongoing | |

| SOB number | Description (scope) | Due date indicated in Annex II | Date of submission | Date resolved (if applicable) | Current status. | Comments if any |
|---|---|---|---|---|---|---|
| SO3 (xiv) | Periodic updates on the stability data (e.g. upon availability of data for 3 months, 4 weeks at 2°C – 8°C, 6 months + 4 weeks at 2° C – 8° C and 12 months and completion of the study) should be provided for the PPQ lots from Rovi. For the first Rovi lot, 3 months at -20 °C + 4 weeks at 2°C – 8°C by 31-05-2021,12 months of data to support overall program (basis of US data) at -20 °C + 4 weeks at 2°C – 8°C by 28.02.2021. The applicant will provide quarterly stability updates starting on 01-04-2021. Completion of study by 01-04-2021 | 28-02-2021 | 31-03-2021 | NA | Ongoing | Latest DP stability update was submitted on 31-08-2021 |
| SOB 010 | In order to confirm the efficacy and safety of COVID-19 Vaccine Moderna, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301. | December 2022 | | | pending | |
| SOB 040 | In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report. | September 2022 | | | pending | |

*CHMP assessment comment:*

All three Quality SOBs are partially fulfilled and various variations impacting the final due date of some SOBs are on-going or extensions to the due date have been requested by the MAH and granted as indicated in the table above. In summary, good progress in providing the SOB data has been made so far and the fulfilment of the remaining SOBs is still expected.

### *2.3. Overall conclusion on Specific Obligations*

During the period covered by this annual renewal, data on the SOBs have been submitted. SOB 001, 002 and 003 are partially fulfilled. The due dates of some SOBs were extended upon the MAH's request or because additional data was requested by the CHMP as part of some quality variation applications. The update of the due dates for some of the SOBs is being implemented in Annex II as part of this renewal procedure.

The due dates for SOB 001 and SOB 003 are 31 July and 15 July 2021, respectively. The applicant submitted a variation and several post-authorisation measures to provide the additional data requested. The evaluation of these submissions is still ongoing.

With regard to SOB 010, the MAH has locked the database of the mRNA-1273-P301 study and is preparing a clinical study report containing data from the blinded (Part A) and unblinded (Part B) of the study with anticipated submission to EMA by 30 October 2021. The study is ongoing with all participants now in the unblinded cross over phase of the study.

The final clinical study report, as required in the cMA's list of SOBs, including the unblinded safety and long-term efficacy analysis through two years of follow up remains on track for submission by the due date of 31 December 2022.

Following approval of the paediatric extension of indication procedure II/021, SOB 040 was added, requesting the MAH to submit the final clinical study report of the paediatric study mRNA-1273-P203 including the full bioanalytical report, by September 2022.

## 3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

### *3.1. Quality*

For several of the remaining Quality SOBs the due date was July 2021 and multiple variation applications are currently under assessment. Fulfilment of the remaining SOBs is expected.

### *3.2. Clinical efficacy*

The MAH has submitted data to support an extension of the age indication for vaccination with mRNA-1273 in children 12 to <18 years of age based on a primary analysis of results obtained in study P203. The analysis was based on a data snapshot of 8 May 2021. The respective variation (procedure EMEA/H/C/005791/II/0021) was submitted on 5 June 2021 and approved in the EU on 23 July 2021. The SOB 040 to submit the final CSR of the paediatric trial was agreed in the context of this procedure:

- The final clinical study report for study mRNA-1273-P203 including the full bioanalytical report will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation. This will provide long-term data.

## *3.3. Clinical safety*

Within the current application for cMA renewal, the MAH has not provided any new safety data.

During the period covered by this annual renewal, new safety data have emerged and have been assessed in procedures summarised below. Also, additional safety assessments based on the data emerged since the DLP have been conducted or are still ongoing as summarised below:

Since the initial marketing authorisation on 6 January 2021 in the EU, the first PSUR was submitted on 26 August 2021; its assessment is currently ongoing.

