EMADOC-1700519818-2079527
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000264109

Invented name: Spikevax

Common name: COVID-19 mRNA vaccine

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**	**Need for discussion**
☐	Submission deadline	25 April 2025	31 March 2025	☐
☐	Validation	12 May 2025	23 April 2025	☐
☐	Start date	13 May 2025	13 May 2025	☐
☐	PRAC Rapporteur AR	23 June 2025	25 June 2025	☐
☐	PRAC comments	27 June 2025	27 June 2025	☐
☐	CHMP comments	30 June 2025	30 June 2025	☐
☐	Updated PRAC Rapporteur AR	1 July 2025	1 July 2025	☐
☐	Start of CHMP written procedure	8 July 2025	8 July 2025	☐
☐	PRAC outcome	8 July 2025	8 July 2025	☐
☐	Request for supplementary information	10 July 2025	10 July 2025	☐
☐	Submission deadline	04 Aug 2025	04 Aug 2025	☐
☐	Start date	05 Aug 2025	05 Aug 2025	☐
☐	PRAC Rapporteur AR	15 Sept 2025	15 Sept 2025	☐
☐	PRAC comments	19 Sept 2025	19 Sept 2025	☐
☐	CHMP comments	22 Sept 2025	22 Sept 2025	☐
☐	Updated PRAC Rapporteur AR	23 Sept 2025	23 Sept 2025	☐
☐	Start of CHMP written procedure	30 Sept 2025	30 Sept 2025	☐
☐	PRAC outcome	30 Sept 2025	30 Sept 2025	☐
☐	2nd Request for supplementary information	02 Oct 2025	02 Oct 2025	☐
☐	Submission deadline	17 Nov 2025	17 Nov 2025	☐
☐	Start date	18 Nov 2025	18 Nov 2025	☐
☐	PRAC Rapporteur AR	22 Dec 2025	11 Dec 2025	☐
☐	PRAC comments	02 Jan 2026	02 Jan 2026	☐
☐	CHMP comments	05 Jan 2026	05 Jan 2026	☐
☐	Updated PRAC Rapporteur AR	06 Jan 2026	06 Jan 2026	☐
☐	Start of CHMP written procedure	13 Jan 2026	13 Jan 2026	☐
☐	PRAC outcome	13 Jan 2026	13 Jan 2026	☐
☒	CHMP Outcome	15 Jan 2026	15 Jan 2026	☐

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain S.L. submitted to the European Medicines Agency on 31 March 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of: C.I.4 Update of section 4.8 of the SmPC in order to update the frequency of the adverse reactions ''Anaphylaxis'' and ''Erythema'' multiforme' from ''Not known'' to ''Rare'', based on final results from study mRNA-1273-P904 listed as a category 3 study in the RMP. This is a Non-Interventional, Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU. The Package leaflet is updated accordingly. An updated RMP (version 11.0) is also included. C.I.13: Submission of the final report from study mRNA-1273-P905 (Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries) listed as a category 3 study in the RMP.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The scope of this procedure is to present and assess the data from the following two completed studies:

- Study mRNA-1273-P904 (P904), a non-interventional, post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine in the European Union (EU), and;
- Study mRNA-1273-P905 (P905), an observational study using routinely collected health data in five European countries to monitor safety of Spikevax in pregnancy.

Based on data from study P904, the MAH proposes updating the product information to revise the frequency terms for anaphylaxis and erythema multiforme. In addition, the MAH proposes removing "use in pregnancy and while breast-feeding" as missing information in the Risk Management Plan (RMP), and accordingly an update of SmPC section 4.6 and PIL section 2. This report also includes responses to requests for supplementary information (RSIs) raised in procedures EMEA/H/C/005791/MEA/003.8 and EMEA/H/C/005791/MEA/004.9.

In addition, upon agreement with the EMA, an updated RMP version 13.0 was submitted to consolidate the RMP v11.0 and RMP v12.0:

- RMP v11.0 was initially submitted in this final CSR P904/P905 procedure.
- RMP v12.0 got approved on 25-July-2025 in the meantime with the introduction of Spikevax LP.8.1 procedure (EMA/VR/0000278795).

In addition, the MAH took the opportunity to implement three additional updates resulting from the following procedures:

1. EMA/VR/0000266225 - (Final CSR P901): opinion received on 03-Jul-025.
2. EMA/VR/0000291533 - (Spikevax LP.8.1 Peds PFS): opinion received on 18-Sep-2025.
3. EMA/VR/0000282182 - (Final CSR P910): opinion received on 02-Oct-2025

The PRAC considers that RMP version 13.0 can be endorsed.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered a global pandemic in 2019. In early 2021, mass vaccination campaigns were initiated in Europe, including the use of the original Spikevax (mRNA-1273). Spikevax received conditional marketing authorisation in the EU on 6 January 2021, which was converted to standard authorisation on 3 October 2022. Since February 2022, it has been indicated for active immunisation against COVID-19 in individuals aged 6 years and older, with the indication extended to children from 6 months of age in October 2022. The bivalent Spikevax Original/Omicron BA.1 booster was authorised in the EU on 1 September 2022, followed by the BA.4-5 booster on 19 October 2022.

Studies P904 and P905 are classified as category 3 studies required in the Spikevax RMP. The current RMP (version 9.1) for Spikevax, including its bivalent formulations (Original/Omicron BA.1, BA.4-5, XBB.1.5, and JN.1—corresponding to elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, and SARS-CoV-2 JN.1 mRNA), lists myocarditis and pericarditis as important identified risks. Missing information includes use in pregnancy and while breast-feeding, as well as long-term safety.

In the initial RMP, anaphylaxis was also considered an important identified risk, and vaccine-associated enhanced disease (VAED)—including vaccine-associated enhanced respiratory disease (VAERD)—was listed as an important potential risk. Additional missing information included:

- Use in immunocompromised individuals
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
- Use in individuals with autoimmune or inflammatory disorders.

Study P904 addresses the following safety concerns listed in the RMP: myocarditis, pericarditis, and long-term safety. Evidence regarding safety concerns already removed from the RMP was also generated: VAED including VAERD, use in frail subjects with co-morbidities, and use in individuals with autoimmune or inflammatory disorders. Study P905 specifically addresses use in pregnancy and while breast-feeding.

General safety study (P904)

Study mRNA-1273-P904 was a multi-database retrospective study using routinely collected secondary data from population registries in Denmark and Norway, and primary care databases in Spain (SIDIAP) and the UK (CPRD).

The study protocol was recommended for approval by the PRAC in September 2021. Since then an updated study protocol version 1.3 and four interim reports have been assessed by the PRAC, the most recent in June 2023.

As an active surveillance study, in addition to the RMP safety concerns, the study also investigated adverse events of special interest (AESI). These were primarily defined by the Safety Platform for Emergency vACcines (SPEAC) by the WHO Global Advisory Committee for Vaccine Safety, by the EMA and by the US CDC.

The primary objective was to assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

The study assessed the association between original Spikevax and AESIs using a two-phase approach: a signal detection phase followed by a signal evaluation phase for identified signals. For Spikevax bivalent, only the signal detection phase was conducted. For the signal detection phase, sex- and age-standardized morbidity ratios (SMR) were obtained in an observed-over-expected analysis based on historical observed rates. For AESIs meeting the threshold of SMR ≥2 and at least five exposed cases, the signal evaluation phase was conducted using AESI-appropriate study designs, selecting either self-controlled designs or cohort designs with historical comparators or contemporaneous comparators who had not received any COVID-19 vaccine. Self-controlled designs were prioritised for AESIs with rapid onset and short, well-defined risk windows (≤42 days), while parallel cohort designs were used when self-controlled approaches were not suitable (e.g. anosmia/ageusia)

Self-controlled designs estimated incidence rate ratios (IRRs), adjusting for time-varying confounders and defining specific risk and control periods. In the matched historical cohort study, Cox regression was used to estimate hazard ratios (HRs), adjusting for age, sex, and comorbidity index (CCI), with more covariates added if event numbers allowed. In the contemporaneous cohort study, Cox regression estimated HRs using time since Spikevax as the time scale, adjusting for age, sex, CCI, and other covariates when possible. The VAED cohort study used logistic regression to estimate odds ratios, adjusting for age, sex, comorbidity, calendar time, and, when possible, smoking, obesity, prior vaccines, and healthcare use. In the myocarditis/pericarditis follow-up study, logistic regression estimated 30-day odds ratios, adjusted for covariates when feasible.

Country-specific estimates were pooled using random-effects meta-analysis.

In addition to stratifications on age and sex, subpopulations examined included women of childbearing age, patients with chronic, autoimmune, or inflammatory conditions, immunocompromised individuals, and those with prior COVID-19 infection. Covariates included age, sex, Charlson Comorbidity Index (CCI), healthcare utilization markers, prior non-COVID-19 vaccinations, smoking, and obesity.

SMRs were estimated for 940 strata per AESI and country. This included 840 strata for the overall population, covering three doses (and any dose), five post-vaccination time windows, three sex categories, and 14 age groups. Additionally, 20 strata were estimated for each of five subpopulations (women of childbearing age, patients with chronic health conditions, patients with autoimmune or inflammatory disorders, patients with indicators of immunocompromised status and patients previously diagnosed with COVID-19 infection), based on dose and time interval.

For analyses of original Spikevax recipients, inclusion began on 11 Jan 2021 (Denmark, Norway, Spain) and 01 Apr 2021 (UK), with follow-up ending on database-specific dates: 31 Dec 2022 (Denmark, Spain), 14 Jan 2023 (Norway), and 07 Jun 2023 (UK). For the signal detection phase for original Spikevax, the number of eligible Spikevax recipients was 564,080 in Denmark, 531,172 in Norway, 621,871 in Spain, and 273,254 in the United Kingdom. For bivalent Spikevax, the eligible number of recipients was 62,958 in Denmark, 30,854 in Norway, and 1,547,772 in the UK, with a median age of 65-71 years.

Overall, while signals were confirmed for anaphylaxis, myocarditis, and pericarditis following original Spikevax, no association was found with the 36 other examined AESIs.

Consistent with previous findings, the study confirmed an increased risk of myocarditis and pericarditis in males aged 12–39 years following the second dose of Spikevax, with combined IRRs of 16.8 and 8.56, respectively, within 0–7 days post-vaccination. The highest risk was observed in males aged 18–24 years. Despite elevated relative risks, the absolute rates were low, and case numbers were limited, particularly for pericarditis and for myocarditis in certain countries, limiting the precision of subgroup analyses. These findings are in line with the current information on myocarditis and pericarditis reflected in the PI and no updates are considered warranted.

Of note, observational studies suggest that COVID-19 infection is associated with a 15-fold increased risk of myocarditis, while Spikevax was associated with less than 4-fold increase in risk. In addition, the data do not indicate worse outcomes after myocarditis or pericarditis in Spikevax-vaccinated individuals compared to unvaccinated cases. This and other risk characterisation aspects are further investigated in the category 3 PASS mRNA-1273-P910 and mRNA-1273-P911.

For anaphylaxis 0-2 days post Spikevax vaccination, the combined IRRs were 4.74 (95% CI: 2.06-10.9) after the first dose and 2.66 (95% CI: 1.09-6.49) after the second dose in females and males aged 12 years or older. However, it is important to note that the incidence of anaphylaxis remains low in both the present study and previous research.

No association was found between original Spikevax and the 36 other examined AESIs, which included conditions related to autoimmunity, the cardiovascular and circulatory systems, hepato-gastrointestinal and renal systems, the nervous and respiratory systems, skin and mucous membranes, musculoskeletal system, as well as all-cause mortality. Although some country-specific associations were observed for certain AESIs (e.g. narcolepsy, Chilblain-like lesions, pulmonary embolism), these were not consistent across settings. In the context of multiple comparisons and other available evidence, the study does not support a causal association between Spikevax and these AESIs.

Analysis of VAED showed no evidence of disease enhancement by Spikevax; vaccination was linked to lower risks of hospitalisation, ICU admission, and death compared to unvaccinated individuals.

For bivalent Spikevax, at least one statistically significant association was detected among 31 AESIs in at least one of the 210 strata per country and AESI. However, these findings are preliminary, as limited vaccine uptake and follow-up time—except in the UK—prevented formal signal evaluation. It is agreed that these associations should not be interpreted as evidence of a safety concern.

The MAH provided a thorough discussion of study limitations which is acknowledged. Most limitations are inherent limitations related to the use of routinely collected observational data. AESI definitions are subject to misclassification and information bias, especially in the context of variable diagnostic intensity during the pandemic. Confounding by indication, healthy vaccinee bias, and time-varying confounders may have affected results across designs, and some estimates lacked precision.

Given the large study size and the appropriate application of bias-reducing methods, including self-controlled designs and covariate adjustments, the PRAC Rapporteur considers the study to be of high quality, with results that are valid and consistent with the extensive body of research on COVID-19 vaccines. In conclusion, the findings confirm that the safety profile of the original Spikevax remains consistent with the known risks of anaphylaxis, myocarditis, and pericarditis. These findings are reflected in the PI, and no updates are considered warranted at this time.

Pregnancy study (P905)

Study mRNA-1273-P905 was an observational, multi-database study investigating whether there is a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes in pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax.

Cohort, prevalence and cross-sectional designs were implemented depending on the nature of the outcome. Routinely collected secondary data from population registries of Denmark and Norway and data from primary care-based databases in Spain (SIDIAP) and the UK (CPRD Aurum) were utilized.

The study protocol was recommended for approval by the PRAC in July 2021. Since then an updated study protocol version 1.2 and three progress reports were assessed by the PRAC. Divergent from the latest study protocol, the Italian ARS data source is no longer included, as the procedure for data access could not be finalised prior to the final study analysis.

The study period was database specific and spanned from Q1 2021 to between December 2023 and June 2023. The numbers of Spikevax-exposed pregnancies were 16,506 in Denmark, 15,330 in Norway, 7,657 in SIDIAP, and 3,175 in CPRD Aurum. The comparison group of pregnancies with no exposure to COVID-19 vaccines was at least 5 times larger across the different countries.

Depending on the outcome, incidence rates (e.g. gestational diabetes), prevalence rates (e.g. MCM) or 27-day mortality risk (neonatal death) were computed as the measure of occurrence. Respectively, hazard ratios, prevalence ratios and risks ratios were computed as the measure of association with no exposure to COVID-19 vaccines as the contrast.

Analyses were adjusted for measured covariates, such as e.g. maternal age at LMP, smoking in pregnancy, parity, and previous COVID-19 infection. Analyses were additionally stratified by subpopulations of interest such as different age groups and different comorbidities. Country specific estimates were pooled via meta-analysis.

In the main meta-analysis of crude and adjusted ratios, there was no statistically significant association between Spikevax exposure and any of the study outcomes compared with no exposure to COVID-19 vaccines. Regardless of statistical significance, the point estimates were mostly below or around 1, and only slightly above 1 for a few outcomes. The results were overall consistent across the subpopulations.

The MAH provided a comprehensive discussion of study limitations which is acknowledged. These cover limitations common for retrospective pregnancy studies based on secondary routinely collected data. Notably, information bias from errors in measuring exposure, outcomes and covariates may have affected the results. While the validity and completeness of COVID-19 vaccination status in the participating databases is generally high, exposure misclassification may still have emerged in pregnant women exposed to COVID-19 vaccines other than Spikevax due to "contamination" of both Spikevax exposed and Spikevax unexposed conditions. Some form of outcome misclassification bias is also expected based on the nature of the study. However, the quality of obstetric data is generally high in the Danish and Norwegian registries, and studies have demonstrated a high validity for most of the outcomes in Denmark. Based on the discussion by the MAH, the magnitude of the impact of outcome misclassification in SIDIAP and CPRD Aurum is less clear.

The MAH also discussed the potential impact of selection bias on the study results. Very early pregnancy losses are almost never recorded, which can lead to selection bias particularly for the outcome MCM due to conditioning on pregnancies that survived long enough to be recognised. No measures to assess the potential impact of selection bias such as e.g. quantitative bias analysis or gestational age restriction were performed.

In CPRD Aurum and SIDIAP, linkage of pregnancies to their offspring was incomplete (20.5% and 70.9%, respectively), which is another potential source of selection bias and may affect generalisability. Moreover, in the UK, women may choose to refer to maternity services and bypass their GP.

The MAH also discussed the potential impact of unmeasured confounding. In addition to the limitations with regards to missing data on BMI and smoking, confounding may also stem from procedures related to the vaccine rollout. Confounding by indication and healthy user bias affecting study estimates in opposite directions may have played a role. However, the impact such bias may have played is difficult to interpret and no sensitivity analyses were performed to further assess this. The study protocol specified that alternative comparators may be explored such as other vaccinations (e.g. influenza), but no such analyses were presented in this report.

Despite a number of generic limitations, the PRAC Rapporteur considers the study of high quality and it is unlikely that the above-discussed biases undermine the validity of the results. The large study size, resulting in estimates of high precision for most outcomes, and the multi-country design including databases with a large coverage are considered particular strengths of the study. Importantly, the results are in line with the extensive existing evidence on the use of COVID-19 vaccines during pregnancy. Therefore, the MAH's conclusion that the results of this study do not suggest an association of Spikevax vaccination during pregnancy with increased risks of the adverse pregnancy, birth or neonatal outcomes is endorsed.

Regulatory implications

Anaphylaxis and erythema multiforme

Based upon the data accumulated in P904, the MAH was requested to propose frequencies for the ADRs "anaphylaxis" and "erythema multiforme", which are currently listed in SmPC section 4.8 with a frequency "Not known". Incidence proportions for anaphylaxis and erythema multiforme were calculated using cases identified during the full follow-up window after any dose of Spikevax, divided by the number of individuals with at least one Spikevax dose, by country. Incidence proportions for anaphylaxis for all countries were classified as rare (ranging from 1.5 to 2.5 per 10,000), and incidence proportions for erythema multiforme for all countries were classified as very rare, ranging from 0.28 to 0.96 per 10,000. The MAH suggests the frequency "Rare" for both terms and revised labelling has been submitted accordingly.

Although study mRNA-1273-P904, conducted in the EU (Norway, Denmark, UK, and Spain), indicated a frequency of erythema multiforme as "very rare" (0.28–0.96 cases per 10,000 vaccine recipients), the MAH proposes the term "rare" for inclusion in the product information. This proposal is based on the totality of evidence, including the US study mRNA-1273-P903, which estimated a frequency of 1.02 cases per 10,000 recipients, corresponding to "rare", and represents a more conservative approach.

One could argue that the frequency term in the EU product information should rely exclusively on EU data (mRNA-1273-P904). However, the PRAC Rapporteur considers that both studies (mRNA-1273-P904 and mRNA-1273-P903) are included in the RMP, are of high quality, and involve populations comparable with respect to risk factors for erythema multiforme. Therefore, it is considered appropriate that the frequency term is based on both studies, with the more conservative frequency term preferred.

In conclusion, the PRAC Rapporteur agrees with the MAH that the frequency term "rare" should be used for erythema multiforme in the EU product information. In addition, the suggested frequency for anaphylaxis is accepted.

