EMA/850007/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the renewal of the marketing authorisation

Procedure no.: EMEA/H/C/005791/R/0074

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.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	18 Jul 2022	18 Jul 2022
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	16 Aug 2022	16 Aug 2022
☐	CHMP and PRAC members comments	22 Aug 2022	22 Aug 2022
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	25 Aug 2022	25 Aug 2022
☐	PRAC endorsed relevant sections of the assessment report	01 Sep 2022	01 Sep 2022
☒	Opinion	15 Sep 2022	15 Sep 2022

Table of contents

1. Background information on the annual renewal

The European Commission issued on 6 January 2021, a conditional marketing authorisation (MA) for Spikevax. 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 MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the 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 4th July 2022 an application for renewal of the conditional MA for Spikevax. The expiry date of the MA is 6th January 2023. A revised RMP version 5.0 was submitted as an addendum to the initial annual renewal application submission.

The period covered by this annual renewal is 6th January 2021 to 5th June 2022.

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 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

Two new clinical specific obligations were 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 (SOB 040);
- in the context of the extension of indication in children 6 to 11 years of age, namely providing the final CSR for the clinical trial mRNA-1273-P204 (SOB 060).

The following table provides a full overview of the current status of fulfilment for all specific obligations.

Number	Description	Status
SOB 001	In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data.	Fulfilled
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 no later than 30.04.2021. Interim reports will be provided monthly prior to and quarterly after this date	Fulfilled
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	Fulfilled
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	Pending 30 June 2023
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.	Pending 31 July 2024
SOB 060	In order to confirm the efficacy of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204.	Pending 31 March 2024

2.2. Outstanding Specific Obligations – status report for period covered

Since the granting of the conditional MA, the MAH has submitted the following SOBs:

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	EMEA/H/C/005791 -anx [SOB-012 (SO1i), SOB-013 (SO1ii), SOB-015 (SO1iv), SOB019 (SO2viii), SOB-020 (SO2ix)	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	EMEA/H/C/005791 -anx [SOB-012 (SO1i), SOB-013 (SO1ii), SOB-015 (SO1iv), SOB019 (SO2viii), SOB-020 (SO2ix)	22-04-2021	Fulfilled

SO1 (iii)	The applicant should provide the updated LNP and finished product appearance testing description including the characterization test of potentially occurring particles no later than 01.02.2021	30-07-2021	30-07-2021 for SOB-Q-014 16-11-2021 for SOB-Q-014.1	EMEA/H/C/005791/ IB/0002 [SOB-Q-014:SO1 (iii)] EMEA/H/C/005791 -anx [SOB-Q-014.1 SO1 (iii)	27-01-2022	Fulfilled
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	EMEA/H/C/005791 -anx [SOB-012 (SO1i), SOB-013 (SO1ii), SOB-015 (SO1iv), SOB019 (SO2viii), SOB-020 (SO2ix)	22-04-2021	Fulfilled
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	31-07-2021				
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 LNP intermediate processes are properly validated at Lonza Visp.	30-04-2021	30-04-2021	EMEA/H/C/005791 -anx [SOB-016 (SO2v), SOB-017 (SO2vi)], SOB-018 (SO2vii)	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	30-04-2021	EMEA/H/C/005791 -anx [SOB-016 (SO2v), SOB-017 (SO2vi)], SOB-018 (SO2vii)	24-06-2021	Fulfilled
SO2 (vii)	The applicant should provide comprehensive comparability data on CX-024414 (mRNA) active substance and LNP 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	30-04-2021	EMEA/H/C/005791 -anx [SOB-016 (SO2v), SOB-017 (SO2vi)], SOB-018 (SO2vii)	24-06-2021	Fulfilled

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	EMEA/H/C/005791 -anx [SOB-012 (SO1i), SOB-013 (SO1ii), SOB-015 (SO1iv), SOB019 (SO2viii), SOB-020 (SO2ix)	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	01-02-2021	12-02-2021	EMEA/H/C/005791 -anx [SOB-012 (SO1i), SOB-013 (SO1ii), SOB-015 (SO1iv), SOB019	22-04-2021	Fulfilled
	than 01.02.2021.			(SO2viii), SOB-020 (SO2ix)		
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	EMEA/H/C/005791/ IB/0008	20-04-2021	Fulfilled
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	EMEA/H/C/005791 -anx [SOB-027 (SO2xv), SOB-029 (SO2xvii)]	16-09-2021	Fulfilled
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.	30-07-2021	02-08-2021	EMEA/H/C/005791 -anx [SOB-028 (SO2xvi), SOB-030 (SO2xviii)]	14-10-2021	Fulfilled
SO2 (xvii)	The MAH should commit to provide a validation report and comparability report covering the finished product intermediates PPQ batches of the LNP of Kit 4 as soon as available, latest June 2021.	30-06-2021	30-06-2021	EMEA/H/C/005791 -anx [SOB-027 (SO2xv), SOB-029 (SO2xvii)]	16-09-2021	Fulfilled
SO2 (xviii)	The MAH should commit to provide a validation report and comparability report covering the finished product intermediates PPQ batches of the LNP of Kit 5 and 6 as soon as available, latest July 2021.	30-07-2021	02-08-2021	EMEA/H/C/005791 -anx [SOB-028 (SO2xvi), SOB-030 (SO2xviii)]	14-10-2021	Fulfilled