Since the initial marketing authorisation, a total of seven monthly safety summary reports (MSSR) have been submitted and assessed. The below list summarises a review period and procedure number for each MSSR:

1st MSSR: EMEA/H/C/005791/MEA/011 (reporting period 18 December 2020 - 17 January 2021)

2nd MSSR: EMEA/H/C/005791/MEA/011.1 (reporting period 18 January - 17 February 2021)

3rd MSSR: EMEA/H/C/005791/MEA/011.2 (reporting period 18 February - 31 March 2021)

4th MSSR: EMEA/H/C/005791/MEA/011.3 (reporting period 01-30 April 2021)

5th MSSR: EMEA/H/C/005791/MEA/011.4 (reporting period 01-31 May 2021)

6th MSSR: EMEA/H/C/005791/MEA/011.5 (reporting period 01-30 June 2021)

7th MSSR: EMEA/H/C/005791/MEA/011.6 (reporting period 01-31 July 2021)

The next MSSR (8th MSSR) is due on 15th September 2021 (reporting period 01-31 August 2021). Safety topics evaluated in the MSSRs as well as a resulting variation are detailed below.

Since the initial marketing authorisation, the following additional post-authorisation measure has been submitted:

EMEA/H/C/005791/LEG/002:

- Following the cluster of 7 cases reporting allergic reactions in California US 12-13 January 2021 associated with lot 041L20A, the MAH was requested to provide information on the investigation of a possible lot-related issue. Based on the information provided by the MAH, no further safety action was taken, as quality of Lot # 041L20A was considered consistent with previous mRNA-1273 vaccine lots, and no significant new safety information was identified from the cases.

Since the initial marketing authorisation, the following safety variations have been submitted:

EMEA/H/C/005791/II/0015/G (**ongoing**):

- Update of section 4.4 of the SmPC to provide additional safety information regarding hypersensitivity and anaphylaxis, as requested by the PRAC in the 2nd MSSR and update of section 4.8 of the SmPC to include 'Delayed injection site reaction' as an adverse reaction, as requested by the PRAC in the 3rd MSSR

Since the initial marketing authorisation, the PRAC has initiated the following signal assessments:

Immune thrombocytopenia EPITT no:19679:

- The PRAC concluded that the evidence assessed to date is not considered strong enough to establish a causal association between immune thrombocytopenia and the administration of COVID-19 vaccine Spikevax. Immune thrombocytopenia will be continuously monitored in future PSURs.

Myocarditis and pericarditis EPITT no: 19713 (**ongoing**):

- A causal association between COVID-19 mRNA Vaccine (nucleoside-modified) Spikevax and myocarditis/pericarditis is considered of at least a reasonable possibility. Myocarditis and pericarditis have been included in the EU product information 4.4 and 4.8 including PL. The PRAC considered also that myocarditis and pericarditis are important identified risks in the RMP. RMP update is ongoing in a separate procedure (EMEA/H/C/005791/II/0028). Direct healthcare professional communication (DHPC) has been distributed 19 July 2021.

Erythema multiforme EPITT no: 19720 (**ongoing**):

- The PRAC has agreed that the MAH for Spikevax (Moderna) should provide a cumulative review of erythema multiforme by 27 August 2021.

Glomerulonephritis and nephrotic syndrome EPITT no: 19724 (**ongoing**):

- The PRAC has agreed that the MAH for Spikevax (Moderna) should provide a cumulative review of glomerulonephritis/nephrotic syndrome by 27 August 2021.