Removal of "Use in Pregnancy and While Breast-feeding" as missing information in the RMP and updates of SmPC section 4.6 and PIL section 2

The justification provided by the MAH for the removal of "Use in pregnancy and while breast-feeding" as missing information from the RMP is considered acceptable. The conclusion is supported by robust data from two large non-interventional PASS (Studies mRNA-1273-P905 and mRNA-1273-P919), which show no increased risk of adverse pregnancy, birth, or neonatal outcomes associated with Spikevax exposure. These findings are consistent with a broad body of published epidemiological evidence. The established use of Spikevax in pregnancy and lactation, as reflected in clinical practice and national guidelines, further supports that this is no longer considered missing information. The Removal of "Use in Pregnancy and While Breast-feeding" as missing information in the RMP is endorsed.

Consequently, the MAH proposed an update of SmPC section 4.6 and PIL section 2. The PRAC considered that an update of the wording in line with the guideline on the harmonisation of labelling with regards to section 4.6, as per EMEA/CHMP/203927/2005, was warranted and an RSI was raised. The requested additional changes to SmPC section 4.6 and PIL 2 were fully implemented by the MAH and the PI can be endorsed.

Considering that "erythema multiforme" and "anaphylaxis" are already established adverse reactions to Spikevax, and that the current update pertains only to their frequency, it is concluded that the benefit–risk balance of Spikevax remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of:

C.I.13: Update of section 4.6 of the SmPC in order to update the information on pregnancy, based on the final results from clinical study mRNA-1273-P905 listed as a category 3 study in the RMP. This is an observational study using routinely collected health data in five European countries monitoring safety of Spikevax in pregnancy. The package leaflet is updated accordingly.

C.I.4: Update of section 4.8 of the SmPC in order to update the frequency of the adverse reactions ''Anaphylaxis'' and "Erythema multiforme" from ''Not known'' to ''Rare'', based on final results from clinical study mRNA-1273-P904 listed as a category 3 study in the RMP. This is a non-interventional, post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the Spikevax in the EU. The package leaflet is updated accordingly. An updated RMP (version 13.0) is approved.

☒is recommended for approval.

Amendments to the marketing authorisation

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

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Spikevax-VR-000264109'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The scope of this procedure is to present and assess the data from the following two completed studies:

- Study mRNA-1273-P904 (P904), a non-Interventional, post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine in the European Union (EU), and
- Study mRNA-1273-P905 (P905), an observational study using routinely collected health data in five European countries to monitor safety of Spikevax in pregnancy.

Based on data from study P904, the MAH proposes updating the product information to revise the frequency terms for anaphylaxis and erythema multiforme. In addition, the MAH proposes removing "use in pregnancy and while breast-feeding" as missing information in the Risk Management Plan (RMP). This report also includes responses to regulatory safety issues (RSIs) raised in procedures EMEA/H/C/005791/MEA/003.8 and EMEA/H/C/005791/MEA/004.9.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered a global pandemic in 2019. In early 2021, mass vaccination campaigns were initiated in Europe, including the use of the original Spikevax (mRNA-1273). Spikevax received conditional marketing authorisation in the EU on 6 January 2021, which was converted to standard authorisation on 3 October 2022. Since February 2022, it has been indicated for active immunisation against COVID-19 in individuals aged 6 years and older, with the indication extended to children from 6 months of age in October 2022. The bivalent Spikevax Original/Omicron BA.1 booster was authorised in the EU on 1 September 2022, followed by the BA.4-5 booster on 19 October 2022.

Studies P904 and P905 are classified as Category 3 studies required in the Spikevax RMP. The current RMP (version 9.1) for Spikevax, including its bivalent formulations (Original/Omicron BA.1, BA.4-5, XBB.1.5, and JN.1—corresponding to elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, and SARS-CoV-2 JN.1 mRNA), lists myocarditis and pericarditis as important identified risks. Missing information includes use in pregnancy and while breast-feeding, as well as long-term safety.

In the initial RMP, anaphylaxis was also considered an important identified risk, and vaccine-associated enhanced disease (VAED)—including vaccine-associated enhanced respiratory disease (VAERD)—was listed as an important potential risk. Additional missing information included:

- Use in immunocompromised individuals
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
- Use in individuals with autoimmune or inflammatory disorders.

Study P904 addresses the following safety concerns listed in the RMP: myocarditis, pericarditis, and long-term safety. Evidence regarding safety concerns already removed from the RMP was also generated: VAED including VAERD, use in frail subjects with co-morbidities, and use in individuals with autoimmune or inflammatory disorders. Study P905 specifically addresses use in pregnancy and while breast-feeding.

6. Non-interventional Post-Authorisation Safety Study (PASS) results

6.1. General Safety Study (P904)

6.1.1 Methods – analysis of data submitted

Research question and objectives

The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Moderna vaccines targeting SARS-CoV-2 in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax?

Primary objective:

- To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

Secondary objectives:

- To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with chronic health conditions and comorbidities, and patients with autoimmune or inflammatory disorders.

Study design

In this multi-database study, the association between original Spikevax and the AESIs was assessed using a phased approach. For the signal detection phase, sex- and age-standardized morbidity ratios (SMR) were obtained in an observed-over-expected analysis based on historical observed rates. For AESIs meeting the threshold of SMR $\geq$2 and at least five exposed cases, signal evaluation was conducted using AESI-appropriate study designs, choosing between self-controlled designs and cohort designs with historical comparators or contemporaneous comparators not vaccinated with any type of COVID-19 vaccine.

As the AESI vaccine-associated enhanced disease (VAED) could not be assessed in prepandemic data, we assed VAED in a cohort of COVID-19 infected individuals, comparing severity of COVID-19 infection between those vaccinated with Spikevax before COVID-19 infection with those not vaccinated with any type of COVID-19 vaccine before COVID-19 infection.

In an exploratory analysis, we examined short- and long-term prognosis following myocarditis and pericarditis, comparing pre-diagnosis vaccination with original Spikevax vs. no COVID-19 vaccination.

Country-specific estimates of association were combined using random-effects meta-analysis.

For bivalent Spikevax, only the signal detection phase analyses were conducted, due to limited use and follow-up for bivalent Spikevax in Denmark and Norway and no use of bivalent Spikevax in Spain within the study period.

Setting

This study was conducted using routinely collected secondary health and administrative data from population registries of Denmark and Norway, and primary-care-based databases in Spain and the United Kingdom. All countries have universal tax-funded health care access for their inhabitants.

Subjects and study size, including dropouts

The overall source population was the population contributing to each database. In Denmark and Norway, the source population were residents in the respective country. In Spain, the source population were residents of Catalonia registered for public primary care. In the United Kingdom the source population were residents enrolled in general practices (GPs) contributing to the Clinical Practice Research Datalink (CPRD) Aurum. Spikevax recipients and contemporaneous comparators were identified between 11 January 2021 and 31 December 2022 in Denmark and Spain, between 11 January 2021 and 14 January 2023 in Norway, and between 1 April 2021 and 07 June 2023 in the United Kingdom. The historical comparators were identified in each participating database before the COVID-19 pandemic (2017-2019; for Norway 2019). Exclusion criteria were missing data on age and sex, and, for the original Spikevax cohorts, receipt of another type of COVID-19 vaccine before the receipt of a given original Spikevax dose. To ensure inclusion of incident AESIs, persons with a given AESI in the 2 years before the follow-up start were excluded.

Variables and data sources

In Denmark and Norway, data were linked from population-based health and administrative registries. In Spain and the United Kingdom, data originated from databases with regional (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Catalonia) and/or GP-membership (CPRD Aurum) coverage based on medical records generated in primary care by healthcare professionals. The exposure was defined based on the record of a given dose and type of Spikevax vaccine. In addition to stratifications on age and sex, subpopulations examined included women of childbearing age, patients with chronic health conditions, patients with autoimmune or inflammatory disorders, patients with indicators of immunocompromised status, and patients previously diagnosed with COVID-19 infection. Covariates' availability was database-specific and included age, sex, comorbidity burden as measured by the Charlson Comorbidity Index (CCI) score, markers of health care resource utilization, previous non-COVID-19 vaccinations, smoking, and obesity. Study variables were defined as recorded in the underlying data sources or using primary- or secondary-care diagnosis codes and/or medication proxies. Data from the four databases were harmonised using the ConcePTION common data model and analysed using a federated approach.

6.1.2 Results

In Norway, Spain, and the United Kingdom, more than half of the persons receiving at least one dose of original Spikevax were ineligible and therefore excluded due to prior receipt of another type of COVID-19 vaccine. For the signal detection phase for original Spikevax, the number of eligible Spikevax recipients was 564,080 in Denmark, 531,172 in Norway, 621,871 in Spain, and 273,254 in the United Kingdom. The vaccinees' median age at the time of their first Spikevax dose ranged from 33 to 42 years in the participating databases.

In signal detection phase for original Spikevax, there were no signals for the AESIs acute disseminated encephalomyelitis, acute aseptic arthritis, and Kawasaki disease. These AESIs were not assessed further.

During signal evaluation using self-controlled case series (SCCS) analyses, we confirmed signals for anaphylaxis, myocarditis, and pericarditis. For all of these AESIs, results are based on a small number

of cases, and their absolute rates were low. For anaphylaxis in 0-2 days post Spikevax vaccination, the combined incidence rate ratios (IRRs) were 4.74 (95% CI: 2.06-10.9) after the first dose and 2.66 (95% CI: 1.09-6.49) after the second dose in persons aged 12 years or older. For myocarditis, the combined IRRs were 16.8 (95% CI: 6.86-41.3) 0-7 days after the second dose of Spikevax and 9.24 (95% CI: 3.77-22.6) 0-14 days after the second dose of Spikevax in males aged 12 to 39 years. For pericarditis, the combined IRRs were 8.56 (95% CI: 3.01-24.4) 0-7 days after the second dose of Spikevax and 4.55 (95% CI: 1.80-11.5) 0-14 days after the second dose of Spikevax in males aged 12 to 39 years.

In signal evaluation, there was no evidence of an association between original Spikevax vaccination and AESIs Guillain-Barré syndrome, narcolepsy, diabetes type 1, (idiopathic) thrombocytopenia, microangiopathy, heart failure, stress-induced cardiomyopathy, coronary artery disease, arrhythmia, cerebrovascular disease, deep vein thrombosis, pulmonary embolism, single organ cutaneous vasculitis, cerebral venous sinus thrombosis, splanchnic vein thrombosis, coagulation disorders, disseminated intravascular coagulation, acute liver injury, acute kidney injury, generalised convulsions, encephalitis/meningoencephalitis, transverse myelitis, Bell's palsy, acute respiratory distress syndrome, erythema multiforme, chilblain-like lesions, anosmia/ageusia, multisystem inflammatory syndrome, myositis, vaccine-induced immune thrombotic thrombocytopenia, sudden death, and death of any cause. Not all results were available for all four countries. For AESIs with country-specific results available for all four countries, the respective pooled association measures ranged between an IRR for deep vein thrombosis of 0.87 (95% CI: 0.70-1.09) for the risk window 1-42 days after any dose of original Spikevax in a SCCS analysis and an age, sex, and CCI score adjusted hazard ratio (HR) for single organ cutaneous vasculitis of 1.28 (95% CI: 0.73-2.25) comparing Spikevax vaccinated with age and sex matched historical comparators.

There was no evidence of an increased risk of VAED following COVID-19 vaccination.

Among persons with myocarditis and pericarditis, pre-morbid vaccination with Spikevax was not associated with the examined markers of prognosis compared with no pre-morbid COVID-19 vaccination. The combined estimates of association ranged from age and sex adjusted odds ratio of 0.55 (95% CI: 0.14-2.15) for 30-day all-cause mortality in myocarditis patients to age and sex adjusted HR of 1.75 (95% CI: 0.64-4.82) for all-cause mortality any time after pericarditis diagnosis and within 30 days of an arrhythmia diagnosis.

For bivalent Spikevax signal detection analysis, the number of eligible persons with at least one dose of bivalent Spikevax was 62,958 in Denmark, 30,854 in Norway, and 1,547,772 in the United Kingdom. Bivalent Spikevax was not used during the study period in Spain. The median age at the time of the first bivalent Spikevax dose ranged from 65 to 71 years, and majority of the bivalent Spikevax vaccinees were ages 65 years or older. There were no signals for the AESIs acute disseminated encephalomyelitis, acute aseptic arthritis, Kawasaki disease, disseminated intravascular coagulation, multisystem inflammatory syndrome, and sudden death. At least one signal was detected for all other examined AESIs within at least one of the possible 210 strata per country and AESI. Most signals originated from the CPRD Aurum database for the risk window 0-end of follow-up.

6.1.3 MAH's discussion

Key results

Original Spikevax and AESIs

This was a population-based study using routinely collected health and administrative secondary data from nationwide registries in Denmark and Norway; the SIDIAP database in Catalonia, Spain; and the

CPRD Aurum database in the United Kingdom. Spikevax vaccines were identified from date of first distribution of Spikevax (11 January 2021 in Denmark, Norway, and Spain; and 01 April 2021 in the United Kingdom). Follow-up ended on the database-specific recommended end date (31 December 2022 in Denmark and Spain, 14 January 2023 in Norway, and 07 June 2023 in the United Kingdom).

In Norway, Spain, and the United Kingdom, more than half of the persons receiving at least one dose of original Spikevax did not meet the eligibility criteria due to prior receipt of another type of COVID-19 vaccine and were therefore excluded. For signal detection for original Spikevax, the included number of Spikevax recipients with at least one dose of original Spikevax was 564,080 in Denmark, 531,172 in Norway, 621,871 in Spain, and 273,254 in the United Kingdom. The vaccinees' median age at the time of their first Spikevax dose ranged from 33 to 42 years in the participating databases.

The signal detection phase for original Spikevax did not identify any signals for the AESIs acute disseminated encephalomyelitis, acute aseptic arthritis, and Kawasaki disease in any country. For the remaining AESIs, a signal was detected within at least one of the possible 940 strata per country and AESI. Therefore, these AESIs entered the signal evaluation for original Spikevax. In addition, VITT entered directly into signal evaluation, as it can only be assessed in vaccinated subjects.

For anaphylaxis 0-2 days post Spikevax vaccination, the combined IRRs were 4.74 (95% CI: 2.06-10.9) after the first dose and 2.66 (95% CI: 1.09-6.49) after the second dose in females and males aged 12 years or older. There were few cases of anaphylaxis, and the absolute rates were low.

For myocarditis, the combined IRRs were 16.8 (95% CI: 6.86-41.3) 0-7 days after the second dose of Spikevax and 9.24 (95% CI: 3.77-22.6) 0-14 days after the second dose of Spikevax in males aged 12 to 39 years. Few cases of myocarditis were available, and in Norway, there were no cases of myocarditis in the control window for the primary analysis; therefore, Norway could not contribute to the combined estimate. Only Denmark had IRRs available for the first and third doses of original Spikevax and the estimates were considerably lower than for the second dose of Spikevax.

For pericarditis, the combined IRRs were 8.56 (95% CI: 3.01-24.4) 0-7 days after the second dose of Spikevax and 4.55 (95% CI: 1.80-11.5) 0-14 days after the second dose of Spikevax in males aged 12 to 39 years. There were few cases of pericarditis, and the absolute rates were low.

For anosmia/ageusia, the combined fully adjusted HR was 1.02 (95% CI: 0.64-1.64) comparing any time after Spikevax vaccination with contemporaneous comparators unexposed to any COVID-19 vaccine among females and males aged 12 years or older. When Spikevax vaccinated were compared with age-and sex-matched historical comparators, the combined fully adjusted HR was 1.74 (95% CI: 1.31-2.31).

The association between Spikevax vaccination and acute respiratory distress syndrome (a symptom associated with COVID-19 infection), varied depending on whether follow-up was censored at diagnosis of COVID-19 infection. The combined IRRs 0-14 days after the second dose of Spikevax in females and males aged 12 years or older were 2.91 (95% CI: 1.25-6.81) when censoring on COVID-19 infection and 0.69 (95% CI: 0.36-1.32) when not censoring on COVID-19 infection. The United Kingdom did not contribute to the combined estimates due to 0 events in the risk window.

For death of any cause, the combined fully adjusted HR was 0.96 (95% CI: 0.47-1.97) for Spikevax vaccinated compared with age-and sex-matched historical comparators among females and males aged 65 years or older.

For narcolepsy, diabetes type 1, heart failure, coronary artery disease, arrhythmia, cerebrovascular disease, deep vein thrombosis, pulmonary embolism, single organ cutaneous vasculitis, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalised convulsions, Bell's palsy, and Chilblain-like lesions, the estimates varied both below and above 1 for different

countries and analyses. The combined estimates from the primary analyses were compatible with no association.

Few cases were available for inclusion in the signal evaluation of Guillain-Barré syndrome, idiopathic thrombocytopenia, microangiopathy, stress-induced cardiomyopathy, cerebral venous sinus thrombosis, disseminated intravascular coagulation, encephalitis/meningoencephalitis, transverse myelitis, erythema multiforme, multisystem inflammatory syndrome, myositis, and sudden death, which resulted in the inability to provide association measures for some countries, and great uncertainty in other countries. However, the available results did not indicate an increased rate of these AESIs following vaccination with Spikevax. No cases of VITT were available in the risk windows in any of the countries and therefore we were not able to provide any estimates for the association between Spikevax and VITT.

VAED

Based on the analysis of VAED, there was no indication that Spikevax could enhance COVID-19 disease as Spikevax before COVID-19 diagnosis was associated with a lower risk of hospitalisations within 14 days of COVID-19 diagnosis and a lower risk of intensive care admission and death within 30 days of COVID-19 diagnosis compared with persons not vaccinated with any COVID-19 vaccine before the COVID-19 diagnosis.

Myocarditis and pericarditis prognosis

For the analysis of outcomes following myocarditis diagnosis, combined estimates were below 1 for outcomes both within 30 days of and any time after myocarditis diagnosis for hospitalisations, arrhythmia diagnosis, heart failure diagnosis, deaths from any cause, and death within 30 days of an arrhythmia diagnosis. The lowest combined estimate occurred for death within 30 days of myocarditis diagnosis with a combined age and sex adjusted OR of 0.55 (95% CI: 0.14-2.15) comparing persons vaccinated with Spikevax before the myocarditis diagnosis with persons not vaccinated with any COVID-19 vaccines before the myocarditis diagnosis. The highest combined estimate occurred for deaths between the date of the myocarditis diagnosis and end of follow-up with a combined age and sex adjusted HR of 0.97 (95% CI: 0.26-3.57).

For the analysis of outcomes following pericarditis, there was a greater variation in the combined estimates according to outcomes, but all combined estimates had CIs crossing the null. The lowest combined estimate occurred for any new hospitalisations after the date of a pericarditis diagnosis with a combined age and sex adjusted HR of 0.92 (0.77-1.09) comparing persons vaccinated with Spikevax before the pericarditis diagnosis with persons not vaccinated with any COVID-19 vaccines before the pericarditis diagnosis. The highest combined estimate was an age and sex adjusted HR of 1.75 (95% CI: 0.64-4.82) for deaths occurring any time after pericarditis diagnosis but within 30 days of an arrhythmia diagnosis.

Bivalent Spikevax and AESIs

Persons vaccinated with bivalent Spikevax, were identified from 01 September 2022 in Denmark and Norway and from 15 August 2022 in the United Kingdom. Bivalent Spikevax was not used in Spain during the study period. Follow-up ended on the database-specific recommended end date (31 December 2022 in Denmark, 14 January 2023 in Norway, and 07 June 2023 in the United Kingdom).