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	30-07-2021	EMEA/H/C/005791 -anx [SOB-031 (SO2xix), SOB-032 (SO2xx)]	14-10-2021	Fulfilled
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	30-07-2021	EMEA/H/C/005791 -anx [SOB-031 (SO2xix), SOB-032 (SO2xx)]	14-10-2021	Fulfilled
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 (400 L scale).	31-08-2021	31-08-2021	EMEA/H/C/005791 -anx [SOB-038 (SO2xxi), SOB-039 (SO2xxii)]	16-12-2021	Fulfilled
SO2 (xxii)	After completion of the process validation, batch release data for all PPQ lots from Recipharm (400 L scale) and from ROVI (Dara line) should be included in the dossier.	31-08-2021	31-08-2021	EMEA/H/C/005791 -anx [SOB-038 (SO2xxi), SOB-039 (SO2xxii)]	16-12-2021	Fulfilled
SO2 (xxiii)	The applicants 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	01-11-2021	EMEA/H/C/005791 -anx [SOB-042 (SO2xxiii), SOB- 043 (SO2xxiv), SOB-045 (SO2xxv), SOB-046 (SO2xxvi), SOB-048 (SO2xxvii)]	27-01-2022	Fulfilled
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	01-11-2021	EMEA/H/C/005791 -anx [SOB-042 (SO2xxiii), SOB- 043 (SO2xxiv), SOB-045 (SO2xxv), SOB-046 (SO2xxvi), SOB-048 (SO2xxvii)]	27-01-2022	Fulfilled
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	01-11-2021	EMEA/H/C/005791 -anx [SOB-042 (SO2xxiii), SOB- 043 (SO2xxiv), SOB-045 (SO2xxv), SOB-046 (SO2xxvi), SOB-048 (SO2xxvii)]	27-01-2022	Fulfilled
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	01-11-2021	EMEA/H/C/005791 -anx [SOB-042 (SO2xxiii), SOB- 043 (SO2xxiv), SOB-045 (SO2xxv), SOB-046 (SO2xxvi), SOB-048 (SO2xxvii)]	27-01-2022	Fulfilled
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	30-11-2021	15-11-2021	EMEA/H/C/005791 -anx [SOB-047 (SO2xxviii), SOB- 049 (SO2xxix), SOB-050 (SO2xxx), SOB-053 (SO2xxxi)]	27-01-2022	Fulfilled

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	01-11-2021	EMEA/H/C/005791 -anx [SOB-042 (SO2xxiii), SOB- 043 (SO2xxiv), SOB-045 (SO2xxv), SOB-046 (SO2xxvi), SOB-048 (SO2xxvii)]	27-01-2022	Fulfilled
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	15-11-2021	EMEA/H/C/005791 -anx [SOB-047 (SO2xxviii), SOB- 049 (SO2xxix), SOB-050 (SO2xxx), SOB-053 (SO2xxxi)]	27-01-2022	Fulfilled
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	15-11-2021	EMEA/H/C/005791 -anx [SOB-047 (SO2xxviii), SOB- 049 (SO2xxix), SOB-050 (SO2xxx), SOB-053 (SO2xxxi)]	27-01-2022	Fulfilled
SO2 (xxxi)	The applicant proposes to perform an extended sampling for characterisation purposes and commits to provide the characterization, in-process controls and release results from these two additional batches not later than November 30, 2021	30-11-2021	15-11-2021	EMEA/H/C/005791 -anx [SOB-047 (SO2xxviii), SOB- 049 (SO2xxix), SOB-050 (SO2xxx), SOB-053 (SO2xxxi)]	27-01-2022	Fulfilled
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	30-06-2021				
SO3 (xi)	An update on all ongoing stability studies on CX-024414 (mRNA) active 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	25-07-2021	23-07-2021	EMEA/H/C/005791 -anx [SOB-022 (SO3xi)]	14-10-2021	Fulfilled
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	30-06-2021	30-06-2021	EMEA/H/C/005791/ II/0024/G	25-11-2021	Fulfilled

	size, polydispersity, osmolality no later than 30.06.2021					
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	EMEA/H/C/005791/ II/0024/G	25-11-2021	Fulfilled
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 SOB010 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	EMEA/H/C/005791 -anx [SOB-025 (SO3xiv), SOB-025.1 (SO3xiv), SOB-025.2 (SO3xiv)] EMEA/H/C/005791/ IB/0044/G	23-06-2022	Fulfilled
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.	30-06-2023			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.	31-07- 2024			pending	
SOB 060	In order to confirm the efficacy of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204.	31-03-2024			pending	

During the period covered by this annual renewal, data on the SOBs have been submitted. The CHMP is of the view that all three quality related SOBs are fulfilled.