In addition, the following adverse reactions have been added in the EU product information following the extension of the indication to individuals 12 years and older (EMEA/H/C/005791/II/021):

- Delayed injection site reactions (frequency 'common')
- Hypoaesthesia (frequency 'rare')
- Dizziness (frequency 'uncommon')

Evaluations of the following safety topics are currently ongoing and MAH's analyses are expected in the next MSSR and/or in the first PSUR:

- Serious hypertension/hypertensive crisis (PSUR)
- Thrombosis and thrombocytopenia (MSSR/PSUR)
- Exacerbation of disease in patients with autoimmune or inflammatory disorders/ autoimmune conditions aggravated (PSUR)
- Blindness (MSSR/PSUR)
- Reactogenicity in subjects previously infected with SARS-CoV-2 (PSUR)
- Extensive swelling of vaccinated limb (PSUR)
- Hypoaesthesia/Paraesthesia (PSUR)
- Immune thrombocytopenia (PSUR)
- Cardiac deaths including sudden deaths with focus on younger adults (MSSR)
- Capillary leak syndrome (MSSR)
- Rhabdomyolysis (MSSR)

- Rheumatoid arthritis and rheumatoid arthritis reactivation (MSSR)
- Menstrual disorder or post-menopausal haemorrhage (MSSR)
- Herpes Zoster (HZ) including HZ complications (MSSR)
- Dizziness and tinnitus (MSSR)

### *3.4. Pharmacovigilance inspections*

A joint EMA/Heath Canada PV inspection (INS/PHV/2021/004) was conducted from 21 June to 2 July 2021. The final outcome of the inspection is not yet available at the time of this report.

## 4. Risk management plan

The RMP v2.0 has been submitted within procedure EMEA/H/C/005791/II/0022 to include clinical safety data from study mRNA-1273-P203 (NCT04649151) in relevant sections of the RMP and is currently under assessment.

In addition, since the DLP of this annual renewal, the RMP v2.1 has been submitted within procedure EMEA/H/C/005791/II/0028 to include the important identified risks myocarditis and pericarditis in the RMP and is also currently under assessment.

## 5. Changes to the Product Information

The Annex II, specifically the due dates of specific obligations, was updated as a consequence of this annual renewal (see Attachment 1).

### *Additional monitoring*

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spikevax (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

The summary of product characteristics and the package leaflet therefore includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 6. Overall conclusions and benefit-risk balance

## *6.1. Specific Obligations (SOBs)*

### *Compliance of SOB data submitted*

During the period covered by this annual renewal, data on Quality SOBs 001, 002 and 003 have been submitted. All three Quality SOBs are only partially fulfilled so far, however several variations impacting the final due date of some SOBs are on-going or extensions to the due date have been requested by the MAH and granted.

The clinical SOBs imposed at the time of the granting of the conditional marketing authorisation as well as at the time of the granting of the extension of indication to include adolescents aged 12 years of age or older remain outstanding with their due date in the future.

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

### *Updated list of specific obligations (SOBs)*

In the framework of a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Number | Description | Due date |
|---|---|---|
| SOB 001 | In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data. | 31 July 2021 |
| SOB 002 | In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data. | 15 November 2021 |
| SOB 003 | In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. | 15 July 2021 |
| SOB 010 | In order to confirm the efficacy and safety of COVID-19 Vaccine Moderna, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301. | December 2022 |
| SOB 040 | In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report. | 30 September 2022 |

## *6.2. Benefit-risk Balance*

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the established benefit-risk balance of Spikevax in the approved indication.

The data collected as part of the specific obligations for Spikevax during the period covered by this annual renewal support its positive benefit-risk balance in the approved indication.

## *Favourable effects*

The favourable effects were demonstrated in the initial marketing authorisation for persons 18 years of age and older and updated in a type II variation to also include adolescents 12-17 years of age. No additional efficacy analyses have been conducted and no additional efficacy data have been submitted during this renewal procedure. Interim follow-up safety and immunogenicity persistence data through Day 119 for the licensed 100 µg dose from phase 1 trial mRNA-1273-P201 were submitted to cover the initial REC 010 (assesses as MEA 007). The submitted immunogenicity data indicate that 100 µg of mRNA-1273 administered with 2 doses separated by 28 days induced robust immune responses with moderate decrease of antibodies. No safety concerns were raised after review of submitted data in any of the dosing groups.