For signal detection for bivalent Spikevax, the number of eligible persons with at least one dose of bivalent Spikevax was 62,958 in Denmark, 30,854 in Norway, and 1,547,772 in the United Kingdom. The median age at the time of the first bivalent Spikevax dose ranged from 65 to 71 years in the contributing databases, and the majority of the bivalent Spikevax vaccinees were aged 65 years or older.

There were no signals for the AESIs acute disseminated encephalomyelitis, acute aseptic arthritis, Kawasaki disease, disseminated intravascular coagulation, multisystem inflammatory syndrome, and sudden death. At least one signal was detected for all the other AESIs within at least one of the possible 210 strata per country and AESI, with most signals identified in the United Kingdom/CPRD database for the risk window 0-end of follow-up.

Limitations

Results presented in this report must be interpreted in the context of several inherent limitations related to observational routinely collected data. In observational studies based on routinely collected data investigators rely on secondary data to define study populations, exposures, outcomes, and covariates; investigators do not control the exposure assignment.

Therefore, it is important to account for the completeness of a given database and for the validity of operational definitions used to identify study variables. Completeness of a database is the proportion of cases of a health state in the source population captured by the database.

Within a given database, validity of event-finding definitions is quantified by their sensitivity, specificity and predictive values (114, 115). Imperfect completeness or validity may lead to systematic error and affect results and their interpretation.

Capturing the source population

Data from Spain and the United Kingdom was based on GP databases, where membership in the database and the study population is determined by registration and deregistration at a participating GP practice. In the SIDIAP database, persons changing GP practice within the Catalan Institute of Health retain the same ID, ensuring continued follow-up for these persons.

Only persons moving outside Catalonia or dying would be deregistered from SIDIAP, if the person, the immediate family, legal representatives of the individual, or a relevant authority initiate the reporting process. Due to collaboration between different authorities within Spain, deaths and within-country migrations are considered to have high completeness.

Deregistration may be delayed relative to reporting to the database for emigrations out of Spain.

In the CPRD Aurum, deregistration is assumed to be reliable in the cases where persons deregister due to moving to another practice within the United Kingdom. Registration at a new practice would prompt a request for the patient's medical records to be transferred from their previous practice, resulting in deregistration from their original practice and thus from the CPRD Aurum database. Some patients move out of the country without deregistering, though emigration during the pandemic may have been low (116). In CPRD Aurum, date of death is based on an algorithm that includes information from various aspects of the GP record in the 330 day period before the death date in the medical record (78). Though the algorithm has not been validated directly in CPRD Aurum, a validation study in the CPRD GOLD showed a 98% sensitivity in identifying deaths when compared against the Office of National Statistics (117). Of the 1.8% of patients that were not recorded as deceased in CPRD GOLD, 82% had transferred out of the practice for a reason other than death. This indicates deregistration had occurred before the GP was informed of their death. The agreement of the death date between CPRD GOLD and data from the Office of National Statistics has increased over time; by 2013 78% had exact agreement, and 98.8% had agreement within +/- 30 days. As the algorithm used to calculate the death date in CPRD Aurum is based on that of the CPRD GOLD algorithm, the impact of missing or imprecise death dates on the results of this study is considered to be minimal. Death data from the Office of National Statistics Death Registration could not be used for this study, as it covers the period 2 January 1998 to 29 March 2021, which does not include the entire study period in our study. If a patient's deregistration had not been completed at the time of moving to a different area, signing up

for a new GP, or dying, this could result in persons in the database appearing, in error, as unexposed to Spikevax and/or without any AESIs. This could result in detection of spurious signals in the cohort designs, however, the potential impact of this is expected to be small due to the way in which record transfer occurs when registering at a new practice and the relatively low likelihood of emigration, as described above. For the self-controlled designs, the bias from delayed deregistration should be minimal as all participants had received at least one Spikevax vaccination indicating that they were present in the database at the time of the vaccination.

Also, we would expect limited bias from incomplete deregistration in the cohort studies of VAED and outcomes following myocarditis and pericarditis, as inclusion in the cohorts were defined by a recording of a medical event (COVID-19 infection, myocarditis, or pericarditis) indicating presence in the database.

The database membership in Denmark and Norway is based on population-based linked registry data with nationwide coverage and high validity and completeness, including follow-up with respect to entry to and exit from the database(76).

Confounding

The COVID-19 vaccination programmes were rolled-out with priorities set according to medical vulnerability, age, and employment (health and social workers) (118), which resulted in changes in the characteristics of COVID-19 vaccinees and associated biases throughout the study period (119). Groups most vulnerable to COVID-19 infection have often been found to have the highest COVID-19 vaccination coverage (120-124). Preferential vaccination of the groups most vulnerable to COVID-19 infection could produce confounding by indication, by conferring a higher risk of AESI in the COVID-19 vaccine exposed compared with those (not yet) vaccinated against COVID-19 (68). At the same time, lower COVID-19 vaccine uptake associated with other markers of health risks, such as homelessness, imprisonment, substance abuse, severe mental illness, and psychiatric hospital admissions (121) could independently increase AESI risks in the unvaccinated populations. Therefore, the magnitude and the direction of the net confounding by indication is unknown.

Persons employed in the health and social sector might be healthier than the average population, potentially inducing a healthy vaccinee bias due to an inherently lower AESI risk among the vaccinees' compared with those (not yet) vaccinated against COVID-19 (68). In the United Kingdom, Spikevax was introduced relatively late compared to other COVID-19 vaccines (125) and therefore we would expect a more prominent healthy vaccinee bias as the most vulnerable would have already received other COVID-19 vaccines before the introduction of Spikevax.

On the other hand, persons vaccinated against COVID-19 have a higher health seeking behaviour than persons not vaccinated against COVID-19 despite similar comorbidity level (126), which could result in increased detection of less severe AESIs in the Spikevax vaccinated.

Any true increased risk of AESI for Spikevax vaccinated compared with COVID-19 unvaccinated would be attenuated by healthy vaccinee bias but increased by confounding by indication and increased health seeking behaviour in Spikevax vaccinated. The net effect on the study results is not possible to assess in this study and would likely differ between different AESIs and between different countries.

Residual confounding could stem from confounders that are not measured well (e.g. inpatient contacts not comprehensively captured in GP notes in United Kingdom), are unmeasured (e.g., socioeconomic indicators were not included in the current data instances), or unknown. Low socioeconomic status has been associated with detrimental health outcomes , and with lower vaccine uptake (120-124, 127-130), potentially resulting in underestimation of the association between Spikevax and AESI.

Confounding in this study was addressed at the design and the analysis stage. Self-controlled designs, used in signal evaluation, inherently adjust for measured, unmeasured, and unknown time-invariant confounding, since comparisons are made within the same individual (62). For the designs other than the self-controlled, all estimates of association were adjusted for age and sex (and, if relevant, for other covariates) as a base confounder adjustment. Estimates from the signal evaluation cohort studies and the studies of VAED and myocarditis and pericarditis prognosis were additionally adjusted, given a sufficient number of events, as described in section 9.8.2.2. We selected for adjustment a subset of the measured, potential confounders, according to availability in a given database. For example, overweight was measured in Spain and the United Kingdom, but not in Denmark and Norway. Furthermore, adjustment was made for the overall comorbidity (CCI score) and health care utilisation, which would partially remove both confounding by indication and healthy vaccinee bias (131) to the extent that the measured data capture the underlying conditions. Incompletely captured concepts could include nursing home residency and employment in health care.

Signal evaluation cohort studies with contemporaneous COVID-19 unvaccinated comparators and the cohort studies of VAED and myocarditis and pericarditis prognosis are judged to be particularly vulnerable to confounding by indication and healthy vaccinee bias (68). We addressed this by using historical comparators for both signal detection and the signal evaluation cohort study with matched historical comparators. However, these designs might be more vulnerable to biases from secular trends related to the changes in patterns of occurrence/recording of health outcomes during the COVID-19 pandemic. The self-controlled designs on the other hand are vulnerable to time-dependent confounding (62), which is partly reduced in the SCCS by dose and SCRI design, owing to a short observation period, minimizing the potential for significant changes over time. In the standard SCCS design, the estimates were adjusted for calendar month and year to remove the influence of changes over time for AESIs where it was relevant.

A core assumption of the self-controlled designs is that previous events should not appreciably affect the occurrence of subsequent exposures (62). But for several of the AESIs we judged that it was likely that occurrence of the AESI could contraindicate or considerably delay subsequent COVID-19 vaccination (Section 10.2.1). Therefore, stopping follow-up at subsequent vaccines would be an indication that the AESI had not occurred and would be informative censoring. This could entail the chance that time with exposure to subsequent doses of Spikevax or other COVID-19 vaccines would be included in the control window and could bias estimates toward unity. However, this potential bias should be negligible, because we designed the control windows to end before the recommendation for subsequent Spikevax doses at day 27 after the first dose of Spikevax and 75 days after the second and third dose of Spikevax (Section 9.1.2.2 and 9.1.2.3). Indeed, the descriptive results from the Spikevax cohorts used for signal detection showed that the maximum proportion getting a subsequent dose of Spikevax or another COVID-19 vaccine within 27 days of the first dose of Spikevax was 1.3% in Spain (calculated based on Table 3.C, Appendix_Table_1_2_3), the maximum proportion getting a subsequent dose of Spikevax or another COVID-19 vaccine within 75 days of the second dose of Spikevax was 0.1% in Spain (calculated based on Table 3.C, Appendix_Table_1_2_3), and the maximum proportion getting a subsequent dose of Spikevax or another COVID-19 vaccine within 75 days of the third dose of Spikevax was 0.04% in the United Kingdom (calculated based on Table 3.D, Appendix_Table_1_2_3).

History of COVID-19 infections has been associated with a lower uptake of COVID-19 vaccine in Denmark (120) and Norway (123). In Spain, COVID-19 vaccines were not given, as a matter of policy, until 6 months after COVID-19 infection (127). For AESIs that might be associated with COVID-19 infection, this confounding might dilute the relative estimates if the unvaccinated have a higher risk of AESI due to COVID-19 infection.

For the signal evaluation cohort study with age and sex matched historical comparators, we indirectly adjusted for seasonality by starting the follow-up for the matched pair on the same day and month (but not year). For the signal evaluation cohort study with contemporaneous comparators, calendar time was the underlying time scale ensuring adjustment for seasonality.

Validity of the measures

Validity of recording of COVID-19 vaccines

In Denmark, no validation study of the register of COVID-19 vaccines (a COVID-19-vaccination-specific subset of the Danish Vaccination Registry) has been performed. Despite potential underreporting of childhood vaccinations to the Danish Vaccination Registry found in an earlier study (132), the organisation of COVID-19 vaccination campaign was different from the routine childhood vaccination program; for example it used COVID-19 vaccination centres rather than GPs. Because of the difference in the organisation and high-level public scrutiny of the COVID-19 vaccination campaign, reporting of COVID-19 vaccines is assumed to have high validity and completeness.

In Norway, the recording of COVID-19 vaccination was mandated by the national authorities and is therefore assumed highly valid and complete. The Institute of Public Health in Norway has published educational materials to support correct registration of all COVID-19 vaccines (133). The vaccination registry also contains information on vaccine doses received abroad when verified by a Norwegian medical doctor (e.g. after presentation of a vaccination card). In a survey of 105,010 adults living in the Norwegian county Viken who self-reported at least one COVID-19 vaccine, 724 (<1%) had received all COVID-19 vaccines abroad (134). Of those, 409 (56%) reported the vaccine to the Norwegian Health service. The proportion of persons with all COVID-19 vaccines administrated aboard was higher among person born outside Norway (3%), particularly those born in Poland, Lithuania, and Latvia (13%) (134). However, the overall underreporting is assumed to be low.

In Spain, COVID-19 vaccination was implemented through primary care and preventive medicine services. All vaccine information was recorded in the primary care electronic health records, and available in the SIDIAP database. The COVID-19 vaccination coverage estimated based on the SIDIAP data is comparable with the official information, provided by the Catalan Institute of Health and the Generalitat de Catalunya (135).

In CPRD Aurum, the recording of COVID-19 vaccinations is likely to be comprehensive as all COVID-19 vaccinations administered at any location in the country, at GP practices, community pharmacies, vaccination centres, and hospitals were reported to each patient's GP within 48 hours of entry into the point of care system (136).

Validity of recording of AESIs

This study aimed to examine a predefined set of potential vaccine-related AESIs as well as specific events identified by emerging evidence. A biological mechanism has not been defined for all AESIs. Operational definitions of the AESIs originating from routinely collected secondary data are subject to inherent information bias, or measurement error, stemming from diagnostic mistakes, recording errors, and misclassification of true events by case defining algorithms (137). For the Final Study Report, the AESI case-finding algorithms and definitions of the covariates underwent review and refinement by a bespoke VAC4EU task force.

Thus, all AESIs are subject to a certain degree of misclassification, including potentially inflated SMRs due to differential misclassification as a result of heightened attention during the pandemic era. For example, the increased media attention on myocarditis following COVID-19 vaccination in the spring of 2021 could lead to detection bias (138, 139). For other AESIs assumed not to be affected by pandemic-related recording trends, use of narrow AESI definitions (prioritising specificity), and the

assumption that any misclassification is nondifferential with respect to Spikevax exposure status (for example, a likely "contamination" of diabetes type 1 by diabetes type 2 exacerbated by age) mean that the relative measures of association are expected to be unbiased at any sensitivity (140). Factors unrelated to Spikevax vaccination might result in differences between the pandemic and historical AESI rates, including changes in coding practices, organization of health care, or differences in other risk factors for the AESIs over time. For example, COVID-19 infection might be a risk factor for some of the AESIs.

Completeness and validity of case-defining algorithms are expected to be database-dependent (115). Some data sources, such as Nordic population registries, can be expected to capture "hard" endpoints well that typically lead to hospital encounters such as acute myocardial infarction. However, they are expected to have lower completeness than e.g., GP-based databases such as SIDIAP or CPRD in capturing AESI primarily defined by symptoms or treated preferentially in primary care. In this analysis, information bias related to AESI misclassification is counteracted to some extent by applying narrow, and therefore relatively more specific, definitions (52). For some AESIs that are symptom-based, rare or may not uniformly lead to contact with health care, the level of available prior evidence is low and may not originate from any of the participating countries. Events that are potentially not equally well measured in all participating databases given the data flow and the available codes for definitions include acute aseptic arthritis, microangiopathy, single-organ cutaneous vasculitis, and erythema multiforme.

To ensure assessment of incident AESIs we excluded persons with a recording of the AESI in the previous two years before start of follow-up for each study. However, if recording or health seeking behaviour for AESIs varied between the comparison groups in the look-back period, this could bias results. For example, the COVID-19 pandemic reduced the health seeking behaviour for some AESIs (141) which could result in recording of prevalent events as incident events during follow-up and therefore an upward bias for relative estimates comparing Spikevax vaccinated with the historical cohort in the signal detection and with age and sex matched historical comparators in the signal evaluation cohort study. On the other hand, there might also be a lower recording of truly incident events.

VAED posed a challenge as it is generally deemed difficult to assess for COVID-19 vaccines due to the large variation in manifestations of COVID-19 disease, but the severity of COVID-19 disease could be used to inform the presence of VAED (142). Therefore, we decided to define three measures of COVID-19 infection severity (hospitalisation, admission to intensive care unit, and mortality) within a defined time window after recording of COVID-19 infection.

As not all case-finding AESI algorithms have been validated in all participating databases, plausibility of the observed historical rates was benchmarked against the existing evidence. The level of evidence available for rate benchmarking differs by AESI and by database. Since the start of the COVID-19 pandemic, rates of potential AESI in multiple databases have been estimated in multiple studies, some of which used VAC4EU methodology, algorithms and data sources (52, 143) and others that did not (144, 145). Validity and rates of AESI estimated using routinely collected data depend heavily on data provenance (primary or hospital care), contact type (inpatient vs outpatient), diagnosis type (main vs secondary), healthcare organisation, data flow, granularity of the available vocabularies, and completeness of recording (52, 115, 144-149). Heterogeneity is common not only between countries, but also between different databases within the same country (150). Difference in data provenance and completeness may produce ten- to one hundred-fold variation in estimates of incidence rates, while secular or seasonal trends may be less important (151). A recent examination of 12 data sources for estimation of AESI following COVID-19 vaccination (including SIDIAP and CPRD, used in this study) reported a wide variation of background rates not explainable by age and database effects previously

observed, as rates could vary by up to 1,000-fold even after adjusting for age and sex. Choice of the anchoring date for the time-at-risk start also affects rates, and the shorter the time-at-risk, the more susceptible the analysis is to the choice of the anchoring date (151).

Despite variation in the between-database magnitude of historical AESI incidence rates, most of the database- or country-specific rates in this study were consistent with those previously reported by studies employing VAC4EU processes or definitions or their precursors (52, 148) or from studies external to the VAC4EU processes and definitions (144, 145). Historical rates of only four out of 37 AESI differed by at least ten-fold between the databases with the highest and lowest incidence: microangiopathy, disseminated intravascular coagulation, Chilblain-like lesions, and MIS. Definitions of microangiopathy and disseminated intravascular coagulation are overlapping, while all four AESIs are difficult to identify using available standard diagnostic coding systems. Thus, these differences are plausibly explained by the nature of the underlying data and definitions. Comparability of the historical AESI rates observed in this study with prior evidence, by country, is discussed below. Given the refinement of the initial ACCESS AESI definitions (52) in the course of this study and the emergence of new and independent evidence regarding background AESI rates, the ACCESS rates were prioritised for benchmarking of the observed rates in this study only if an alternative benchmark source was unavailable. The overview of country-specific AESI rates from other studies is presented below. In most cases, direction of the differences could be attributable to variability in specific sets of codes or data provenance.

Denmark

Following the COVID-19 pandemic and the subsequent vaccine rollout, multiple studies estimated background rates of the vaccine AESIs in Denmark individually or as part of multinational benchmarking (52, 145, 147, 148, 152-177).

Rates observed in Denmark for the current study were similar or broadly consistent for the AESI Guillain-Barré Syndrome (145, 170, 173, 177); idiopathic thrombocytopenia (145, 158, 172) (with the exception of substantially higher rates among adolescents compared with an older estimate that relied on inpatient diagnoses only for part of the ascertainment period (173)), microangiopathy (52, 168); disseminated intravascular coagulation (145, 172); heart failure (160, 174, 178); stress-induced cardiomyopathy, (156, 161); coronary artery disease (158, 172); myocarditis (138, 145, 164, 179); pericarditis (145, 164, 179); deep vein thrombosis (158, 172); pulmonary embolism (158, 172); cerebral venous sinus thrombosis (145, 158, 172); splanchnic vein thrombosis (145, 158, 172); Kawasaki disease (158, 162, 177, 180); generalised convulsions (145, 173, 181); encephalitis/meningoencephalitis (152); transverse myelitis (145, 173); Bell's palsy (145, 173); chilblain-like lesions (52), and erythema multiforme (52). The number of deaths of any cause were consistent with published national statistics and peer-reviewed literature (159, 172).