With regard to the clinical SOB 010, the study milestones for mRNA-1273-P301 are updated due to delays in last subject last visit (LSLV) scheduled for Dec 2022. Study P301 continues to follow the safety and effectiveness of the 2-dose primary series of mRNA-1273 in adults 18 years of age and older for 24 months. Data summarising 6 months post dose 2 follow up have been provided and the safety profile demonstrated no unexpected reactogenicity or any new safety signals. The currently available data base from study P301 in terms of vaccine efficacy and safety is considered sufficiently comprehensive to allow for a confirmatory conclusion on the benefit risk ratio at this point in time. It is not expected that the remaining outstanding data in P301 will alter the benefit-risk profile of Spikevax. The clinical SOB 010 can therefore be reclassified as a Category 3 study in the RMP and removed from Annex II.

With regard to the clinical SOB 040, results from mRNA-1273-P203 evaluating the overall safety profile of mRNA-1273 in the adolescents aged ≥12 to <18 years are generally consistent with the findings to date in the Phase 3 Study P301 in adults 18 years of age and older. Study P203 was amended to offer booster doses to all participants and will continue follow-up also including the administration of a booster dose. No new safety signals have been observed so far and it is not expected that the remaining outstanding data in P203 will alter the benefit risk profile of Spikevax in this age group. The clinical SOB 040 can therefore be reclassified as a Category 3 study in the RMP and removed from Annex II.

Regarding the clinical SOB 060, study mRNA-1273-P204 will continue to monitor the safety, immunogenicity, and efficacy of mRNA-1273 in children 6 to < 12 years of age. The safety and data reactogenicity data for the mRNA 1273 vaccine are consistent with events commonly seen in the paediatric population according to the safety follow-up analysis up to data cut off 21 February 2022. The benefit risk profile of Spikevax in children 6-11 years of age is well established and it is not expected that the remaining outstanding data in P204 will alter the benefit risk profile of Spikevax in this age group. The clinical SOB 060 can therefore be reclassified as a Category 3 study in the RMP and removed from Annex II.

In summary, it is not expected that the remaining outstanding data in Studies P301, P203 and P204 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Spikevax in the respective age groups. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data.

As part of this annual renewal the CHMP is of the opinion that SOBs 010, 040 and 060 can therefore be deleted from Annex II.

2.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, data on the quality related SOBs 001, 002 and 003 have been submitted and assessment completed. All three quality-related SOBs are now fulfilled. From the clinical point of view, the available safety and efficacy data available for Spikevax is considered comprehensive and supportive of the positive benefit-risk balance of Spikevax. The clinical SOBs 010, 040 and 060 may be reclassified as Category 3 studies in the RMP, with a final CSR to be submitted at a later stage as supportive data. They can therefore be deleted from Annex II.

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

3.1. Quality

All the requested quality data was provided, and all remaining SOBs were fulfilled (see status report above).

3.2. Clinical efficacy

Since the initial conditional marketing authorisation, the indication was extended for use in individuals 6 years of age and above. A booster dose at least 3 months after the 2nd dose of the primary vaccination was approved for individuals of 18 years of age and older.
An application for use in children aged 6 months to 5 years is under review. The application for a booster dose of an updated vaccine including ancestral mRNA and Omicron BA.1 mRNA (mRNA.1273.214) in children aged 12 years and older is currently under review in the EU, US, Canada, Australia and Switzerland.

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 previous annual renewal (DLP 05.06.2021), two periodic safety update reports (PSUR) have been submitted PSUR#1 (PSUSA/00010897/202106) and PSUR#2 (PSUSA/00010897/202112), for which PSUR#1 was assessed and finalised within the period whereas PSUR #2 was finalised after DLP. The procedures had the following outcomes:

PSUR#1: Update of section 4.8 of the SmPC to add the adverse reaction "paraesthesia" with a frequency "rare". The package leaflet is updated accordingly.

PSUR#2: Update of section 4.8 of the SmPC to add the adverse reaction "extensive swelling of vaccinated limb" with a frequency "not known". The package leaflet is updated accordingly.

Since the previous annual renewal, a total of seven summary safety reports have been submitted and assessed. The below list summarises a review period and procedure number for each report:

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

8th MSSR: EMEA/H/C/005791/MEA/011.7 (reporting period 01-31 August 2021).

9th MSSR: EMEA/H/C/005791/MEA/011.8 (reporting period 01-30 September 2021).

10th MSSR: EMEA/H/C/005791/MEA/011.9 (reporting period 01-31 October 2021).

11th SSR: EMEA/H/C/005791/MEA/011.10 (reporting period 01 November-31 December 2021).

12th SSR: EMEA/H/C/005791/MEA/011.11 (reporting period 01 January-15 February 2022).

13th SSR: EMEA/H/C/005791/MEA/011.12 (reporting period 16 February-15 April 2022).