The most important favourable effects are briefly summarised below.

Efficacy in adults

Clinical efficacy has been investigated in a placebo-controlled study conducted with about 30,000 participants of which about 14,000 received two doses the vaccine 1 month apart. Participants were monitored for a median of 92 days for the development of COVID-19 disease. Results are summarised in the table below for vaccine efficacy in terms of protection from COVID-19 of any severity starting 14 days post 2nd dose:

| Age group (years) | Moderna COVID-19 Vaccine | | | Placebo | | | % Vaccine efficacy (95% CI)* |
|---|---|---|---|---|---|---|---|
| | Participants N | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years | Participants N | COVID-19 cases n | Incidence rate of COVID-19 per 1,000 person-years | |
| Overall (≥18) | 14,134 | 11 | 3.328 | 14,073 | 185 | 56.510 | 94.1 (89.3, 96.8) |
| 18 to <65 | 10,551 | 7 | 2.875 | 10,521 | 156 | 64.625 | 95.6 (90.6, 97.9) |
| ≥65 | 3,583 | 4 | 4.595 | 3,552 | 29 | 33.728 | 86.4 (61.4, 95.2) |

In participants in the primary efficacy analysis population, no cases of severe COVID-19 were reported in the vaccine group compared with 30 cases reported in the placebo group. Vaccine efficacy against severe COVID-19 was thus 100%.

Efficacy in adolescents 12 through 17 years of age

An ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and efficacy of Spikevax in adolescents aged 12 to 17 years was/is conducted in the United States. 3,732 participants were randomised 2:1 to receive 2 doses of Spikevax or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 1 year after the second dose. The study showed that Spikevax produced a comparable antibody response in 12- to 17-year-olds to that seen in young adults (aged 18 to 25 years), as measured by the level of antibodies against SARS-CoV-2. In addition, none of 2,163 children receiving the vaccine developed COVID-19, compared with four of 1,073 children given a dummy injection. These results allowed to conclude that the efficacy of Spikevax in children 12 to 17 years old is similar to that in adults.

## *Uncertainties and limitations about favourable effects*

The uncertainties and limitations of favourable effects are the same as for the initial assessment. The principal uncertainties relate to the duration of protection and efficacy in risk groups, e.g. pregnant women and immunocompromised subjects. Another uncertainty relates to vaccine efficacy against upcoming virus variants of concern. In order to comply with the planned additional Pharmacovigilance activity milestone included in the Risk Management Plan for Spikevax, the MAH submitted on 25 February 2021 the Protocol for a real-world study to evaluate mRNA-127 effectiveness and long-term effectiveness in the US (MEA 009). The protocol is currently under review.

During the renewal procedure, the paediatric extension of indication procedure II/021 was finalised and SOB 040 to submit the final CSR of the paediatric trial was agreed in the context of this procedure.

Results from some of the defined endpoints were not provided as the study is still ongoing. While this was acceptable at time of approval, as the relevant results supporting the immunobridging were provided, final study results should be submitted as soon as available.

The CHMP considered the following measure necessary to address the missing safety data:

- The final clinical study report for study mRNA-1273-P203 including the full bioanalytical report will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation. This will provide long-term data.

## *Unfavourable effects*

The safety profile for Spikevax is based on data generated in a placebo-controlled clinical study on 30,351 participants ≥ 18 years of age, a placebo-controlled clinical study on 3,732adolescents aged 12 to 17 years and from post-marketing data.

Data from clinical study in adults

Solicited adverse reactions are reported more frequently among vaccine than placebo recipients. The most frequently reported adverse reactions after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70% any grade; 10.1% grade ≥ 3), headache (64.7% any grade; 5.7% grade ≥ 3), myalgia (61.5% any grade; 9.1% grade ≥ 3) and chills (45.4% any grade; 1.4% grade ≥ 3). The majority of local and systemic adverse reactions had a median duration of 1 to 3 days.