The overall historical population rates in Denmark were higher than previously reported for narcolepsy (173, 176, 177) ,(especially in adolescents for whom rates were nearly ten-fold higher in the present study than previously reported in Denmark (173)), acute disseminated encephalomyelitis (145) (though rates in paediatric population were consistent with those previously reported (153)), diabetes type 1 (157, 173, 175); acute respiratory distress syndrome based on clinical, rather than administrative, ascertainment (169, 171); cerebrovascular disease (158); coagulation disorders (158); anosmia/ageusia (52); anaphylaxis (166, 173); and myositis (167) (though no solid recent evidence exits on identifying this AESI).

For single-organ cutaneous vasculitis, no evidence outside the ACCESS study (52) or Danish language clinical handbook (182) was available. Refinement of the ACCESS definitions led to a two-thirds reduction in the rate observed in this study compared with the ACCESS rate.

Overall, the historical rate of sudden death in Denmark in this study was considerably lower than previously reported (164, 173); however, the previously reported estimates are not directly comparable as the only available estimates were for the broader conditions of death of unknown cause or cardiac arrest (with or without resuscitation). Rates of acute kidney injury were, as expected, grossly underestimated by relying on diagnosis codes and not laboratory data (165). In the published evidence, rates for acute kidney injury depend strongly on the definition used, with laboratory-based definitions producing incidence rates that are higher than diagnosis-code rates (183-185).

Norway

In Norway, most of the evidence (52, 143, 172, 186-195) regarding the historical AESI rates originated from earlier studies that used VAC4EU or similar methodologies and definitions (52, 143). The observed historical rates were consistent with those previously published for the AESI Guillain-Barré Syndrome (189); acute disseminated encephalomyelitis (52); narcolepsy (110); acute aseptic arthritis (52); stress-induced cardiomyopathy (52); myocarditis (143); pericarditis (143); cerebral venous sinus thrombosis (143); splanchnic vein thrombosis (172); disseminated intravascular coagulation (143); acute kidney injury (52); generalised convulsions (52); encephalitis/meningoencephalitis (143); transverse myelitis (143); Bell's palsy (143); chilblain-like lesions (143); and death of any cause (194).

The observed historical rates were higher than those previously reported for Norway for the AESIs heart failure (191, 192); anaphylaxis (52); myositis (188); pulmonary embolism (190); deep vein thrombosis (190); coronary artery disease (193, 194); cerebrovascular disease (193, 194); arrhythmia (193, 194); acute respiratory distress syndrome (143); and acute liver injury (143). Differences in the rates were generally in the direction expected given the differences among the case definitions.

The observed historical rates were lower than those previously reported in Norway for the AESIs idiopathic thrombocytopenia (52); microangiopathy, (186) single organ cutaneous vasculitis (52); coagulation disorders (143); erythema multiforme (52); sudden death (143); Kawasaki disease (186); multisystem inflammatory syndrome (143); and anosmia/ageusia (143).

For diabetes type 1, historical rates were similar in some (195) and higher in other (187) sources of evidence.

In Norway, the post-hoc investigation, described in Section 10.1.4.1, revealed misclassification of the ICD-10 code R95 "Suden infant death syndrome" by calendar year and age. More frequent use in 2021 produced a differential misclassification, with potentially inflated rates among Spikevax vaccinated compared with the historical cohort in the signal detection and matched historical comparators in the signal evaluation cohort design, resulting in inflated estimates. In the sensitivity analyses where signal evaluation cohort analyses excluded the ICD-10 code R95, the resulting IRRs changed in both the magnitude and the direction from well-above 1 to below 1 (see sections 10.2.4.3.7 and 10.2.5.3.7). We speculate that this represents an erroneous use of R95 code in ICD-10 instead of R95 code in ICPC "Chronic obstructive pulmonary disease". Such misclassification of R95 could have been more frequent in 2021 owing to a focus on severe COVID-19-predisposing morbidities during the pandemic.

Spain

In Spain, historical rates were consistent with those previously reported for the AESIs Guillain-Barré Syndrome (144); acute disseminated encephalomyelitis (144); narcolepsy (144); idiopathic thrombocytopenia (144); arrhythmia (52); myocarditis (144); pericarditis (144); deep vein thrombosis (144, 196); pulmonary embolism (144, 196); Kawasaki disease (197, 198); disseminated intravascular coagulation (144, 199); acute liver injury (52); acute kidney injury (52); generalised convulsions (52); encephalitis/meningoencephalitis (144); (144); transverse myelitis (144); Bell's palsy (144); acute

respiratory distress syndrome (52); erythema multiforme (52); microangiopathy (52); single organ cutaneous vasculitis (200); anosmia/ageusia (52); anaphylaxis (144); myositis (201); and cerebrovascular disease (202). Rates of death of any cause were aligned with the ACCESS estimates and with the official public statistics (52, 203).

Historical rates for diabetes type 1 were aligned with those previously reported though were lower than published rates in some age subgroups in men (204).

Historical rates observed in the present study were higher than those reported previously for stress-induced cardiomyopathy (52); coronary artery disease (52); cerebral venous sinus thrombosis (199); splanchnic vein thrombosis (199).

Historical rates were lower than those reported in the ACCESS project for chilblain-like lesions (52). At the same time, there have been reports of an unusually high number of cases of chilblains in southern Europe compared to in northern Europe, suggesting decreased physical activity related to prolonged confinement (introduced in e.g., Spain but not in e.g., Norway or Denmark) being one of the potential mechanisms (205).

For heart failure, rate estimates were unavailable, but the number of cases reported in 2016 are consistent with the number of incident cases in the present study (206).

There was little evidence available for comparison for AESI coagulation disorders except for rate estimates of specific component conditions, which may not be comparable with the overall rate of coagulation disorders (199, 207). There was no evidence available for comparison for multisystem inflammatory syndrome. And there were no codes in ICD-10 CM for sudden death.

United Kingdom

For the United Kingdom, some rates were available from independent sources while for others only rates estimated in other VAC4EU studies were available (52, 143-145, 208-223). The following AESI, identified based on diagnoses present in general practice notes, had similar or broadly consistent rates with those previously reported in United Kingdom databases: narcolepsy (52, 144); Kawasaki disease (214, 219, 222); myocarditis and pericarditis (52, 143, 145); cerebrovascular disease (217); pulmonary embolism (144, 145); single organ cutaneous vasculitis (52, 143); splanchnic vein thrombosis (145); coagulation disorders; (143); disseminated intravascular coagulation (52); acute liver injury; acute kidney injury (52, 143); anaphylaxis (144, 145); myositis (223); transverse myelitis (144, 145); Bell's palsy (144, 145); acute respiratory distress syndrome (52, 143, 215); erythema multiforme (52, 143); and chilblain-like lesions (52, 143, 215). Rates of death of any cause were consistent with those reported by population statistics (208). Rates of diabetes type 1 were higher than those reported in the ACCESS study (52, 143) but lower than those in an earlier study (224); which is plausible given rate increases over time (218).

Higher rates than those previously estimated for the United Kingdom were observed for the AESIs Guillain-Barré Syndrome (though the age gradient was as expected) (145, 211); stress-induced cardiomyopathy (52); and anosmia/ageusia (52, 143). Rates of acute disseminated encephalomyelitis were lower than in one (145) but higher than in another, substantially older study, which may have captured only the more severe cases (209).

However, rates in all studies were very low and low case counts tend to lead to instability in rate estimates.

Rates of arrhythmia in this study were substantially higher in the present study than those previously reported using CPRD GOLD (216); however, this earlier study reported rates of atrial fibrillation, the most prevalent arrhythmia and no other types. We speculate that increasing rates over time (216) and

introduction of health checks in 2009 may have contributed to a greater proportion of arrhythmias being recorded in primary care (225).

Lower rates than those previously reported in the United Kingdom were observed in this study for the following AESIs: heart failure, possibly due to lack of data from Hospital Episode Statistics (210, 212); deep vein thrombosis (144); idiopathic thrombocytopenia (though higher rates among females were consistent with previous evidence) (144, 145); microangiopathy (52); and coronary artery disease, likewise possibly due to lack of Hospital Episode Statistics data (though higher rates among males were as expected) (221).

Rates for generalised convulsions in the current study were lower than reported in a study more than 10 years before in children (220) and substantially higher than those reported in a more recent VAC4EU analysis (143). This difference was in the expected direction given that the operational definition in the current study uses a broader set of codes than the VAC4EU analysis.

Rates of encephalitis/meningoencephalitis were similar to those found in an older study using Hospital Episode Statistics data, (213).

Rates of cerebral venous sinus thrombosis were higher in the present study than in a recent VAC4EU paper (52, 143, 145). The differences are in an unexpected direction given the differences in data provenance, i.e., previous study based on hospital data was expected to capture more events (145).

Rates of sudden death in this study were lower compared with the rates in two previous VAC4EU studies (52, 143), and no cases of multisystem inflammatory syndrome were observed which contrasts previous reports (52, 143). These differences may be due to the use of broader code lists in the previous studies.

No rates were available for comparison for the AESI acute aseptic arthritis.

Validity of recording of other measures

Demographic characteristics like age and sex are generally regarded to have high validity in the participating databases (76-78).

With respect to defining the RMP-specified subgroups, the available routinely collected data has inherent limitations. For example, the RMP-defined subgroup "frail subjects with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)" was represented by persons in the study population with any history of a qualifying condition recorded during the 2-year lookback period, regardless of age or frailty, as frailty is a difficult concept to define in routinely collected data. Thus, this subgroup in the current study cannot be restricted to subjects who are frail; instead, it represents subjects with a history of any specific chronic condition regardless of frailty or whether or not the condition is stable.

Recordings of diagnosis of COVID-19 or positive PCR tests for COVID-19 were used to identify COVID-19 infections and define the subpopulation of persons previously diagnosed with COVID-19, selecting persons to be included in the cohort study of VAED, and censoring on COVID-19 infections in some of the designs. Validity and completeness of the recording of COVID-19 infection likely varied over the course of the pandemic and between countries, subject to availability of testing kits and testing policies (226). Although for a large period of the pandemic mass testing was not severity-dependent, we would expect higher severity of COVID-19 infection to be associated with higher likelihood of being recorded with COVID-19 infection due to episodic changes in testing availability and policies. Thus, the study subpopulations of persons previously diagnosed with COVID-19 infection and in the analysis of VAED may differ slightly from the true eligible population of COVID-19 infected. Furthermore, we restricted the subpopulations of persons previously diagnosed with COVID-19 infections and the population for

the cohort study of VAED to persons who had been recorded before the country-specific discontinuation of mass testing, which should also reduce the selection into these populations.

Health care utilization, including primary care, hospital encounters, and use of vaccines other than COVID-19 vaccines is generally likely to have some non-differential misclassification. In Denmark a new data structure for the Danish National Patient Registry was introduced in 2019 changing the variables available to distinguish between inpatient and outpatient contact (227). In the signal evaluation cohort study with age and sex matched historical comparators, there was only a slight increase in the proportion with outpatient contact in the previous year and a slight decrease in the proportion with inpatient hospital contact within the previous year for Spikevax vaccinated compared with historical comparators in Denmark (see section 10.2.4.2.1). However, there were also some changes in other measures of health care utilization in Denmark (see section 10.2.4.2.1) and in other countries (see section 10.2.4.2.2, 10.2.4.2.3, and 10.2.4.2.4).

Overweight/obesity and smoking are likely underreported in Spain due to barriers in the implementation of health promotion in primary care (228). The barriers are primarily related to lack of consultation time and difficulty managing competing day-to-day demands. An earlier study of smoking data in CPRD data from the United Kingdom found that the prevalence of current smoking was similar to the prevalence from a national health survey (229).

Errors in delivered death data from 2017 and 2018 in Norway

A review of the initial signal detection results from Norway revealed an implausibly low number of deaths in the historical cohort when compared with the national statistics. This was caused by incomplete delivery by the data custodian of data on deaths for 2017 and 2018 (more information can be found in deviation no 1, Section 9.8.5). As a data update would jeopardize the reporting timelines, data from Norway were used with the following modifications of the design. In the signal detection for original and bivalent Spikevax we used a historical cohort covering 2019 instead of the per-protocol 2017-2019. There is no reason to believe that the 2019 historical cohort systematically differs from the 2017-2019 historical cohort, and it should therefore serve the intended purpose of estimating historical rates, affecting precision of the SMR estimates, but not their validity. The signal evaluation cohort design with matched historical comparators was also modified in Norway to select matched comparators 2 years before the vaccination of the Spikevax exposed instead of the per protocol 4 years, with follow-up ending on 31-DEC-2019 for the historical comparators to ensure no follow-up into the period of the COVID-19 pandemic. To apply the same approach in the exposed cohort, we ended the follow-up for the Spikevax exposed on 31-DEC-2021. These modifications reduced the number of observed events in Norway and thereby the precision of the estimates. Accordingly, in the Norwegian population, we were unable to report on observed AESIs occurring more than 1 year after original Spikevax vaccination in the cohort study with matched historical comparators. However, as the preplanned design was used in all other databases for the signal evaluation cohort design with matched historical comparators, and all other signal evaluation analyses (including cohort study with contemporaneous comparators) proceeded per-protocol in all countries, including Norway, the impact on the overall results was judged to be minor.

Quality control

The per-protocol quality controls have been implemented. Level 1 and level 2 checks were reviewed by each DEAP and the PIs, and any identified issues were fixed before the final run and sign-off of the level checks. Two programmers implemented the analyses supervised by investigators. For all parts of signal detection of original Spikevax (e.g. population selection, characteristics, comparative analyses), double programming was implemented successfully.

Estimates of the AESI historical rates have undergone plausibility benchmarking against published evidence as detailed in Section 11.2.3.2. In addition, all study results were reviewed by the PI and DEAPs for internal and external consistency and for clinical plausibility.

Definition of signals arbitrary

A "signal" in this study was arbitrarily defined as SMRs of ≥2 based on ≥5 cases exposed to original/bivalent Spikevax. These criteria were chosen to balance the risks of false positive against false negative signals and to identify signals with a clinically important magnitude of risk increase observable in routinely collected data, combined with precision afforded by the set minimum number of exposed cases. As signals were evaluated in the 940 strata for original Spikevax for each AESI in each country (in total, 124,320 strata) and for 210 strata for bivalent Spikevax for each AESI in each country (in total, 31,080 strata), the large number of comparisons carried out will produce false-positive findings by chance. This, by design (in addition to uncontrolled confounding), is one rationale for interpreting signal detection results not as evidence of causal relation, but as a screening tool for further signal evaluation.

Same data used for signal detection and signal evaluation

One potential limitation is at least partial circularity of the evidence by using overlapping data for both signal detection and signal evaluation. At the same time, signals detected in one database are evaluated in all databases, which is a strength of the current approach, along with the typically recommended refinement of exploration of biases in sensitivity analyses as applied in this study (230).

Limitations of meta-analysis

The relative association measures are undefined when there are no events in at least one of the exposure groups (231). Therefore, the meta-analysis creating the combined estimates only included association measures from countries with events both in the exposed and nonexposed.

This could result in overestimation of the combined estimates when one or more countries are excluded from the meta-analysis due to zero events in exposed/risk window (but with events in the unexposed/control window), underestimation of the combined estimate when one or more countries are excluded from the meta-analysis due to zero events in unexposed/control window (but with events in the exposed/risk window). The combined estimate might be both over- or under-estimated if there are zero events in both the exposed/risk window and the unexposed/control window.

Interpretation

Overall, this study implemented a triangulation approach including data from four different databases, spanning diverse population types, data flow, health care settings, and study designs with different bias structures (67). Therefore, the interpretation will focus on the totality of evidence and general patterns identified across the different countries and designs.

Original Spikevax and AESIs

Anaphylaxis is a well-established, rare AESI after vaccines in general (232). In the present study, results from the different databases and designs (SCCS and SCRI) suggested an association between Spikevax vaccination and anaphylaxis in the risk window 0-2 days after the second dose of Spikevax in females and males aged 12 years or older. For the first dose, the rate of anaphylaxis was more than 4 times as high in the risk window 0-2 days following vaccination than in the control period in the analysis combining all countries. A similar pattern for first and second dose of Spikevax was observed in a US claims based study (232). This supports that the likelihood of anaphylaxis is greater after the first dose than after the second dose of Spikevax, but that the rate is increased for both doses. However, it is important to note that the rate of anaphylaxis was low both in the current study and in

other studies. A study based on members aged 12 years or older from several US health maintenance organizations, reported an incidence rate of 5.1 (95% CI=3.3-7.6) cases of confirmed anaphylaxis per million Spikevax doses (233).

The occurrence of myocarditis and pericarditis following COVID-19 vaccination have been extensively examined, but often without differentiation among different vaccines (234) or using myocarditis and pericarditis as a composite outcome (235). The present study found that the rate of myocarditis was approximately 9 times higher, and the rate of pericarditis was approximately 4 times higher 0-14 days after the second dose of Spikevax compared with 43-75 days after the second dose in males aged 12 to 39 years, while there was a minor increase for the first and third dose in the available analyses. A review and meta-analysis of myocarditis and pericarditis combined following Spikevax vaccination also found that the risk of myocarditis and pericarditis was highest after the second dose of Spikevax (235). The risk of myocarditis and pericarditis after the second dose of Spikevax was highest in males aged 18-24 years (risk ratio=14.14; 95% CI=8.35-23.96), followed by males aged 25-39 (risk ratio=11.54; 95% CI=5.98-22.26), females aged 18-25 years (risk ratio=11.39; 95% CI=1.66-77.9) and females aged 25-39 (risk ratio=10.65; 95% CI=1.46-77.74), but the risk was increased in all age and sex groups (235). Due to the limited number of myocarditis and pericarditis cases in our study, we could not fully assess the potential association for narrowly defined age and sex groups. However, we note that the IRR for pericarditis was higher for males aged 12 to 29 years compared to males aged 12 to 39 years and that the combined estimate was close to unity for males aged 40 years or older. For myocarditis the rate was approximately 6 times higher 0-14 days after the second dose of Spikevax compared with 43-75 days after the second dose in the analysis including all females and males aged 12 years and older. In the sensitivity analysis of the risk window 0-7 days in males aged 12-39 years, the rate of myocarditis was approximately 17 times higher 0-7 days after the second dose of Spikevax compared with 43-75 days after the second dose, and the rate of pericarditis was approximately 8 times higher 0-7 days after the second dose of Spikevax compared with 43-75 days after the second dose. This is in line with other studies that found indications of a higher risk with shorter risk windows (233). Overall, the present study confirms the findings from other studies that Spikevax vaccination (especially the second dose) increase the rate of myocarditis and pericarditis (235). An important context is that COVID-19 infection is associated with a 15-fold increase of myocarditis risk, while Spikevax was associated with less than 4-fold increase in risk (236). Despite the risk increases, the absolute risks remain low in both vaccinated and unvaccinated populations.