Since the previous annual renewal, the following additional post-authorisation measures have been submitted:

EMEA/H/C/005791/LEG/055:

Variation to update PI to implement the outcome of a PRAC signal recommendation: implementation of wording pregnancy (LEG) agreed by the competent authority that require additional minor assessment submitted 03 February 2022 and approved 15 February 2021.

Since the previous annual renewal, the following safety variations have been submitted:

EMEA/H/C/005791/II/0022:

- Safety variation to update the RMP to include Clinical Safety Data for mRNA-1273 P203 submitted 11 June 2021 and approved 2 February 2022.

EMEA/H/C/005791/II/0031:

- Update of section 4.2 and 4.4 of the SmPC in order to introduce a third dose of Spikevax in the primary vaccination schedule for individuals 12 years of age and older who are severely immunocompromised, based on published literature data; the Package Leaflet is updated accordingly. Submitted 19 August 2021 and approved 4 October 2021.

EMEA/H/C/005791/II/0034:

- Update of sections 2, 4.2, 4.4, 4.8, 5.1, 6.5 and 6.6 of the SmPC to include a booster dose for Spikevax. The package leaflet was updated accordingly. Submitted 3 September 2021 and approved 29 October 2021.

EMEA/H/C/005791/II/0041:

- Update of section 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC in order to include information about extension of indication concerning use in children 6–11 years of age. The package leaflet was updated accordingly. The variation was submitted 09 November 2021 and approved 24 February 2022.

EMEA/H/C/005791/II/0042:

- Update of section 4.2 and 5.1 of the SmPC in order to include information on heterologous boosting using a 50 ug dose of Spikevax to boost subjects that have previously completed a primary vaccination series with any authorised COVID-19 vaccine, and to shorten the duration of the interval between the primary series and the booster dose to 3 months. The variation was submitted 10 November 2021 and approved 2 March 2022.

EMEA/H/C/005791/II/0047:

- Update of section 5.1 of the SmPC in order to introduce data on the immunogenicity of Spikevax against the B.1.617.2 (Delta) variant in adults and children. The variation was submitted 15 December 2021 and approved 2 March 2022.

EMEA/H/C/005791/II/0057 (**ongoing**):

- Update of section 4.2 of the SmPC to include an adolescent booster dose submitted 22 February 2022 and evaluation is still ongoing at time of submission of the renewal application.

EMEA/H/C/005791/II/0062:

- Safety variation to change the RMP to include some administrative changes and request updates to some of the study milestones to mRNA-1273-P301, mRNA1273P-203, mRNA-1273-P201, mRNA-1273-P901, mRNA-1273-P903 and m-RNA-1273-P910. Submitted 6 April 2022 and approved 23 June 2022.

EMEA/H/C/005791/II/0066 (**ongoing**):

- Update of section 4.5 and 5.1 of the SmPC due to new quality, preclinical, clinical or pharmacovigilance data for Spikevax concerning concomitant administration with high-dose quadrivalent influenza vaccine. Submitted 28 April 2022 and evaluation is still ongoing at time of submission of the renewal application.

Since the previous annual renewal, the PRAC has initiated the following signal assessments:

Myocarditis and pericarditis (Procedure nr: SDA 033 and SDA 033.1; EPITT no: 19713):

- The PRAC has agreed that based on the evidence assessed, a causal association between COVID-19 mRNA Vaccine (nucleoside-modified) Spikevax (previously COVID-19 vaccine Moderna) and myocarditis/pericarditis is considered of at least a reasonable possibility. A variation to update the PI in section 4.4 and 4.8 to implement the signal recommendations from the PRAC was submitted by 09 July 2021 and approved 13 July 2021 (EMEA/H/C/005791/IAIN/0027). In addition, the RMP was updated to further characterise the risk in a separate procedure: RMP version 2.1 with DLP 31 May 2021 was updated to include myocarditis and pericarditis as important identified risks and submitted to the EMA by 19 July 2021 and approved by 10 February 2022 (EMEA/H/C/005791/II/0028). Direct healthcare professional communication (DHPC) has been distributed 19 July 2021.

Erythema Multiforme (EPITT no: 19720):

- The PRAC concluded that a causal relationship between Spikevax and Erythema multiforme is at least a reasonable possibility and that the MAH should submit a variation to amend the product information in section 4.8 to include "Erythema multiforme" with frequency "Not Known" under the SOC: "Skin and subcutaneous tissue disorders". The PIL should be updated accordingly. Variation to update the PI (EMEA/H/C/005791/IAIN/0040) was submitted by 01 November 2021 and approved 11 November 2021.

Glomerulonephritis and Nephrotic Syndrome (EPITT no: 19724):

- The PRAC concluded that the MAH should closely monitor the issue of 'glomerulonephritis/nephrotic syndrome', including exacerbations, and present a cumulative review of cases from all sources and relevant literature in the upcoming PSUR submissions.