Overall, there was a higher reported rate of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. In the participants who received the vaccine, solicited systemic adverse reactions were reported numerically more frequently by vaccine participants after Dose 2 than after Dose 1. Grade 3 systemic adverse reactions (fatigue, myalgia, arthralgia, and headache) were reported more frequently after Dose 2 than after Dose 1.

Unsolicited adverse events that occurred within 28 days following each vaccination were reported by 23.9% of participants who received mRNA-1273 and 21.6% of participants who received placebo. Unsolicited AE that occurred in ≥ 1% of study participants who received mRNA-1273 and at a rate at least 1.5-fold higher rate than placebo, were lymphadenopathy related events (1.1% versus 0.6%) and delayed injection site reactions reported >7 days after vaccination (1.2% versus 0.4%). All of the lymphadenopathy events are similar to the

axillary swelling/tenderness in the injected arm reported as solicited adverse reactions. Delayed injection site reactions included one or more of the following: erythema, pain and swelling, and are likely related to vaccination.

Serious adverse events were reported at the same rates in participants who received mRNA-1273 (0.6%) and placebo (0.6%) from the first dose until 28 days following the last vaccination. Serious adverse events were reported at the same rates in participants who received mRNA-1273 (1.0%) and placebo (1.0%) from the first dose until the last observation.

Data from clinical study in adolescents 12 through 17 years of age

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

Post-marketing data

The product information has been updated since approval as new data has emerged. Since the initial approval of the vaccine in EU, the following safety variations have been submitted to EMA:

- Safety variation to update the EU SmPC in line with CCDS version 4.0 (from 5 May 2021) to include delayed reactions at the site of injection, as well as 30 minutes waiting time postvaccination for people considered at increased risk of anaphylaxis. A type II variation was submitted to EMA on 17 May 2021. The respective statement has meanwhile been included in the SmPC.
- PRAC has initiated a Signal Assessment on immune thrombocytopenia on 8 March 2021 with preliminary assessment report from 23 June 2021 A respective warning statement has been included in the SmPC.
- Most recently, the PRAC initiated a Signal Assessment on myocarditis and pericarditis on 9 June 2021 (SDA 033). A respective warning statement has been included in the SmPC.

### *Uncertainties and limitations about unfavourable effects*

The principal uncertainties are related to long-term effects, and effects in specific risk groups, e.g. pregnant or breast-feeding women, immunocompromised subjects and frail subjects with unstable health conditions, co-morbidities or with autoimmune or inflammatory disorders.

### *Benefit-risk assessment and discussion*

The benefits of Spikevax in terms of protection against COVID-19 clearly outweigh the identified risks, and no new information has emerged during this renewal period that would necessitate a re-consideration of the initially concluded positive risk-benefit-balance. The quality related SOBs are ongoing according to plan. The fulfilment of the clinical SOBs is due by 31 December 2022.

## Importance of favourable and unfavourable effects

N/A.

### Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk balance of Spikevax remains positive.

# 7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the marketing authorisation holder has complied with the specific obligations and the benefit-risk balance for Spikevax in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable, and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

## *Amendments to the marketing authorisation*

The renewal requires some minor amendments to Annex II.E.

## *Conditions of the marketing authorisation*

The marketing authorisation is subject to the following conditions:

### Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## *Specific obligations to complete post-authorisation measures for the conditional marketing authorisation*

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data. | 31 July 2021 |

| Description | Due date |
|---|---|
| In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data. | 15 November 2021 |
| In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. | 15 July 2021 |
| In order to confirm the efficacy and safety of COVID-19 Vaccine Moderna, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301. | December 2022 |
| In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report. | 30 September 2022 |

### 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.

## 8. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

### *Scope*

Renewal of conditional marketing authorisation

### *Summary*

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional marketing authorisation for Spikevax, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

Please refer to Scientific Discussion 'Spikevax/H/C/005791/R/25'