For narcolepsy, diabetes type 1, heart failure, coronary artery disease, arrhythmia, cerebrovascular disease, deep vein thrombosis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, anosmia/ageusia, acute liver injury, acute kidney injury, generalised convulsions, Bell's palsy, single organ cutaneous vasculitis, acute respiratory distress syndrome, Chilblain-like lesions and death of any cause, there was no clear pattern in the magnitude of the relative country-specific and combined estimates even though some country-specific associations were observed. Taken together, in the context of the multitude of comparisons in this analysis and in the context of other available evidence, this study does not support the presence of an association between Spikevax and these AESIs. Other studies have not identified an association between Spikevax and the following AESIs coronary artery disease (232, 233), cerebrovascular disease (232, 233), deep vein thrombosis (232), pulmonary embolism (232, 233), coagulation disorders (232, 233), anosmia/ageusia (237), generalised convulsions (233), Bell's palsy(232, 233), and death of any cause (238-241).

Particularly, for death of any cause healthy vaccinee bias might result in reduced death rates in the Spikevax vaccinated (126). All country specific analyses of death of any cause had HRs and upper CI bounds below 1, expect for Spain in the analysis with age and sex matched historical comparators. In section 11.2.1, we described that there could be potential issues with lacking recordings of deaths in

Spain, if this was more prominent in the historical cohort this could result in an overestimation of the association between Spikevax and mortality when using historical comparators.

In the signal evaluation only a small number of cases/events of Guillain-Barré syndrome, idiopathic thrombocytopenia, microangiopathy, stress-induced cardiomyopathy, cerebral venous sinus thrombosis, encephalitis/meningoencephalitis, transverse myelitis, erythema multiforme, multisystem inflammatory syndrome and myositis were available for analysis and if any estimates where available for the intended analyses they had low precision and no clear pattern. However, there was no indication that Spikevax vaccination is associated with an increased rate of these AESIs. We also note that other studies have not identified an association between Spikevax and the following AESIs Guillain-Barré syndrome (232, 233), cerebral venous sinus thrombosis (233), encephalitis/meningoencephalitis (232, 233), and transverse myelitis (232, 233).

A very limited number of cases of disseminated intravascular coagulation resulted in the Document Number: inability to perform any SCRI analyses and only few SCCS analyses for this AESI were available. The estimates that could be obtained were high but imprecise, precluding conclusions about an association. Other studies did not find an association between Spikevax and disseminated intravascular coagulation (232, 233).

For sudden death, no codes were available in ICD-10CM used in Spain, and during the conduct of the study we identified an issue with wrong recording of sudden infant death syndrome to non-infants in Norway (see Section 10.1.4.1). Therefore, our interpretation for sudden death is based on the sensitivity analysis removing the sudden infant death code in Norway and there was no indication of an increased rate of sudden death following Spikevax vaccination.

In the signal detection stage, there were no signals for acute disseminated encephalomyelitis, acute aseptic arthritis, and Kawasaki disease in any country and they did not enter the signal evaluation phase. We note that other studies also did not find an association between Spikevax and acute disseminated encephalomyelitis (233) and Kawasaki disease (233).

No cases of VITT were available for any of the risk windows for either primary or sensitivity analysis, this indicates that VITT do not seem to be related to Spikevax.

VAED

There was no evidence in this study of an association between Spikevax and VAED. Results of this study were in agreement with other evidence, reporting that Spikevax was associated with a considerably reduced risk of hospitalisations, intensive care admissions, and deaths following COVID-19 infections (242, 243). A US study that specifically examined VAED and included patients admitted for COVID-19 infection, reported a lower risk of severe COVID-19, ICU admission and in-hospital death among patients who had completed the primary COVID-19 vaccination series (including 21% receiving Spikevax) compared to patients unvaccinated against COVID-19 (244).

Myocarditis and pericarditis diagnosis

The number of cases of myocarditis or pericarditis identified in this study was small, resulting in imprecise estimates. Furthermore, among the Spikevax exposed we included anyone who had received Spikevax (and no other type of COVID-19 vaccine) before the diagnosis of myocarditis/pericarditis. Thus, there might not be a temporal association between Spikevax vaccination and the diagnosis of myocarditis/pericarditis and a lower likelihood that the occurrence of myocarditis/pericarditis was related to Spikevax. This would result in more similarity in outcomes between Spikevax exposed and the unvaccinated. It is important to consider these limitations when interpreting the results, which should be considered preliminary.

There was no evidence from the present study that Spikevax vaccination before myocarditis or pericarditis diagnosis was associated with adverse outcomes within 30 days of diagnosis or any time after diagnosis compared with persons who had not received any COVID-19 vaccines before diagnosis. Also, the limited evidence from other sources do not indicate that patients with myocarditis or pericarditis following COVID-19 vaccination would have a worse prognosis than non-COVID-19 vaccinated patients (245, 246) and several studies did not identify severe outcomes of myocarditis or pericarditis in COVID-19 vaccinated patients (247-251). A bespoke study evaluating of outcomes in myocarditis and pericarditis following Spikevax vaccination is ongoing (mRNA-1273-P910: Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 (EUPAS105009 https://catalogues.ema.europa.eu/node/3726/administrative-details).

Bivalent Spikevax and AESI

We stress that the results for bivalent Spikevax are preliminary, and a formal signal evaluation will be required to assess these signals systematically, but it was not possible within this report, due to no distribution of bivalent Spikevax in Spain during the study period, and the limited period with distribution of bivalent Spikevax in Denmark and Norway. The signal detection did not identify any signals for the AESIs acute disseminated encephalomyelitis, acute aseptic arthritis, Kawasaki disease, disseminated intravascular coagulation, multisystem inflammatory syndrome, and sudden death. At least one signal was identified for all the other AESIs within at least one of the possible 210 strata per country and AESI, with most signals identified in the United Kingdom/CPRD database for the risk window 0-end of follow-up. We note that for original Spikevax, we also identified signals for most AESIs, but that the signal evaluation only could clearly confirm the signals for anaphylaxis, myocarditis, and pericarditis (see section 11.3.1). The safety of the bivalent Spikevax has been assessed in several randomised studies (252-254) and observational studies have also been performed. A study including persons receiving bivalent Spikevax and included the Vaccine Safety Datalink in the USA, did not identify any diagnosis clusters associated with bivalent Spikevax using a tree based scan statistics (255). A large nationwide observational cohort study using Danish registries (256) assessed the bivalent mRNA booster vaccines used in Denmark with respect to 27 adverse events in persons aged 50 years or older, while adjusting the estimates of association for age, sex, residence, calendar time, and comorbidities. The study concluded that bivalent Spikevax was not associated with an increased risk of the examined adverse events (256).

Generalisability

The country-specific results are generalisable to their source populations. To the extent the associations reported in this study validly reflect underlying biological causal mechanisms, the results are generalisable beyond the population in which the results were obtained. However, in the context of this study, factors other than biological mechanisms may affect generalisability of the country-specific results to other settings. Importantly, procedures and principles used for rolling out the COVID-19 vaccine were country-specific. Denmark promoted homologous vaccination for original COVID-19 vaccines, whereby persons were offered the same vaccine for the first and second dose (unless a vaccine was discontinued like Astra Zeneca and Johnson and Johnson). Thus, in Denmark a low proportion of the base population was excluded due to previous receipt of a COVID-19 vaccine other than Spikevax. In Norway, Spain, and the United Kingdom, where homologous vaccination was not strongly promoted, more than half of the persons in the base population were ineligible for this study due to previous receipt of a COVID-19 vaccine other than Spikevax. Thus, the results are not directly generalisable to vaccine schedules mixing different types of COVID-19 vaccines, but we took the approach of only assessing homologous Spikevax schedules to ensure that any association between

original Spikevax and the AESI could not be attributed to receipt of other COVID-19 vaccines. There is no indication of more severe adverse events following heterologous boosting with Spikevax (257).

MAH's conclusion

The results of this report confirm findings from other studies that original Spikevax is associated with an increased rate of anaphylaxis 0-2 days after vaccination in females and males aged 12 years or older and an increased rate of myocarditis and pericarditis 0-14 days after vaccination in males aged 12-39 years, with the highest increase after the second dose.

We did not find clear and consistent indications of associations between original Spikevax and the other 36 examined AESIs which covered AESIs within auto-immune diseases, the cardiovascular system, the circulatory system, the hepato-gastrointestinal and renal system, the nerves and central nervous system, the respiratory system, skin and mucous membrane, bone and joints system, and other types of AESIs like VAED and death. Among patients diagnosed with myocarditis or pericarditis, we did not find any indication that those vaccinated with original Spikevax before the myocarditis or pericarditis diagnosis had worse outcomes than those not vaccinated with any type COVID-19 vaccine before the myocarditis or pericarditis diagnosis. The results for the original Spikevax do not provide evidence of safety concerns beyond those previously reported.

For bivalent Spikevax, we detected at least one signal within at least one of the possible 210 strata per country and AESI for 31 AESIs. However, these analyses should be regarded as preliminary, as signal evaluation was not feasible in the present study due to insufficient number of bivalent Spikevax vaccinees and follow-up time except in the United Kingdom and thus cannot be interpreted as indicative of any safety concerns for bivalent Spikevax.

6.1.4 Responses to RSI

Response to EMA on RSI based on EMEA/H/C/005791/MEA003.8 outcome

This inquiry was received in the context of an interim analysis for completed study mRNA-1273-P903 as a request to explore a preliminary increased risk of Chilblain-like lesions. This association did not appear in the final analysis of that study, however the MAH was requested to consider sensitivity analyses similar to those considered for mRNA-1273-P903 in study mRNA-1273-P904 in the event that an increased risk was observed. Now that the mRNA-1273-P904 study has been completed, responses to these questions as they apply specifically to mRNA-1273-P904.

Question 1

Assess whether the potential underlying bias from the association between COVID-19 and Chilblain-like lesions changes over time (e.g. restriction of the analyses to a period in which the COVID-19 incidence was lower).

Sponsor Response

Assessment of bias was requested to explore a potential association; however, the P904 study found no overall association between Spikevax and Chilblain-like lesions. This conclusion was further supported by the lack of corroborating evidence from other studies (mRNA-1273-P903 and mRNA-1273-P920). Given this lack of association, assessing potential bias from COVID-19 incidence over time is not warranted, as no signal was identified that would require further investigation.

Assessment of the MAH's Response

The MAH argues that, since the association between Spikevax and Chilblain-like lesions observed in the interim analysis was not confirmed in the final analysis, and this finding is further supported by

evidence from studies mRNA-1273-P903 and mRNA-1273-P920, an assessment of potential bias due to changes in COVID-19 incidence over time is not warranted. This rationale is accepted.

Conclusion

Issue resolved.

Question 2

With regards to the proposal to share analysis plans to further evaluate the robustness of increased risks (see RSI 1, ITEM 3), the MAH should include these plans—or results of additional analyses if available—within the interim reports and not in a follow-up submission.

Sponsor Response

As per Item 1, this item was received and responded to in the context of the mRNA-1273-P903 study. No additional analysis plans are anticipated at this time.

Assessment of the MAH's Response

The MAH has accommodated the request to include the analysis plans within the interim reports rather than submitting them in a subsequent follow-up.

Conclusion

Issue resolved.

Question 3

If interim results of study p904 corroborate an increased risk of Chilblain-like lesions, the MAH should conduct relevant sensitivity analyses as was done in this PASS, provide a comprehensive discussion of the robustness of the data and convey clearly whether an evaluation in a signal management process is considered warranted.

Sponsor Response

As noted in the final study report for P904, the study results do not support an association between original Spikevax and chilblain-like lesions. For signal evaluation of chilblain-like lesions, the predefined primary analysis was a self-controlled case series design. The risk window was defined as 0-42 days post-administration of any dose of Spikevax in individuals aged 12 years or older. Adjusting for month and year, the country-specific incidence rate ratio (IRR) of chilblain–like lesions was 0.64 (95% CI: 0.086-4.68) in Denmark, 0.71 (95% CI: 0.25-2.03) in the United Kingdom and 1.55 (95% CI: 1.11-2.17) in Spain. No cases of chilblain–like lesions were identified in the risk window in Norway. Given that there were no results available for Norway, the meta-analysis could not include this null result, which could lead to inflation of the combined IRR from the meta-analysis. The combined IRR from the meta-analysis was 1.25 (95% CI: 0.73-2.12).

In this analysis, the control window began on the date of first distribution of Spikevax (11 January 2021 in Denmark, Norway, and Spain; and 01 April 2021 in the United Kingdom) and lasted until end of follow-up. Periods within risk windows, healthy vaccinee window, or induction/washout windows were not included in the control window. Follow-up ended at the earliest occurrence of death, database disenrollment, record of another COVID-19 vaccine or fourth dose of original Spikevax, COVID-19 infection, or last date with available data (31 December 2022 in Denmark and Spain, 14 January 2023 in Norway, and 07 June 2023 in the United Kingdom).

The results from Spain had a considerable impact on the combined estimates due to the IRR above 1 and because most of the cases originated from SIDIAP (Spain-Catalonia). SIDIAP was the only Data Access Partner (DAP) using the ICD-10-CM coding system. In the context of the P904 study, T69.1XXA ("Chilblains, initial encounter") was utilized to categorize chilblain-like lesions. Chilblains, also known as perniosis, are inflammatory skin lesions resulting from prolonged exposure to cold and humidity. Verbal consultation with primary care physicians from the Catalan Institute of Health indicated that T69.1XXA might be assigned to similar conditions in routine clinical practice. We note that there is a broad range of skin conditions that could be in the differential diagnosis of chilblain-like lesions (1). This indicates that there could be an overestimation of the observed rates of chilblain-like lesions in Catalonia.

Chilblain-like lesions can be primary or secondary to many different conditions including inflammatory conditions, infections, and environmental factors (1). Overall, the occurrence of chilblain-like lesions could have increased during the COVID-19 pandemic (2, 3), but it might be related to a co-occurrence with low temperatures (4) and potentially exacerbated by lifestyle changes due to COVID-19 restrictions (5).

In the study P904 analyses, we ended follow-up after a diagnosis of COVID-19 in order to minimize the risk of confounding due to COVID-19. However, not all COVID-19 infections are identifiable in the databases, subject to availability of testing kits, testing policies, and healthcare seeking behaviour (6).

Before the COVID-19 pandemic, chilblains occurred with a seasonal pattern during the cold months (7). Despite adjustment of the analyses for month and year, we cannot rule out residual confounding from season or COVID-19 infections, which had distinct peaks (8) as did COVID-19 vaccination (9).

In light of the overall lack of association in meta-analysis and lack of corroborating evidence for an increased risk of Chilblain-like lesions in other studies (mRNA-1273-P903 and mRNA-1273-P920), the MAH does not propose further evaluation in a signal management process at this time.

Assessment of the MAH's Response

While a statistically significant increased IRR was observed in Spain (1.55; 95% CI: 1.11–2.17), no overall association was found between original Spikevax and Chilblain-like lesions in the final study report for P904. No significant associations were observed in Denmark or the UK, and data from Norway were not available, potentially inflating the combined meta-analytic IRR, which was 1.25 (95% CI: 0.73–2.12). The absence of a consistent signal across countries, combined with negative findings from related studies (mRNA-1273-P903 and mRNA-1273-P920), supports the conclusion that further signal evaluation is not warranted at this time.

Conclusion

Issue resolved.

Response to EMA on Spikevax (EMEA/H/C/005791) - MEA 004.9 Rapporteur's assessment report

Question 4

The MAH should propose a frequency of "anaphylaxis" based upon the data accumulated in this study (for guidance on the estimation of frequency of adverse reactions from safety studies please refer to 'A Guideline on Summary of Product Characteristics' revision 2).

Sponsor Response

Based on the data accumulated in the study, the frequency of anaphylaxis has been assessed as rare. The product information has been updated accordingly and is included in the submission.

Assessment of the MAH's Response

In the Clinical Overview, the MAH states that incidence proportions for anaphylaxis and erythema multiforme were calculated using cases identified during the full follow-up window after any dose of Spikevax, divided by the number of individuals with at least one Spikevax dose, by country. Frequency categories were assigned according to the following convention: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). Based on this convention, incidence proportions for anaphylaxis for all countries were classified as rare (ranging from 1.5 to 2.5 per 10,000), and incidence proportions for erythema multiforme for all countries were classified as very rare, ranging from 0.28 to 0.96 per 10,000. The MAH was requested to propose frequencies for "anaphylaxis" and "erythema multiforme" based upon the data accumulated in P904. The frequency has been assessed as "Rare" for both terms and revised labelling has been submitted accordingly.

The suggested frequency for anaphylaxis is accepted.

Conclusion

Issue resolved for anaphylaxis.

Question 5

Erythema multiforme is an identified risk and is labelled in the EU SmPC section 4.8 with a frequency "Not known". In the final report, the MAH should propose a frequency of Erythema multiforme based on the data accumulated in this study (for guidance on the estimation of frequency of adverse reactions from safety studies please refer to 'A Guideline on Summary of Product Characteristics' revision 2).

Sponsor Response

Based on the data accumulated in the study, the frequency of erythema multiforme has been assessed as rare. The product information has been updated accordingly and is included in the submission.

Assessment of the MAH's Response

As stated in the assessment of the MAH's response to Question 4, the incidence proportions of erythema multiforme across all countries were classified as 'very rare'. However, the MAH proposes using the frequency term 'rare' in the product information. The rationale for selecting 'rare' rather than 'very rare' is not clearly explained and remains unclear to the assessor.

Conclusion

Issue not resolved.

The MAH is requested to clarify the rationale for proposing the frequency term 'rare' instead of 'very rare' for inclusion in the product information, given that the incidence proportions for erythema multiforme were classified as 'very rare' across all countries.

6.1.5 PRAC Rapporteur's discussion

Study mRNA-1273-P904 was a multi-database retrospective study using routinely collected secondary data from population registries in Denmark and Norway, and primary care databases Spain (SIDIAP) and the UK (CPRD). The study was a category 3 PASS required in the Spikevax RMP to address the safety concerns: myocarditis, pericarditis, and long-term safety. Evidence regarding safety concerns already removed from the RMP was also generated: VAED including VAERD, use in frail subjects with co-morbidities, and use in individuals with autoimmune or inflammatory disorders.

The study protocol was recommended for approval by the PRAC in September 2021. Since then an updated study protocol version 1.3 and four interim reports have been assessed by the PRAC, the most recent in June 2023.

As an active surveillance study, in addition to the RMP safety concerns, the study also investigated adverse events of special interest (AESI). These were primarily defined by the Safety Platform for Emergency vACcines (SPEAC) by the WHO Global Advisory Committee for Vaccine Safety, by the EMA and by the US CDC.

The primary objective was:

- To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

Secondary objectives were:

- To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with chronic health conditions and comorbidities, and patients with autoimmune or inflammatory disorders.
- To assess whether vaccination with Spikevax bivalent Omicron BA.1 and/or other formulations as observed and feasible is associated with increased rates of the AESI compared with the expected rates, overall, by sex and age group.

The following AESIs were included in this study: Guillain-Barré Syndrome, Acute disseminated encephalomyelitis, Narcolepsy, Acute aseptic arthritis, Diabetes type, Idiopathic thrombocytopenia, Kawasaki disease, Microangiopathy, Heart failure, Stress-induced cardiomyopathy, Coronary artery disease, Arrhythmia, Myocarditis, Pericarditis, Cerebrovascular disease, Deep vein thrombosis, Pulmonary embolism, Single organ cutaneous vasculitis, Cerebral venous sinus thrombosis, Splanchnic vein thrombosis, Coagulation disorders, Disseminated intravascular coagulation, Acute liver injury, Acute kidney injury, Generalised convulsions, Encephalitis/meningoencephalitis, Transverse myelitis, Bell's palsy, Acute respiratory distress syndrome, Erythema multiforme, Chilblain-like lesions, Anosmia/ageusia, Anaphylaxis, Multisystem inflammatory syndrome, Myositis, Sudden death, Death of any cause, Vaccine-induced immune thrombotic thrombocytopenia (VITT).