Multisystem inflammatory syndrome for Children (EPITT no: 19732):

- The PRAC concluded that the data is currently insufficient to support regulatory action and therefore no update of the PI in relation to MIS is currently warranted. The PRAC agreed that all the MAHs of COVID-19 vaccines should continue to closely monitor MIS, and all new cases should be reported in SSRs and PSURs. In addition, a dedicated questionnaire should be implemented to retrieve an appropriate level of information to facilitate the assessment of the cases of suspected MIS, as agreed by the PRAC.

Myocarditis and pericarditis (SDA 033.2, FU EPITT no: 19713):

- Having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the MAH, the PRAC concluded that the MAH should submit a variation to amend section 4.4 and 4.8 of the SmPC. The PIL should be updated accordingly (EMEA/H/C/005791/IAIN/0045).

Capillary Leak Syndrome/Capillary permeability (EPITT no: 19743):

- The PRAC concluded that the few cases of capillary leak syndrome (CLS) flare-ups reported with Spikevax merited a warning in the product information. The PRAC agreed that the MAH of Spikevax should amend the product information to include a warning in section 4.4 of the SmPC. The PIL should be updated accordingly. A variation to update PI in section 4.4 to implement the signal recommendations from the PRAC Signal assessment report on capillary leak syndrome + MAH address with Spikevax was submitted by 7 April 2022 and approved 29 April 2022 (EMEA/H/C/005791/IAIN/0063/G).

Autoimmune Hepatitis (EPITT no: 19750):

- The PRAC recommended that the signal of autoimmune hepatitis should be kept under close monitoring with an updated cumulative review to be submitted in the next PSUR (DLP: 30 June 2022).

Amenorrhoea (SDA 058; EPITT no: 19781):

- The PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present. The PRAC agreed that the MAH should provide an updated analysis of amenorrhea events post-vaccination in the PSUR with the DLP of 18 Dec 2022.

Heavy Menstrual Bleeding (SDA 059; EPITT no: 19780) (ongoing):

- The PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present. The PRAC has agreed that the MAH should provide an updated cumulative review of heavy menstrual bleeding post-vaccination by 24 August 2022.

Corneal Graft Rejection (EPITT no: 19792) (ongoing): The initial submission was on 10 May 2022 and evaluation is still ongoing.

Evaluations of the following safety topics are currently ongoing and MAH's analyses are expected in the next PSURs (PSUR#3: PSUSA/00010897/202206 and PSUR#4: PSUSA/00010897/202212):

- Chronic urticaria/chronic spontaneous urticaria (PSUR#3)
- Polymyalgia Rheumatica (PSUR#3)
- Solid organ cutaneous vasculitis (PSUR#3)
- Delayed onset urticaria presenting >48 hours after vaccination (PSUR#3)
- Neuralgic Amyotrophy (PSUR#3)
- Myasthenia Gravis (PSUR#3)
- Acquired haemophilia (PSUR#3)
- Autoimmune hepatitis (PSUR#3)
- Amenorrhea (PSUR#4)

3.4. Pharmacovigilance inspections

Various Health Authorities around the globe performed inspections of the Moderna pharmacovigilance system.

Swissmedic from 21st to 22nd December 2020 and a re-inspection from 8th to 9th March 2021

The scope of the 21st-22nd December 2020 inspection was to evaluate the pharmacovigilance system in place at Moderna in accordance with applicable Swiss legislation and international pharmacovigilance guidelines. The inspectors raised 1 critical finding, 3 major and 1 minor. Following the inspection report, a CAPA plan was developed by Moderna and endorsed by the inspection team.

The scope of the 8th to 9th March 2021 re-inspection was to verify the implementation of the agreed CAPA plan from the previous inspection and the adherence to the applicable regulation. The inspectors raised 4 major findings and 2 minor. Following the inspection report, a CAPA plan was developed by Moderna and endorsed by the inspection team.

MHRA from 1st February to 4th February 2021

The scope of the inspection included the routine and enhanced pharmacovigilance activities described in the Spikevax RMP and in sections 6b-g of the MHRA Guidance on Pharmacovigilance and Risk Management Plan Requirements for COVID-19 Vaccines in the UK. The inspection included a review of the local (UK) and global pharmacovigilance systems as they apply to the Spikevax and was performed remotely due to the COVID- 19 pandemic. As EU supervisory authority for the PSMF MFL17546, the HPRA attended the inspection as observers. Personnel from Moderna and IQVIA were available for interview sessions to participate in the inspection.

The inspectors raised 1 critical finding and 1 major finding related to the management and reporting of adverse reactions. Following the inspection report, a CAPA plan was developed by Moderna and endorsed by the inspection team. It was recommended that "when the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation."

EMA/Health Canada joint inspection from 21st June to 2nd July 2021

The CHMP asked for an inspection to be carried out of the conduct of pharmacovigilance for Spikevax (CX-024414, mRNA-1273). The inspection was conducted at the PSMF site by the HPRA and the DKMA. The inspection was systems- based and the scope was in accordance with GVP Module III and the IREQ.

A copy of this inspection report has been made available to the EMA and to the competent authorities of other EU member states. Health Canada and the MHRA (as observer) also received a copy.

The inspectors raised 5 major findings and 5 minors. Following the inspection report, a CAPA plan was developed by Moderna and endorsed by the inspection team.

In accordance with Union procedures (EMA/INS/PhV/192230/2014) as the CAPA proposed was acceptable, the inspection was considered complete and closed by the inspectors on the date of issuance of the Final IR (16th September 2021).

TGA inspection from 14th to 17th March 2022

The inspection was conducted under the provisions of the Therapeutic Goods Act 1989. The purpose of the inspection was to assess compliance with the pharmacovigilance legislation and guidelines, as well as the conditions specified in the relevant approvals for registration or listing, and subsequent variations.

The inspectors raised 1 critical deficiency in collection of the safety data, 1 major deficiency in QMS and 2 minor deficiencies. A CAPA plan has been developed by Moderna and endorsed by the inspection team.

Health Canada re-inspection from 1st to 2nd June 2022

This re-inspection was conducted remotely by one inspector (Regulatory Compliance and Enforcement Specialist) who served as the Lead Health Canada inspector during the combined EMA / Health Canada GVP inspection of Moderna conducted 21st June to 2nd July 2021. The re-inspection focused on the verification of Corrective and Preventive Actions (CAPA) taken to remediate non-compliance noted by Health Canada in the fourteen (14) observations cited during the 2021 joint inspection.

The inspector raised no findings and concluded that the CAPAs from the previous inspection (June- July 2021) were satisfactorily implemented, and no further actions are requested.

3.5. Discussion

In summary, the benefit-risk profile of Spikevax in individuals 6 years of age and older is confirmed. It is not expected that the remaining outstanding data in Studies P301, P203, and P204 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Spikevax. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data. The conditional marketing authorisation can therefore be converted into a standard marketing authorisation not subject to Specific Obligations.

4. Risk management plan

The RMP v4.1 has been submitted within procedure EMEA/H/C/005791/II/0067 to update the Spikevax indication to include individuals 6 months of age and older and to update clinical trial exposure data for mRNA-1273-P204 to include the use of Spikevax in children 6 months to < 2 years of age and 2 years to < 6 years of age. Furthermore, the RMP is updated to include the 0.10 mg/mL dispersion for injection supplied as a multidose vial and associated strengths and posology as well as including the international non-proprietary name (INN) to elasomeran in line with SmPC. The RMP is currently under assessment.

After the initial submission of the renewal material (04 July 2022), the MAH submitted additional documents (20 July 2022) such as addendum with the comprehensiveness of the clinical studies covered by SOBs (P301, P203 and P204) along with supportive clinical data, updated PI, and updated RMP v5.0. The rationale for an update of the RMP with a reclassification of the clinical studies mRNA-1273-P301, mRNA-1273-P203, and mRNA-1273-P204 from category 2 to category 3 studies in the Pharmacovigilance Plan is based on the application to convert the conditional marketing authorisation for Spikevax to a full marketing authorisation.

The updated RMP version 5.0 summary table of additional pharmacovigilance activities is shown below.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 55: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
None				
Category 3 – Required pharmacovigilance activities				
Study mRNA-1273-P301	Evaluate long-term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced	Interim CSR	15 Oct 2021
			Long-term follow-up	31 Dec 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing		disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis Pericarditis Long-term safety	Part B & C Interim CSR	
			Final CSR	30 Jun 2023
Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age Study Status: Ongoing	Evaluate the safety, reactogenicity, and effectiveness of the vaccine	Myocarditis Pericarditis Long-term safety	Interim long-term safety CSR for Part A & B	30 Sep 2022
			Final CSR	31 Jul 2024
Study mRNA-1273-P204 Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age Study status: Ongoing	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety	Study start	15 Mar 2021
			Final CSR	31 Mar 2024

The CHMP considered that the efficacy of Spikevax is sufficiently described and that Studies P301,

P203, and P204 are no longer key to the benefit-risk of the product. The CHMP therefore supports the reclassification of the studies as Category 3 studies in the RMP. The revised RMP version 5.0 is agreed.

5. Changes to the Product Information

Annexes I, II and IIIA of the current marketing authorisation were amended to reflect the granting of a marketing authorisation not subject to Specific Obligations for Spikevax.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spikevax (elasomeran) 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.

Therefore, the summary of product characteristics and the package leaflet 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 the SOBs have been submitted. The quality related SOBs 001, 002 and 003 are now fulfilled.

With regard to SOB 010, the study milestones for mRNA-1273-P301 are updated due to delays in last subject last visit (LSLV) scheduled for Dec 2022. Study P301 continues to follow the safety and effectiveness of the 2-dose primary series of mRNA-1273 in adults 18 years of age and older for 24 months. Data summarising 6 months post dose 2 follow up have been provided and the safety profile demonstrated no unexpected reactogenicity or any new safety signals. It is not expected that the remaining outstanding data in P301 will alter the benefit risk profile of Spikevax.
With regard to SOB 040, results from mRNA-1273-P203 evaluating the overall safety profile of Spikevax in the adolescents aged ≥12 to <18 years are generally consistent with the findings to date in the Phase 3 Study P301 in adults 18 years of age and older. Study P203 was amended to offer booster doses to all participants and will continue follow-up also including the administration of a booster dose. No new safety signals have been observed so far and it is not expected that the remaining outstanding data in P203 will alter the benefit risk profile of Spikevax in this age group.