The study assessed the association between original Spikevax and AESIs using a two-phase approach: a signal detection phase followed by a signal evaluation phase for identified signals. For Spikevax bivalent, only the signal detection phase was conducted. For the signal detection phase, sex- and age-standardized morbidity ratios (SMR) were obtained in an observed-over-expected analysis based on historical observed rates. For AESIs meeting the threshold of SMR ≥2 and at least five exposed cases, the signal evaluation phase was conducted using AESI-appropriate study designs, selecting either self-controlled designs or cohort designs with historical comparators or contemporaneous comparators who

had not received any COVID-19 vaccine. Self-controlled designs were prioritised for AESIs with rapid onset and short, well-defined risk windows (≤42 days), while parallel cohort designs were used when self-controlled approaches were not suitable (e.g. anosmia/ageusia)

Self-controlled designs estimated incidence rate ratios (IRRs), adjusting for time-varying confounders and defining specific risk and control periods. In the matched historical cohort study, Cox regression was used to estimate hazard ratios (HRs), adjusting for age, sex, and comorbidity index (CCI), with more covariates added if event numbers allowed. In the contemporaneous cohort study, Cox regression estimated HRs using time since Spikevax as the time scale, adjusting for age, sex, CCI, and other covariates when possible. The VAED cohort study used logistic regression to estimate odds ratios, adjusting for age, sex, comorbidity, calendar time, and, when possible, smoking, obesity, prior vaccines, and healthcare use. In the myocarditis/pericarditis follow-up study, logistic regression estimated 30-day odds ratios, adjusted for covariates when feasible.

Country-specific estimates were pooled using random-effects meta-analysis.

In addition to stratifications on age and sex, subpopulations examined included women of childbearing age, patients with chronic, autoimmune, or inflammatory conditions, immunocompromised individuals, and those with prior COVID-19 infection. Covariates included age, sex, Charlson Comorbidity Index (CCI), healthcare utilization markers, prior non-COVID-19 vaccinations, smoking, and obesity.

SMRs were estimated for 940 strata per AESI and country. This included 840 strata for the overall population, covering three doses (and any dose), five post-vaccination time windows, three sex categories, and 14 age groups. Additionally, 20 strata were estimated for each of five subpopulations (women of childbearing age, patients with chronic health conditions, patients with autoimmune or inflammatory disorders, patients with indicators of immunocompromised status and patients previously diagnosed with COVID-19 infection), based on dose and time interval.

For analyses of original Spikevax recipients, inclusion began on 11 Jan 2021 (Denmark, Norway, Spain) and 01 Apr 2021 (UK), with follow-up ending on database-specific dates: 31 Dec 2022 (Denmark, Spain), 14 Jan 2023 (Norway), and 07 Jun 2023 (UK). For the signal detection phase for original Spikevax, the number of eligible Spikevax recipients was 564,080 in Denmark, 531,172 in Norway, 621,871 in Spain, and 273,254 in the United Kingdom. For bivalent Spikevax, the eligible number of recipients was 62,958 in Denmark, 30,854 in Norway, and 1,547,772 in the UK, with a median age of 65-71 years.

Overall, while signals were confirmed for anaphylaxis, myocarditis, and pericarditis following original Spikevax, no association was found with the 36 other examined AESIs.

Consistent with previous findings, the study confirmed an increased risk of myocarditis and pericarditis in males aged 12–39 years following the second dose of Spikevax, with combined IRRs of 16.8 and 8.56, respectively, within 0–7 days post-vaccination. The highest risk was observed in males aged 18–24 years. Despite elevated relative risks, the absolute rates were low, and case numbers were limited, particularly for pericarditis and for myocarditis in certain countries, limiting the precision of subgroup analyses.

Of note, observational studies suggest that COVID-19 infection is associated with a 15-fold increased risk of myocarditis, while Spikevax was associated with less than 4-fold increase in risk. In addition, the data do not indicate worse outcomes after myocarditis or pericarditis in Spikevax-vaccinated individuals compared to unvaccinated cases. This and other risk characterisation aspects are further investigated in the category 3 PASS mRNA-1273-P910 and mRNA-1273-P911.

For anaphylaxis 0-2 days post Spikevax vaccination, the combined IRRs were 4.74 (95% CI: 2.06-10.9) after the first dose and 2.66 (95% CI: 1.09-6.49) after the second dose in females and males

aged 12 years or older. However, it is important to note that the incidence of anaphylaxis remains low in both the present study and previous research. A U.S. study among individuals aged 12 and older reported 5.1 (95% CI: 3.3–7.6) confirmed cases per million Spikevax doses administered.

No association was found between original Spikevax and the 36 other examined AESIs, which included conditions related to autoimmunity, the cardiovascular and circulatory systems, hepato-gastrointestinal and renal systems, the nervous and respiratory systems, skin and mucous membranes, musculoskeletal system, as well as all-cause mortality. Although some country-specific associations were observed for certain AESIs (e.g. narcolepsy, Chilblain-like lesions, pulmonary embolism), these were not consistent across settings. In the context of multiple comparisons and other available evidence, the study does not support a causal association between Spikevax and these AESIs.

Analysis of VAED showed no evidence of disease enhancement by Spikevax; vaccination was linked to lower risks of hospitalisation, ICU admission, and death compared to unvaccinated individuals.

For bivalent Spikevax, at least one statistically significant association was detected for 31 AESIs in at least one of the 210 strata per country and AESI. However, these findings are preliminary, as limited vaccine uptake and follow-up time—except in the UK—prevented formal signal evaluation. It is agreed that they should not be interpreted as evidence of a safety concern.

The MAH provided a thorough discussion of study limitations which is acknowledged. Most limitations are inherent limitations related to the use of routinely collected observational data. AESI definitions are subject to misclassification and information bias, especially in the context of variable diagnostic intensity during the pandemic. Confounding by indication, healthy vaccinee bias, and time-varying confounders may have affected results across designs, and some estimates lacked precision.

Given the large study size and the appropriate application of bias-reducing methods, including self-controlled designs and covariate adjustments, the PRAC Rapporteur considers the study to be of high quality, with results that are valid and consistent with the extensive body of research on COVID-19 vaccines. In conclusion, the findings confirm that the safety profile of original Spikevax remains consistent with known risks of anaphylaxis, myocarditis, and pericarditis.

6.1.6 Regulatory implications - changes to the SmPC

MAH's review of data supporting the update of the SmPC

To update the SmPC for anaphylaxis and erythema multiforme, incidence proportions were calculated using cases identified during the full follow-up window after any dose of Spikevax, divided by the number of individuals with at least one Spikevax dose, by country. Frequency categories were assigned according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). Based on this convention, incidence proportions for anaphylaxis for all countries were classified as rare (ranging from 1.5 to 2.5 per 10,000), and incidence proportions for erythema multiforme for all countries were classified as very rare, ranging from 0.28 to 0.96 per 10,000. The MAH was requested to propose frequencies for "anaphylaxis" and "erythema multiforme" based upon the data accumulated in P904. The frequency has been assessed as "Rare" for both terms and revised labelling has been submitted accordingly.

Anaphylaxis is a well-established but rare AESI after vaccines in general. In mRNA-1273-P904, results from various databases and study designs (SCCS and SCRI) suggest a potential association between Spikevax vaccination and anaphylaxis within the 0–2 day risk window following the second dose in individuals aged 12 years or older, regardless of sex. For the first dose, the incidence rate of anaphylaxis within the 0–2 day risk window following vaccination was more than four times higher

than during the control period in the pooled analysis across all countries. A similar pattern for first and second dose of Spikevax was observed in a US claims-based study. These findings suggest a higher likelihood of anaphylaxis following the first dose compared to the second dose of Spikevax, while also indicating an elevated incidence rate for both doses. However, it is important to note that the overall incidence of anaphylaxis remains low, both in the present study and in prior research. A separate study conducted among individuals aged 12 years and older from multiple U.S. health maintenance organizations reported an incidence rate of 5.1 (95% CI: 3.3–7.6) confirmed cases of anaphylaxis per million doses of Spikevax administered.

Assessor's comments

Reference is made to the assessment of the MAH's responses.

6.2. Pregnancy Study (P905)

6.2.1 Methods – analysis of data submitted

Research question and objectives

The overarching research question is: Is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes in pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?

Primary objective

To determine whether exposure to Spikevax during pregnancy was associated with an increased risk of: pregnancy complications and adverse pregnancy outcomes (hereafter pregnancy outcomes); major congenital malformations (MCMs); and adverse birth and neonatal outcomes.

Secondary objectives

To describe utilisation of Spikevax in pregnancy.

To describe utilisation of Moderna vaccines targeting SARS-CoV-2 in pregnancy (should vaccines other than Spikevax become available).

Study design

In this multi-database study, cohort, prevalence, and cross-sectional designs were implemented depending on the nature of each outcome considered. The measure of occurrence was incidence rate for the pregnancy outcomes, birth prevalence for MCMs and birth outcomes, and risk for neonatal death. The respective measures of association were hazard ratios (HRs), prevalence ratios (PRs), and risk ratios, with associated 95% confidence intervals (CIs). Country-specific estimates of association, crude and adjusted for measured confounding, were combined using random-effects meta-analysis.

Setting

This study was conducted using routinely collected secondary data from population registries of Denmark and Norway, and data from primary care-based databases in Spain and the UK. All countries have universal tax-funded health care access for its inhabitants.

Subjects and study size, including dropouts

The study population included eligible pregnancies (and their linkable offspring) ending between the country-specific start date of Spikevax availability (11 January 2021 in Denmark, Norway and Spain, 01 April 2021 in the UK) and the data source-specific recommended end date (31 December 2022 in Denmark, 14 January 2023 in Norway, 30 June 2023 in Spain, and 07 June 2023 in the UK). Subsets of these pregnancies contributed to different analyses depending on meeting outcome-specific eligibility criteria, availability of the data, and mother-offspring linkage.

Pregnancies were identified using a pregnancy algorithm in Denmark, Norway and Spain, and the CPRD Aurum Pregnancy Register in the UK.

Variables and data sources

In Denmark and Norway, data were linked from population-based health and administrative registries. In Spain and the UK, data originated from databases with regional (SIDIAP, Catalonia) or practice-membership (CPRD Aurum) coverage based on records generated in primary care by primary care health professionals. Exposure was defined as a record of at least one dose of Spikevax between 30 days before the first date of the last menstrual period (LMP) and pregnancy end. The comparator/contrast was no exposure to any COVID-19 vaccines. For the outcome MCM, first-trimester exposure (including 30 days pre-LMP) was used. For the birth and neonatal outcomes, in addition to exposure any time in pregnancy, trimester-specific exposure was examined. Study variables were defined based on the source data either as recorded in the underlying data sources or using diagnosis codes. Data from the four databases were harmonised using the ConcePTION common data model and analysed using a federated approach.

6.2.2 Results

There were 142,192 pregnancies in Denmark, 141,869 pregnancies in Norway, 84,778 pregnancies in SIDIAP, and 79,226 pregnancies in CPRD Aurum eligible for comparative analysis based on availability of the required lookback period. Between 17% and 32% received a COVID-19 vaccine other than Spikevax. The numbers of Spikevax-exposed pregnancies were 16,506 in Denmark, 15,330 in Norway, 7,657 in SIDIAP, and 3,175 in CPRD Aurum. Median age of pregnant persons varied between 30 and 33 years, and the proportion of pregnancies in persons younger than 18 years did not exceed 3% in any data source. The proportions of pregnancies linkable to a child were 100.0% in Denmark, 99.9% in Norway, 70.9% in SIDIAP, and 20.5% in CPRD Aurum.

For the pregnancy outcomes occurring during an pregnancy (hypertensive disorders, bleeding, gestational diabetes), the adjusted hazard ratios (HRs) (95% confidence interval (CI) were 0.54 (0.47-0.61), 0.90 (0.76-1.08) and 0.50 (0.46-0.54). For the outcomes that were also a type of pregnancy end (foetal death, elective termination), the adjusted HRs (95% CI) were 1.17 (0.91-1.49) and 1.18 (0.91-1.54). For the outcomes measured after pregnancy end (pregnancy-related death and postpartum haemorrhage), the adjusted HRs (95% CI) were 0.76 (0.23-2.59) and 1.14 (0.96-1.35). For the outcome any MCM, the adjusted PR (95% CI) was 1.00 (0.91-1.10).

Though the country-specific PRs fluctuated, for the specific MCMs, most adjusted PRs (95% CI) were consistent with a null association and ranged from 0.63 (0.12-3.31) for respiratory MCM and 1.41 (0.88-2.25) for other MCMs.

The adjusted PRs (95% CI) were 0.89 (0.84-0.94) for preterm birth, 0.81 (0.76-0.87) for low birth weight, 0.95 (0.80-1.13) for SGA defined by birth weight >2SD below sex- and gestational length mean, 0.92 (0.79-1.08) for SGA defined by birth weight below 10th percentile of sex- and gestational-

length distribution, and 0.88 (0.72-1.09) for low 5-minute Apgar score. For neonatal death, the adjusted risk ratio (95% CI) was 0.70 (0.41-1.20).

There were 144,670 pregnancies in Denmark, 144,721 in Norway, 89,411 in SIDIAP, and 92,135 in CPRD Aurum eligible for the Spikevax utilisation analysis. Among these, at least one dose of Spikevax was recorded for 16,744 (11.6%) pregnancies in Denmark, 15,556 (10.8%) in Norway, 8,030 (9.0%) in SIDIAP, and 3,814 (4.1%) in the CPRD Aurum. Nearly all pregnancies were exposed to the original Spikevax only. Proportions of pregnancies with heterologous vaccine schedule varied by database.

6.2.3 MAH's discussion

This study is a regulator-mandated PASS that examined the safety and utilisation of the Spikevax vaccine during pregnancy, regardless of exposure to other COVID-19 vaccines before or during pregnancy. The study is based on data from four countries and their sources of routinely collected data that differ in coverage, completeness, and data flow. In Denmark and Norway, data with nationwide coverage were linked from the relevant population-based medical and administrative registries. In Spain and the UK, data originated from databases with regional (SIDIAP) or practice-based (CPRD Aurum) coverage, based on records generated in primary care.

Key results on characteristics of the populations

After applying the eligibility criteria for examining utilisation of Spikevax in pregnancy, there were 144,670 pregnancies in Denmark, 144,721 in Norway, 89,411 in SIDIAP, and 92,135 in CPRD Aurum. Among these, there were 142,192 pregnancies in Denmark, 141,869 pregnancies in Norway, 84,778 pregnancies in SIDIAP, and 79,226 pregnancies in CPRD Aurum eligible for comparative analysis based on availability of the lookback period. Among the eligible pregnancies, between 17% and 32% received a COVID-19 vaccine other than Spikevax and were excluded from the analyses that did not involve time-varying exposure. The number of pregnancies with at least one record of Spikevax exposure between the start of the first trimester and the pregnancy end date was 16,506 in Denmark, 15,330 in Norway, 7,657 in SIDIAP, and 3,175 in CPRD Aurum. Median age of pregnant persons varied between 30 and 33 years.

Subpopulations with autoimmune or inflammatory disorders comprised between 1.0% and 2.2% of the analysis set, and subpopulations with indicators of immunocompromised status, between 3.4% and 5.0% of the analysis set. Prevalence of heterologous vaccine schedule during pregnancy varied by country and was the highest in Norway (36.4%) and the lowest in Denmark (2.9%). The proportions of pregnancies among women younger than 18 years ranged among those with a record of at least one Spikevax dose ranged between 0.0% in Denmark and 0.8% in both SIDIAP and CPRD Aurum. The absolute number of such pregnancies in any data source did not exceed 61. Because of the small group size, this subpopulation is reported descriptively only. The proportions of pregnancies linkable to a child or a foetus were 100.0% in Denmark, 99.9% in Norway, 70.9% in SIDIAP, and 20.5% in CPRD Aurum. For the first-trimester exposure analysis of the MCMs, the population included 103,704 foetuses or newborns in Denmark, 89,373 in Norway, 45,803 in SIDIAP, and 12,040 in CPRD Aurum. The number of foetuses or newborns with a first-trimester exposure to Spikevax was 7,091 in Denmark, 5,231 in Norway, 2,426 in SIDIAP, and <5 in CPRD Aurum. In the analysis of the birth outcome there were 86,396 live births in Denmark, 77,341 live births in Norway, 39,729 live births in SIDIAP, and 10,429 in CPRD Aurum.

In Denmark, the characteristics of the pregnancy population (103) were aligned with published evidence for caesarean delivery (104), pregnancy-associated hypertensive disorders (105), bleeding in pregnancy (106), gestational diabetes (107), postpartum haemorrhage (83), spontaneous abortions

(76, 77, 103), elective terminations (76, 77, 103), and stillbirth (76, 77, 103), preterm birth (108, 109), low birth weight (76), and low 5-minute Apgar score (76).

In Norway, the characteristics of pregnant population were aligned with published evidence, including comorbidities, caesarean delivery (110), pregnancy-associated hypertensive disorders (111), gestational diabetes (110, 111), miscarriage (112) terminations (113) stillbirth (110), MCM (110), preterm birth (110), low 5-miute Apgar score (110), and low birth weight (110). There were higher counts of neonatal death than reported in the Medical Birth Registry of Norway (111).

In SIDIAP, characteristics of the pregnancy population were largely consistent with published statistics (61). The prevalences of caesarean delivery, mental health conditions, and cancer were slightly lower in this study compared with those previously reported, however, this is attributable to broader definitions used (61). The results were aligned with previous evidence for pregnancy hypertensive disorders (78), gestational diabetes (114), stillbirth (61), postpartum haemorrhage (115), pregnancy-related death (116), and any MCM (117-119).

In the UK, prevalence of pregnancy-associated hypertensive disorders (120), gestational diabetes (121) and postpartum haemorrhage (122) were slightly lower than reported from other sources, potentially attributable to diagnoses being made by midwives/in secondary care and therefore not necessarily reaching the GP record. Occurrence of spontaneous abortions (123), terminations of pregnancy (67, 73), and stillbirths (124) were consistent with previously published data. Despite a similar prevalence, there was a higher rate of elective pregnancy terminations in CPRD Aurum than in the other data sources, presumably due to shorter follow-up available. The type of pregnancy end in CPRD Aurum was determined using the database's own algorithm, rather than the pregnancy algorithm used by the other participating databases. The rate of pregnancy-related death was consistent with the published statistics (125). The prevalences of MCM (126), low 5-minute Apgar score, (127), preterm birth (128), and low birth weight (129) were broadly aligned or slightly lower than the published national statistics, with lower rates possibly attributable to incomplete GP records compared with the national statistics, due to lack of transfer of information from midwife notes. There were no events of neonatal death identified from CPRD Aurum, which is not consistent with the reported overall neonatal mortality of 2.7-2.9 per 1000 live births in England and Wales (130, 131). In accordance with the database flow, infants who die before registering with a GP practice will not have records in CPRD. Therefore, early life care events are recorded retrospectively by the GP once an infant is registered at a practice, and often only if this is relevant to ongoing clinical care. CPRD has advised that the database is not a good source of data for early neonatal events (correspondence on file at the DSRU). Thus, the observed differences between the study results and published statistics on early neonatal events such as low birth weight, preterm birth, or Apgar score are consistent with the expected incomplete ascertainment within CPRD Aurum.

Key results on the primary objectives

Spikevax exposure and pregnancy outcomes

For the pregnancy outcomes occurring during an ongoing pregnancy (hypertensive disorders, bleeding, gestational diabetes), the adjusted HR (95% CI) from random-effects meta-analysis were, respectively 0.54 (0.47-0.61), 0.90 (0.76-1.08) and 0.50 (0.46-0.54). The estimates were slightly higher for hypertensive disorders of pregnancy in the posthoc sensitivity analysis, whereby pregnancies and person-time exposed to COVID-19 vaccines other than Spikevax were excluded or censored. For these outcomes results of the random-effects meta-analyses or crude HRs were generally in agreement with those of Mantel-Haenszel pooling.

For the outcomes that were also a type of pregnancy end (foetal death and elective termination), the adjusted HR (95% CI) from random-effects meta-analyses were, respectively 1.17 (0.91- 1.49) and

1.18 (0.91-1.54). For these outcomes, estimates from Mantel-Haenszel pooling were generally lower than those from the random-effects meta-analyses. This poorer alignment between meta-analysis results and Mantel-Haenszel pooling may reflect violation of the proportional-hazard assumption for these outcomes than for outcomes that may occur while a pregnancy is ongoing, as they are concentrated at the pregnancy end. This may indicate that HRs are not optimal estimates of the underlying IRRs.

For the outcomes measured after pregnancy end (pregnancy-related death and postpartum haemorrhage), the adjusted HRs (95% CI) from the random-effects meta-analyses were, respectively, 0.76 (0.23-2.59) and 1.14 (0.96-1.35). The results of meta-analysis of the crude HRs generally aligned well with the results from Mantel-Haenszel pooling.

There was little variation in HRs across the subpopulations of interest.

Spikevax exposure and MCMs

For the MCM outcomes, all pooled estimates in the main analysis were based on data from a maximum of three out of four databases, as in CPRD Aurum, there were no observations in the first-trimester exposed population with available mother-child link. For the outcome any MCM, the adjusted PR (95% CI) from the random-effects meta-analysis in the main analysis was 1.00 (0.91-1.10). Though country-specific PRs fluctuated, for the specific MCMs, most adjusted PRs (95% CI) from the random-effects meta-analyses were consistent with a null association and ranged from 0.63 (0.12-3.31) for respiratory MCM and 1.41 (0.88-2.25) for other MCMs. Pooled estimates from meta-analysis of the crude estimates generally aligned well with those from Mantel-Haenszel pooling for the MCM outcomes.

Spikevax exposure and birth and neonatal outcomes

The adjusted PRs (95% CI) from the random-effects meta analyses were 0.89 (0.84-0.94) for preterm birth, 0.81 (0.76-0.87) for low birth weight, 0.95 (0.80-1.13) for SGA defined by birth weight >2SD below sex- and gestational-length mean, 0.92 (0.79-1.08) for SGA defined by birth weight below 10th percentile of sex- and gestational-length mean, and 0.88 (0.72-1.09) for low 5-minute Apgar score. For neonatal death, the adjusted risk ratio (95% CI) from random-effects meta-analysis was 0.70 (0.41-1.20). Pooled estimates from meta-analysis of the crude estimates generally aligned well with those from Mantel-Haenszel pooling for the birth and neonatal outcomes.

Key results on the secondary objectives

The utilisation of Spikevax during pregnancy was assessed in 144,670 pregnancies in Denmark, 144,721 pregnancies in Norway, 89,411 pregnancies in SIDIAP, and 92,135 pregnancies in CPRD Aurum. Among those, at least one dose of Spikevax was recorded for 16,744 (11.6%) pregnancies in Denmark, 15,556 (10.8%) in Norway, 8,030 (9.0%) in SIDIAP, and 3,814 (4.1%) in the CPRD Aurum. Nearly all pregnancies were exposed to the original Spikevax only. The proportion of pregnancies with a dose of Spikevax before the included pregnancy varied by database and was the lowest (0.5%) in CPRD Aurum and the highest (14.6%) in SIDIAP.

Limitations

Systematic error

This observational study is based on secondary routinely collected data, which were used to define study populations, exposures, outcomes, and covariates. Though hypothesis-free routine accumulation of such data is an important advantage (132), measurement errors and administrative, data flow-related errors are inevitable in such settings (133). Limitations related to the underlying data flow include only partial mother-offspring linkage in SIDIAP and CPRD Aurum, and, in the observations with linkage, a large proportion of missing data on birth weight and Apgar score, and a lack of data on

some outcomes (ectopic pregnancies, microcephaly). A selection bias cannot be ruled out if there are systematic vaccination- and outcome-related differences between pregnancies that are linkable to an offspring and those that are not.

Furthermore, regardless of the method of pregnancy identification, only pregnancies generating records in a given database are identifiable in principle, making this study subject to selection bias due to missing information on pregnancies that end early in abortive outcomes.

The ConcePTION Pregnancy Algorithm has several limitations. First, potential misclassification of live birth type of end can occur due to the preferential assignment of live birth when, for instance, there is a diagnosis code of caesarean delivery and no other codes or records of pregnancy end. This may be incorrect since this diagnosis code indicates the end of pregnancy rather than the outcome of the pregnancy. Also, misclassification of live birth/stillbirth status can occur in case of discordant records for a pregnancy, as the algorithm chooses "the best" outcome, which is live birth. Because stillbirths represent less than 0.5% of deliveries, the impact of this limitation is low. Additionally, despite the retrieval strategy being restricted to records that strictly imply pregnancy at the record date, with subsequent DEAPs' verification, no validation against an external reference standard was conducted, therefore some retrieved records might not be referring to a true pregnancy. Furthermore, a concern remains about the potential mismatch between the training dataset and the prediction set in the random forest model. Specifically, individuals with potentially unfavourable pregnancy outcomes may exhibit different behaviours, such as more frequent or earlier pregnancy monitoring, which could affect prediction accuracy of the start of pregnancy date. Finally, the algorithm may misclassify imputed pregnancy start dates, with pregnancies ending in abortive outcomes more susceptible to this error than pregnancies ending in a delivery, whereby gestational age is likely to be recorded based on ultrasound examinations. The prevalences of the types of pregnancy ends observed in the present study were plausible when compared with those previously published. This limitation is expected to affect primarily pregnancies ending in abortive outcomes delivery by causing underestimation of rates of the outcomes measured in the pregnancy analysis set in this study.

Limitations related to the initial rollout of vaccine include the initial shortages of COVID-19 vaccines, which resulted in authorities prioritising the most vulnerable population and/or health care personnel for the first vaccination waves. Furthermore, the decision not to get vaccinated might be related to other personal characteristics and values. For instance, in Norway, partner vaccine uptake, infection, and migrant status were strongly associated with COVID-19 vaccine uptake in pregnancy, while history of adverse pregnancy outcome or high-risk pregnancy were not (134). Taken together, these mechanisms may produce important systematic differences between vaccinated and unvaccinated pregnant populations. The authorities in the different countries covered by this study used different principles for rolling out the COVID-19 vaccines, resulting in the proportion of pregnancies with a heterologous vaccination schedule varying by data source. For example, Denmark followed (unless a vaccine was discontinued like AstraZeneca and Johnson and Johnson) the principle of homologous vaccination for original COVID-19 vaccines, meaning that the proportions of pregnancies with heterologous vaccination schedule varies by data source. In the UK, Pfizer and Moderna vaccines were the preferred vaccines for pregnant women of any age, and anyone who had already started vaccination was recommended to have a second dose with the same vaccine unless they had a serious side effect after the first dose. In Norway, on the other hand, the vaccination policy allowed for more prevalent heterologous vaccination.

Measurement error is inevitable in routinely collected data. Measurement error, potentially leading to information bias, affects different variables and databases to a different degree. The validity and completeness of COVID-19 vaccination status in the participating databases is generally high. In Denmark, though no validation study of the register of COVID-19 vaccines has been performed, and

underreporting of vaccinations may occur for non-COVID-19 childhood vaccines (135), given that the COVID-19 vaccination campaign was implemented mainly through dedicated vaccination centres, rather than at GP surgeries, we speculate that the quality of recording for COVID-19 vaccines is likely to be greater than that of the non-COVID-19 childhood vaccines. In Norway, the recording of COVID-19 vaccination was mandated by the national authorities and is therefore assumed highly valid. The Institute of Public Health in Norway has published educational materials to support correct registration of all COVID-19 vaccines (136).

The vaccination registry also contains information on vaccine doses received abroad when verified by a Norwegian medical doctor (e.g. after presentation of vaccination card). Some underreporting in adults was associated with being vaccinated abroad (137), which, in turn may be associated with migrant status. In Spain, COVID-19 vaccination was implemented via the primary care and preventive medicine services. All vaccine information was recorded in the primary care electronic health records, and is available in SIDIAP database. The COVID-19 vaccination coverage in SIDIAP data is comparable with that reported by the Catalan Institute of Health and the Generalitat de Catalunya (138). In CPRD Aurum in the United Kingdom, the recording of COVID-19 vaccinations is likely to be comprehensive as COVID-19 vaccinations administered at any location in the country at GP practices, community pharmacies, vaccination centres, and hospitals were reported to each patient's GP within 48 hours of entry into the point of care system (139). The utilisation of Spikevax during pregnancy was consistent with the expectation based on each country's official statistics (22, 78, 134, 140-144). Nevertheless, misclassification of COVID-19 vaccination status and timing cannot be completely ruled out. In the comparative analysis, misclassification of the exposure status may stem from pregnancies exposed to COVID-19 vaccines other than Spikevax, especially in the analysis of the pregnancy outcomes with time-varying exposure. This bias may be towards the null, as is suggested by the results of the sensitivity analysis for the outcome hypertensive disorders of pregnancy.

The measurement error associated with the operational definitions of the outcomes of interest is related to the completeness of the recording of specific outcomes in a given database. The high quality of obstetric data in Danish and Norwegian registries, including maternal-offspring linkage, has been previously documented (59), as has high quality of data on hospital diagnoses (58, 145-147) and outpatient dispensings (148), all of which were used in this study. In Denmark, most routinely recorded obstetric diagnoses have high validity, with validation studies available on postpartum haemorrhage (149), spontaneous abortion (150), pre-gravid BMI (79), all diabetes disorders (79), caesarean section (79), gestational diabetes (79), 5-minute Apgar score (79), birth weight (79), and MCM (77, 87, 151). A recent study reported that both sensitivity and the positive predictive value were low for diagnoses of hypertensive disorders of pregnancy (79). In the Medical Birth Registry of Norway positive predictive value of preeclampsia or hypertensive disorder of pregnancy record was between 64 and 88% (152, 153), while validity of birth weight and gestational age was high (153). The validity of any diabetes registration in the Medical Birth Registry of Norway has been assessed against filled prescription records for antidiabetic medications, yielding a sensitivity and specificity of 72% and 99% (154). External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text. Pregnancies and pregnancy outcomes have been identified in SIDIAP and used in several pregnancy studies (61, 78). The CPRD Aurum Pregnancy Register used for this study has been validated against the CPRD GOLD Pregnancy Register (155), linked Hospital Episode Statistics, and the Office of National Statistics live birth data. Across the whole CPRD Aurum Pregnancy Register, there is good concordance between pregnancy episodes found in CPRD Aurum and linked Hospital Episode Statistics.

However, both CPRD Aurum and CPRD GOLD Pregnancy Registers saw a decline in the number of documented pregnancy episodes from 2007 onwards, which was steeper than that observed in Hospital Episode Statistics or Office of National Statistics birth data. This may be due to changes in

antenatal care policies in the UK, which have led to declining numbers of pregnancies in electronic healthcare records of primary care data, whereby nearly half of pregnant women access prenatal services directly via a midwife, without first attending their GP practice (67).

The INTERGROWTH-21 growth curves (89), used to define the SGA outcomes, were constructed using data from global populations of newborns. The global population is likely to differ from the affluent European populations of the participating countries. Though use of these curves resulted in a lower proportion of the SGA outcomes than would be expected based on internal curves (156), this definition provides a uniform standard in a multinational setting and increases specificity of the outcome definition.

Selection bias in studies of safety of treatments in pregnancy stems inevitably from the reliance on clinically manifested and subsequently recorded pregnancies. As a result, very early pregnancy losses are rarely, if ever, available, making it impossible to ascertain the true denominator for the pregnancy outcomes (51). This selection bias may be especially pronounced for the outcome MCM, whereby most malformations have their onset in early pregnancy, but are recorded at birth. Chromosomal malformations that lead to early foetal death or severe malformations ending in a TOPFA are especially susceptible to such selection bias (157-159). In this study we ascertained, to the extent possible in the available data, malformations recorded in liveborn infants, stillbirths, and pregnancies recorded as TOPFA. Another potential source of selection bias stems from incomplete linkage of pregnancies ending in live or stillbirth to their offspring in CPRD Aurum and SIDIAP. It introduces potentially an unknown bias and may affect generalisability. Furthermore, in the UK women are able to self-refer to maternity services, bypassing their GP (160). The CPRD Aurum Pregnancy Register relies on primary care records to determine pregnancy episodes, based on records relating to antenatal care, pregnancy outcome (including delivery and pregnancy loss codes), and postnatal diagnoses. This may lead to a bias whereby women who are more likely to meet with their GP (e.g. those with comorbidities or who are more health conscious) are more likely to report their early pregnancy to the GP, and therefore their GP record may be more likely to capture e.g. abortive outcomes. It is possible that this could partly explain the higher IRs of e.g. abortive outcomes seen among the vaccines in the CPRD Aurum if the more health conscious were those likely to come forward for vaccination. However, the prevalence of comorbidities was similar between the exposed and unexposed groups. Therefore, differences in the IRs between groups are unlikely due to the effect of comorbidities on the frequency of GP visits and consequently reporting of, for example, abortive outcomes. Another potential reason for the higher incidence rates seen for the abortive outcomes in the time-varying exposure analysis could be related to the computation of person-time. The Spikevax-exposed person-time in CPRD Aurum was shorter than that in the other databases and shorter than would be expected based on the size of the exposed population. This could be due to a larger proportion of Spikevax vaccinations occurring later in pregnancy in the UK compared with the other DEAPs (Table 10 shows that 38.8% of first Spikevax vaccinations in pregnancy occurred in the third trimester in the UK, compared with 14.9-19.1% in other countries).

There may be unmeasured or unknown confounding stemming from unmeasured or undermeasured variables. For example, a large proportion of missing data on BMI and smoking may have impeded the confounding control by these variables. Confounding could also stem from procedures related to the vaccine rollout. In the beginning of the vaccine rollout, pregnant women were excluded from COVID-19 vaccination. However, it may have been possible to be vaccinated if the potential benefits of vaccination were judged to outweigh the potential harms. This introduced the possibility for upward confounding in the beginning of the period. After introduction of the general recommendation to vaccinate pregnant women, Denmark and Norway still reserved vaccinations in the first trimester to high-risk pregnant women (Table 1) which could prolong the potential for upward confounding by indication for first trimester exposure for a longer period of time. After the general recommendation

there might still be the possibility for confounding by indication if high-risk pregnant women were more obliged to receive COVID-19 vaccinations. A Norwegian study (134) reported no association between high-risk pregnancies and vaccination uptake. At the same time, healthy vaccinee bias could ensue if pregnant women with healthier lifestyles are more likely to take the COVID-19 vaccination.

Random error/precision

Due to a low uptake of Spikevax in pregnancy relative to other COVID-19 vaccines, the exposed group was small compared with groups receiving other COVID-19 vaccines, which were excluded from analysis (other than main analysis with time-varying exposure) to avoid confounding estimates with multiple COVID-19 vaccines. In CPRD Aurum, the number of first-trimester exposed pregnancies linkable to a child was not sufficient to examine the outcome MCM in this data source. Several specific MCMs had varying and imprecise prevalences in country-specific databases. Among pregnancies linkable to an offspring, there was a large proportion of missing data on birth weight and Apgar score in SIDIAP and CPRD Aurum, reducing the precision of the associated estimates.

Limitations of the statistical methods

In the analysis of pregnancy outcomes as with a time-varying Spikevax exposure, the proportional-hazards assumption was not tested and is assumed to be violated (94). Nonproportional hazard may produce biased HR estimates (161), and non-alignment between the crude incidence rates and unadjusted HR, which was the case in this study for several pregnancy outcomes, and was especially pronounced for the abortive outcomes, which, by definition, are concentrated at pregnancy and therefore do not satisfy the proportional-hazards assumption. The decision to use HR to examine the outcomes occurring during pregnancy was made to avoid immortal time bias by correctly allocating exposed and unexposed person time. Immortal time bias is likely to produce spurious protective associations (91), which would not be desirable in this setting of vaccine safety assessment (50). Therefore, in interpreting results from the time-varying exposure, we triangulated findings stemming from analyses with different sources of bias, including the Mantel-Haenszel nonparametric pooling, country-specific estimates of associations, and results of random-effects meta-analysis. For the cohort analyses of the outcomes pregnancy-related death and postpartum haemorrhage, dichotomising exposure may produce a downward bias in HRs if the vaccinated status is associated with both longer pregnancy duration and reduced outcome risk.

Interpretation

This study is based on secondary routinely collected data from four databases in Europe: two Scandinavian population-based registries with nationwide coverage, and two databases stemming from general practice with regional (SIDIAP) and/or practice-based (CPRD Aurum) coverage. The databases vary with respect to the underlying populations, data flow, data provenance, health sectors, and the degree of mother-child linkage. Spikevax vaccination during a relevant period of pregnancy, compared with receipt of no COVID-19 vaccines during the same pregnancy period, was not associated with an increased hazard of gestational diabetes, bleeding, or hypertensive disorders of pregnancy. The HRs for pregnancy termination and spontaneous foetal loss, though slightly elevated among the Spikevax-exposed compared with unexposed, were also consistent with no association. The strongest country-specific association was observed only in a single database (CPRD Aurum), where it is potentially attributable to the data flow and patient behaviour inducing a positive selection bias. Spikevax exposure during the first trimester was not associated with prevalence of MCMs. Similarity of the results for spontaneous and induced foetal loss suggests that MCM are likely not the underlying cause of the loss. Overall and trimester-specific exposure to Spikevax were not associated with the examined birth and neonatal outcomes. Healthy vaccine bias cannot be ruled out on the basis of this study as an explanation for some potentially exaggerated protective effects. Some estimates had low precision.

Results of this study, taken together with the existing evidence, do not suggest an association of Spikevax vaccination during pregnancy with increased risks of the adverse pregnancy, birth or neonatal outcomes examined in this study. The observed utilisation of Spikevax in pregnancy was consistent with the country-specific vaccination policies.