With regard to SOB 060, study mRNA-1273-P204 will continue to monitor the safety, immunogenicity, and efficacy of Spikevax in children 6 to < 12 years of age. The safety and data reactogenicity data for the mRNA 1273 vaccine are consistent with events commonly seen in the paediatric population

according to the safety follow-up analysis up to data cut off 21 February 2022. The benefit risk profile of Spikevax in children 6-11 years of age is well established and it is not expected that the remaining outstanding data in P204 will alter the benefit risk profile of Spikevax in this age group.

In summary, it is not expected that the remaining outstanding data in Studies P301, P203 and P204 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Spikevax in the respective age groups. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data.

As part of this annual renewal the CHMP is of the opinion that SOBs 010, 040 and 060 can therefore be deleted from Annex II.

Conversion of the Specific Obligations (SOBs) to Category 3 studies in the RMP (MEAs)

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a full marketing authorisation. The three remaining Specific Obligations (SOBs) may be reclassified as Category 3 studies in the RMP (MEAs) and final study reports for the ongoing clinical trials should be submitted as supportive data according to the agreed due dates, as shown in the below table.

Description	**Due date**	**Status of the MEAs**
MEA 010 - 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-P301	30 June 2023	All interim reports have been provided as per agreement with EMA. The study milestones for mRNA-1273-P301 are updated due to delays in last subject last visit (LSLV) scheduled for Dec 2022. However, an additional interim CSR to capture long term Part B safety and Part C booster to support the sBLA in the US will be generated and shared with EMA in Dec 2022.
MEA 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.	31 July 2024	All interim reports have been provided as per agreement with EMA. The study milestones for mRNA-1273-P203 are updated due to the inclusion of a booster (homologous and heterologous) and lower dose arms at the request of the FDA, leading to the addition of an interim long-term safety CSR for Part A & B to capture 6 months of safety data and an update to the final CSR milestone respectively. As the lower dose arms of P203 have not begun enrolling, the final CSR timeline is significantly delayed. The interim long-term safety CSR for Part A&B is intended to provide a comprehensive update as initially agreed.
MEA 060 - In order to confirm the efficacy of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204.	31 March 2024	Timelines were agreed and study is on track.

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 benefit-risk of Spikevax in the approved indications.

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

Favourable effects

Since the initial conditional marketing authorisation for use in individuals 18 years of age and older, the indication has been extended for use in children 6 years and above.

An application for use in children aged 6 months to 5 years is under review. A booster dose at least 3 months after the second dose of the primary vaccination was approved for individuals of 18 years of age and older.

An application for a booster dose of 50 micrograms to be given at least 3 months after the second dose to adolescents aged 12-17 years and older has been approved but it has not been part of this renewal period.

An additional dose may be given to people aged 6 years and older with a severely weakened immune system, at least 28 days after their second dose.

The application for a booster dose of an updated vaccine including ancestral mRNA and omicron mRNA (mRNA.1273.214) in individuals aged 12 years and older is currently under review in the EU, US; Canada, Australia and Switzerland.

The most important favourable effects are briefly summarised below.

Clinical 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)	Spikevax			Placebo			
	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	% Vaccine efficacy (95% CI)*
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)**
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

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 ages 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.

Clinical efficacy in children 6 through 11 years of age

An ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of Spikevax in children ages 6 through 11 years was/is conducted in the United States and Canada. Participants with a known history of SARS-CoV-2 infection were excluded from the study. 4,011 participants were randomised 3:1 to receive 2 doses of Spikevax or saline placebo 1 month apart. A secondary efficacy analysis evaluating confirmed COVID-19 cases was performed in 3,497 participants who received two doses (0.25 mL at 0 and 1 month) of either Spikevax (n=2,644) or placebo (n=853), and had a negative baseline SARS- CoV-2 status. There were three COVID-19 cases (0.1%) in the Spikevax group and four COVID-19 cases (0.5%) in the placebo group, started 14 days after the second dose. An analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in a subset of children aged 6 through 11 years (n=319) in the paediatric study and in participants aged 18 through 25 years (n=295) in the adult study. The GMR of the neutralising antibody titers in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.239 (95% CI: 1.072, 1.432). The difference in seroresponse rate was 0.1% (95% CI: -1.9, 2.1) and the non-inferiority criteria were met. Based on the immunobridging, the VE of Spikevax in children 6 to <12 years of age is expected to match the vaccine efficacy observed in adults, where VE was 94.1%.

Uncertainties and limitations about favourable effects

The uncertainties and limitations of favourable effects are the same as in the initial assessment. The principal uncertainties relate to 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. Regarding this point, the MAH has already submitted a grouped Type II variation, on 20th July 2022 to introduce bivalent Original/Omicron BA.1 vaccine mRNA-1273.214.

Unfavourable effects

The safety profile of Spikevax is based on data generated in a placebo-controlled clinical study on 30,351 adults ≥ 18 years of age, another placebo-controlled clinical study with 3,726 participants 12 through 17 years of age, another clinical study with 4,002 participants 6 through 11 years of age, and post-marketing experience.

Solicited adverse reactions are reported more frequently among vaccine than placebo recipients. The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

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

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 Spikevax and 21.6% of participants who received placebo. Unsolicited AE that occurred in ≥ 1% of study participants who received Spikevax 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 Spikevax (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 Spikevax (1.0%) and placebo (1.0%) from the first dose until the last observation.

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 injection site pain (97%), headache (78%), fatigue (75%), myalgia (54%), chills (49%), axillary swelling/tenderness (35%), arthralgia (35%), nausea/vomiting (29%), injection site swelling (28%), injection site erythema (26%), and fever (14%).

Children 6 through 11 years of age

In a clinical study, the most frequent adverse reactions in participants 6 through 11 years of age following administration of the primary series were injection site pain (98.4%), fatigue (73.1%), headache (62.1%), myalgia (35.3%), chills (34.6%), nausea/vomiting (29.3%), axillary swelling/tenderness (27.0%), fever (25.7%), injection site erythema (24.0%), injection site swelling (22.3%), and arthralgia (21.3%).

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

Uncertainties and limitations about unfavourable effects

The principal uncertainties are related to long-term effects, and effects in specific risk groups.

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 benefit-risk balance. The three quality related SOBs are fulfilled. The fulfilment of the remaining Category 3 studies in the RMP and submission of the final CSRs is due by 31 July 2024.

Balance of benefits and risks

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

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

The benefit-risk profile of Spikevax in children, adolescents, and adults, 6 years of age and older is well established from the clinical data obtained thus far in the clinical program, and corroborated by post-authorisation data.

Cumulatively, a total of 1,091,443,760 doses of Spikevax had been delivered to 88 countries, and more than 663 million vaccine doses having been administered globally as of 15 June 2022. Statistically significant vaccine efficacy to prevent COVID-19 was demonstrated during the ongoing pandemic in interim and primary analyses.

In the adult clinical development program, two doses of 100 µg Spikevax demonstrated 93.2% efficacy against COVID-19 in more than 30,000 participants over a median observation period of over 5.3 months.

In addition, immunobridging demonstrated non inferiority for the age groups from 6 to 17 years, based on comparable antibody response to that seen in young adults (aged 18 to 25 years).

The clinical benefit of Spikevax is supported by evidence of a robust immune response both in terms of binding and neutralising antibodies as well as the induction of CD4+ and CD8+ T cells with a Th-1 dominant phenotype.

The overall safety profile of two doses of Spikevax observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as post-marketing surveillance. Based on administration of Spikevax across all clinical studies and in the extensive post-authorisation setting, there have been no emergent safety concerns and the AE profile is manifested largely by mild to moderate reactogenicity lasting 2 to 3 days. This has not changed since the granting of the initial marketing authorisation. Also, across the paediatric age groups, the adverse event profile of Spikevax is characterised primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration.

In the post-authorisation period, there have been rare reports of anaphylaxis following Spikevax administration. Following the identified safety signal of events of myocarditis and pericarditis after vaccination with mRNA based COVID-19 vaccines, the MAH had implemented an enhanced surveillance on the events of myocarditis and pericarditis. The MAH has submitted periodic safety update reports (PSUR).

According to the Guideline on the conditional MA (EMA/CHMP/509951/2006, Rev.1), section 6. MA not subject to SOB:

"When the specific obligations have been fulfilled, the CHMP may, in accordance with Article 7 of Commission Regulation (EC) No 507/2006, adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').This can be done at the time of renewal of the conditional marketing authorisation or at the time of assessment of the data submitted to fulfil the last remaining specific obligation."

Based on the comprehensive data available from multiple sources, it is agreed that the remaining specific obligations regarding the Studies P301, P203 and P204 may be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data. The conditional marketing authorisation can therefore be converted into a standard marketing authorisation not subject to Specific Obligations.

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Spikevax in its approved indications (please refer to the Summary of Product Characteristics) continues to be favourable. As all Specific Obligations have either been fulfilled or reclassified as category 3 studies in the RMP, there are no remaining grounds for the marketing authorisations to remain conditional and the CHMP therefore recommends the granting of a standard marketing authorisation not subject to Specific Obligations for Spikevax.

Amendments to the marketing authorisation

In view of the data submitted with the annual renewal, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a full marketing authorisation not subject to Specific Obligations. As a result, it is recommended that the final study reports for the three ongoing clinical trials are reclassified as category 3 studies in the RMP and are therefore deleted from the Annex II to this opinion.

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.

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.