Generalisability

The country-specific results are generalisable to their source populations. To the extent the associations reported in this study reflect the underlying causality, the results are generalisable beyond the populations in which the results were obtained.

MAH's conclusion

The results of this study indicate that Spikevax vaccination during pregnancy, regardless of prior or concurrent receipt of other COVID-19 vaccines, is not associated with adverse pregnancy, birth, or neonatal outcomes when compared with not receiving any COVID-19 vaccines during pregnancy.

Utilisation of Spikevax was aligned with the reported country-specific vaccination policies.

6.2.4 PRAC Rapporteur's discussion

Study mRNA-1273-P905 was an observational, multi-database study investigating whether there is a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes in pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax.

Cohort, prevalence and cross-sectional designs were implemented depending on the nature of the outcome. Routinely collected secondary data from population registries of Denmark and Norway and data from primary care-based databases in Spain (SIDIAP) and the UK (CPRD Aurum) were utilized.

The study was a category 3 PASS required in the Spikevax RMP to address the missing information "Use during pregnancy and while breastfeeding". The study protocol was recommended for approval by the PRAC in July 2021. Since then an updated study protocol version 1.2 and three progress reports were assessed by the PRAC. Divergent from the latest study protocol, the Italian ARS data source is no longer included, as the procedure for data access could not be finalised prior to the final study analysis.

The following outcomes were assessed:

- Pregnancy complications
    - Hypertensive disorders of pregnancy (preeclampsia, eclampsia, gestational hypertension)
    - Gestational diabetes
    - Bleeding during pregnancy
    - Postpartum haemorrhage
    - Pregnancy-related death
- Adverse pregnancy outcomes
    - Foetal death (spontaneous abortion or stillbirth)
    - Termination of pregnancy for foetal anomaly (TOPFA)

    - Any elective pregnancy termination
    - Ectopic pregnancy
- Adverse neonatal outcome
    - Foetal growth restriction/small for gestational age (SGA), using sex- and gestational age-specific cutoffs
    - Preterm birth (<37 full gestational weeks)
    - Low birth weight (<2500 g)
    - Major congenital malformations (composite and organ-specific MCMs)
    - Microcephaly (based on head circumference)
    - Low 5-minute Apgar score
    - Neonatal death (death within 28 days of birth)

The study period was database specific and spanned from Q1 2021 to between December 2023 and June 2023. The numbers of Spikevax-exposed pregnancies were 16,506 in Denmark, 15,330 in Norway, 7,657 in SIDIAP, and 3,175 in CPRD Aurum. The comparison group of pregnancies with no exposure to COVID-19 vaccines was at least 5 times larger across the different countries.

Depending on the outcome, incidence rates (e.g. gestational diabetes), prevalence rates (e.g. MCM) or 27-day mortality risk (neonatal death) were computed as the measure of occurrence. Respectively, hazard ratios, prevalence ratios and risks ratios were computed as the measure of association with no exposure to COVID-19 vaccines as the contrast.

Analyses were adjusted for measured covariates, such as e.g. maternal age at LMP, smoking in pregnancy, parity, and previous COVID-19 infection. Analyses were additionally stratified by subpopulations of interest such as different age groups and different comorbidities. Country specific estimates were pooled via meta-analysis.

In the main meta-analysis of crude and adjusted ratios, there was no statistically significant association between Spikevax exposure and any of the study outcomes compared with no exposure to COVID-19 vaccines. Regardless of statistical significance, the point estimates were mostly below or around 1, and only slightly above 1 for a few outcomes. The results were overall consistent across the subpopulations.

Country-specific analyses revealed a few statistically significant elevations in adjusted ratios, corresponding to increases of 11% to 74% in the respective outcomes. Notably, each of these elevations occurred in only a single country.

The MAH provided a comprehensive discussion of study limitations which is acknowledged. These cover limitations common for retrospective pregnancy studies based on secondary routinely collected data. Notably, information bias from errors in measuring exposure, outcomes and covariates may have affected the results. While the validity and completeness of COVID-19 vaccination status in the participating databases is generally high, exposure misclassification may still have emerged in pregnant women exposed to COVID-19 vaccines other than Spikevax due to "contamination" of both Spikevax exposed and Spikevax unexposed conditions. For the time-varying analyses, the impact of such bias was assessed in a post-hoc sensitivity analysis in which pregnancies and person-time exposed to COVID-19 vaccines other than Spikevax were excluded or censored. This did not considerably change the estimates for most outcomes; however, the adjusted HR of hypertensive disorders increased from 0.55 (0.47-0.65) in the main analysis to 1.09 (1.02-1.17) suggesting

exposure misclassification bias towards the null at least for this outcome. Some form of outcome misclassification bias is also expected based on the nature of the study. However, the quality of obstetric data is generally high in the Danish and Norwegian registries, and studies have demonstrated a high validity for most of the outcomes in Denmark. Based on the discussion by the MAH, the magnitude of the impact of outcome misclassification in SIDIAP and CPRD Aurum is less clear.

The MAH also discussed the potential impact of selection bias on the study results. Very early pregnancy losses are almost never recorded, which can lead to selection bias particularly for the outcome MCM due to conditioning on pregnancies that survived long enough to be recognised. Given the secondary use of data context of the study, outcome definition measures to circumvent this bias were adequately implemented (malformations recorded in liveborn infants, stillbirths and pregnancies recorded as TOPFA). However, the negative control analysis based on Spikevax exposure during the 2nd and 3rd trimester does not address this bias (conditioning on surviving pregnancies as in the main analysis), and no other measures to assess the potential impact of selection bias such as e.g. quantitative bias analysis or gestational age restriction were performed.

In CPRD Aurum and SIDIAP, linkage of pregnancies to their offspring was incomplete (20.5% and 70.9%, respectively), which is another potential source of selection bias and may affect generalisability. Moreover, in the UK, women may choose to refer to maternity services and bypass their GP. While no estimates could be obtained from CPRD Aurum for MCM (due to very limited exposure during the first trimester), some pregnancy outcome estimates differed in CPRD compared to results from the other databases (e.g. spontaneous abortion with an adjusted HR of 1.74 [1.57-1.92]).

The MAH also discussed the potential impact of unmeasured confounding. In addition to the limitations with regards to missing data on BMI and smoking, confounding may also stem from procedures related to the vaccine rollout. Based on individual B/R evaluation, high-risk pregnancies may have been vaccinated at the start of the study despite the initial general recommendation not to vaccinate pregnant women. In addition, confounding by indication could have also been maintained in the period where COVID-19 vaccinations were recommended for all pregnant women if high-risk pregnancies were more obliged to receive vaccination. At the same time, healthy vaccinee bias could have acted in the other direction if pregnant women with healthier lifestyles are more likely to take the COVID-19 vaccination. This is indeed compatible with the exaggerated protective effects of Spikevax for some of the study outcomes. The impact such bias may have played is difficult to interpret and no sensitivity analyses were performed to further assess this. The study protocol specified that alternative comparators may be explored such as other vaccinations (e.g. influenza), but no such analyses were presented in this report.

Despite a number of generic limitations, the PRAC Rapporteur considers the study of high quality and it is unlikely that the above-discussed biases undermine the validity of the results. The large study size, resulting in estimates of high precision for most outcomes, and the multi-country design including databases with a large coverage are considered particular strengths of the study. Importantly, the results are in line with the extensive existing evidence on the use of COVID-19 vaccines during pregnancy. Therefore, the MAH's conclusion that the results of this study do not suggest an association of Spikevax vaccination during pregnancy with increased risks of the adverse pregnancy, birth or neonatal outcomes is endorsed.

6.2.5 Regulatory implications - removal of "Use in Pregnancy and While Breast-feeding" as missing information in the RMP and update of SmPC section 4.6

MAH's review of pregnancy data on Spikevax

Use in pregnancy and while breast-feeding was included as missing information in the Spikevax RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 Jan 2021). In addition, previous information included in the SmPC, Section 4.6, did not include safety information on pregnancy outcomes following vaccination with Spikevax during the first trimester of pregnancy.

Use of ModernaTx, Inc. Spikevax and its variant-containing vaccines during pregnancy and while breastfeeding is an area of missing information in the RMP given that no CTs were conducted among pregnant women or lactating women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or postnatal development, and developmental and reproductive toxicology showed maternal to rat pup transfer of antibodies; however, no data were available on vaccine excretion in human breast milk.

Since Spikevax became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications (WHO 2021; Berman 2022). However, there is recognition that in absence of clinical trials, vigilant post-authorisation passive report monitoring, and real-world evidence was needed to continue monitoring the safety of Spikevax vaccination in pregnant women and their offspring.

There have been no specific safety concerns identified for COVID-19 maternal immunisation, including vaccinated breast-feeding women and/or their breastfed children. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small for gestational age birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy (Fell et al 2022a; Magnus et al 2021; Kharbanda et al 2021; Lipkind et al 2022; Magnus et al 2022; Shimabukuro et al 2021; Ruderman et al 2022; Matsumoto et al 2022; Hall et al, 2025), or in the mother or the breastfed child, or decreased milk production (Kachikis et al 2022; Bertrand et al 2021; Golan et al 2021a; Golan et al 2021b; Golan et al 2021c).

Published data regarding use of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA, and SARS-CoV-2 KP.2 mRNA (Spikevax and its variant-containing vaccines) during pregnancy and while breastfeeding, shows no increased risk of adverse pregnancy outcomes or during breastfeeding among people vaccinated against SARS-CoV-2 during pregnancy or breastfeeding, supporting current recommendations for vaccination of pregnant and lactating women against SARS-CoV-2.

The possible removal of use in pregnancy and while breast-feeding as missing information from the Spikevax RMP was previously raised in the PRAC assessment of Study mRNA-1273-P301 (EMEA/H/C/005791/II/0120), in which in Part A and B, 135 pregnancies were reported, and in addition, there were 51 additional pregnancies reported in Part C. Available data from pregnancies reported do not suggest a safety concern. Most pregnancies were followed until a known outcome was determined (116 in Part A/B and 43 in Part C). Most pregnancies resulted in a full-term live birth (78 in Part A/B and 30 in Part C). Furthermore, as per the PRAC assessment report received for PBRER #4 (Reporting period 19 Jun 2022 to 17 Dec 2022) indicated "several studies addressed outcomes such as spontaneous abortion, stillbirth, preterm birth and small-for-gestational-age and no increased risk following vaccination with Spikevax was observed" (Magnus et al 2022; Kharbanda et al 2021; Lipkind et al 2022; Magnus et al 2021; Ruderman et al 2022), the PRAC Rapporteur considered there to be an acceptable level of evidence to conclude that Spikevax is not associated with any of the pregnancy outcomes presented above.

Major congenital malformations (MCMs) are considered an important pregnancy outcome, especially related to exposure during the first trimester in the pregnancy. Supporting real-world data collected by the MAH are now available from the completed PASS mRNA-1273-P905 and mRNA-1273-P919 that provide robust data for characterising the safety concern for Spikevax and its variant-containing

formulations. This is in addition to the MAH post-marketing safety information collected in the global safety database and relevant literature information.

A new retrospective cohort study by Hall et al, 2025, assessed the safety of COVID-19 vaccination during pregnancy within the unique population of active-duty U.S. military service members. This retrospective cohort study analysed data from the Department of Defense Birth and Infant Health Research (BIHR) program, including 7,184 singleton live births in 2021. Of these, 39.9% (2,867) of pregnancies were exposed to the first COVID-19 vaccine dose during pregnancy, while 60.1% (4,317) were unexposed. Researchers assessed the association between vaccine exposure and adverse neonatal outcomes, including preterm birth, small for gestational age, low birth weight, and neonatal intensive care unit (NICU) admission in the first 28 days of life. Using inverse probability of treatment weighting (IPTW) and statistical modelling, the study found no significant increase in the risk of these outcomes among vaccinated pregnancies. Specifically, adjusted hazard and risk ratios for preterm birth (HR: 1.02, 95% CI: 0.83–1.26), small for gestational age (HR: 1.01, 95% CI: 0.78–1.30), low birth weight (HR: 1.01, 95% CI: 0.80–1.28), and NICU admission (RR: 0.90, 95% CI: 0.75–1.07) indicated no association between vaccination and increased adverse outcomes. Sensitivity analyses further confirmed that different vaccine types (BNT162b2 and mRNA-1273) did not alter these findings. The study concludes that COVID-19 vaccination during pregnancy did not show any signal of adverse neonatal outcomes in this military cohort, reinforcing existing evidence supporting the safety of maternal vaccination.

MAH's conclusion

The removal of use in pregnancy and while breast-feeding as missing information in the RMP is supported by the following considerations:

- Extended use of the Spikevax vaccines during pregnancy and while breast-feeding has provided extensive safety information in this group to no longer be considered missing information.
- Data from Study mRNA-1273-P905, a large non-interventional PASS found that Spikevax vaccination during pregnancy, irrespective of prior receipt of other COVID-19 vaccines, is not associated with adverse pregnancy, birth, or neonatal outcomes when compared to no COVID-19 vaccination.
- This is supported by data from Study mRNA-1273-P919 that found no increased risk of MCMs and other perinatal outcomes following exposure to Spikevax and the risk for preterm delivery, stillbirth, spontaneous abortion, and respiratory distress in the newborn was lower among vaccinated pregnant women than all comparators. While there was a weakly elevated risk of preeclampsia, gestational hypertension, and gestational diabetes among women who were vaccinated when compared with women who were distantly exposed or unexposed to Spikevax, this may be partially explained by competing risks given observed longer duration of pregnancy in exposed women, and was not considered to be a significant risk in absence of corroboration from study mRNA-1273-P905.
- Use of Spikevax and its variant-containing vaccines in pregnancy and while breast-feeding is already included in the SmPC and embedded in clinical practice and included in relevant health guidelines and no longer constitutes missing information in the safety profile of Spikevax.

In conclusion, Moderna considers there is sufficient justification for removing use in pregnancy and while breast-feeding as missing information from the Spikevax RMP and proposes to continue monitoring use in pregnancy and while breast-feeding through routine surveillance.

In addition, the MAH is submitting an updated Summary of Product Characteristics (SmPC). This update incorporates real-world evidence from two large post-authorization safety studies (PASS) conducted in the United States and Europe, encompassing data from over 60,000 pregnancies.

The findings from both studies do not suggest any safety concerns associated with Spikevax administration during pregnancy. In the U.S.-based claims study (mRNA-1273-P919), no increased risk of adverse infant outcomes was observed when compared with three control groups: women distantly exposed to SPIKEVAX (≥60 days before the last menstrual period with no exposure during pregnancy), unvaccinated women, and women with COVID-19 who were unvaccinated. A small but statistically significant increase in gestational diabetes and hypertensive disorders was observed; however, the clinical significance of these findings remains uncertain.

In the European study (mRNA-1273-P905), the available data did not indicate increased risks of major congenital malformations, adverse pregnancy outcomes, or complications such as gestational diabetes or hypertensive disorders.

Assessor's comments

The justification provided by the MAH for the removal of "Use in pregnancy and while breast-feeding" as missing information from the RMP is considered acceptable. The conclusion is supported by robust data from two large non-interventional PASS (Studies mRNA-1273-P905 and mRNA-1273-P919), which show no increased risk of adverse pregnancy, birth, or neonatal outcomes associated with Spikevax exposure. These findings are consistent with a broad body of published epidemiological evidence. The established use of Spikevax in pregnancy and lactation, as reflected in clinical practice and national guidelines, further supports that this is no longer considered missing information. Continued monitoring through routine pharmacovigilance is considered appropriate.

Further, the MAH proposed an update of SmPC section 4.6 to incorporate real-world evidence from two post-authorization safety studies. The PRAC Rapporteur agrees that an update of SmPC section 4.6 is warranted based on the above-mentioned data and in line with the removal of this missing information from the RMP. However, the MAH's current proposal is too elaborate and not acceptable. The PRAC Rapporteur considers that the wording should be amended in line with the recommendations on the harmonisation of labelling with regards to section 4.6, as per EMEA/CHMP/203927/2005.[1]

The MAH proposed to reflect the small but statistically significant increase in gestational diabetes and hypertensive disorders seen in US study P919. However, as this finding is of uncertain clinical significance and was not confirmed by other studies, the PRAC Rapporteur does not consider inclusion in the SmPC warranted.

The following amendment is considered sufficient (deleted text ~~strike through~~). Refer to Attachment 1 for the wording proposed by the MAH and the PRAC Rapporteur's comments.

Pregnancy

A large amount of observational data from pregnant women vaccinated with Spikevax ~~during the second and third trimester~~ has not shown an increase in adverse pregnancy outcomes. ~~While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects~~

[1] Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling

~~*with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3).*~~ *Spikevax can be used during pregnancy.*

With regards to the adapted Spikevax vaccines (Spikevax bivalent Original/Omicron BA.1, Spikevax bivalent Original/Omicron BA.4-5, Spikevax XBB.1.5, Spikevax JN.1), data on pregnancy outcomes from the PASS remain limited. In the final study report of US PASS P919, women exposed to the bivalent vaccines were not included in the analysis due to limited exposure. In the EU study P905, exposure to bivalent Spikevax was below 1% and no analyses of pregnancy outcomes were presented. Moreover, based on the study periods of these PASS, no data on any of the other adapted Spikevax vaccines could be generated. However, despite a lack of data, use during pregnancy was already recommended for the adapted Spikevax products since differences between products are confined to the spike protein sequence, and there are no clinically meaningful differences in reactogenicity. In the current SmPC, a statement on the lack of data regarding the adapted Spikevax products is reflected. While data remains limited or absent, this is no longer considered appropriate, as no further data is expected from regulatory studies. Moreover, use is recommended regardless of the absence of data and therefore the statement has no clinical implications. The PRAC Rapporteur considers the following update with regard to the adapted Spikevax products sufficient:

~~*No data are available yet regarding the use of Spikevax <bivalent Original/Omicron BA.1> <bivalent Original/Omicron BA.4-5> <XBB.1.5> <JN.1> during pregnancy.*~~

~~*However, a*~~***A*** *large amount of observational data from pregnant women vaccinated with Spikevax (original)* ~~*during the second and third trimester*~~ *has not shown an increase in adverse pregnancy outcomes.* ~~*While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3).*~~ *Since differences between products are confined to the spike protein sequence, and there are no clinically meaningful differences in reactogenicity, Spikevax <bivalent Original/Omicron BA.1> <bivalent Original/Omicron BA.4-5> <XBB.1.5> <JN.1> can be used during pregnancy.*

Regarding the PIL, the PRAC Rapporteur considers the following amendment sufficient (refer to Attachment 1 for the wording proposed by the MAH and the PRAC Rapporteur's comments):

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine. Spikevax can be used during pregnancy. A large amount of information from pregnant women vaccinated with Spikevax ~~*during the second and third trimester*~~ *ha****s***~~*ve*~~ *not shown negative effects on the pregnancy or the newborn baby.* ~~*While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.*~~

The MAH is asked to implement the wording proposed by the PRAC Rapporteur regarding SmPC section 4.6 and PIL 2. (**OC**)

7. Risk management plan

The MAH submitted an updated RMP version 13.0 with this application.

Rationale for submitting an updated RMP:

Consolidation of 2 EU RMPs (EU RMP v11.0 and EU RMP v12.0), addition of Spikevax LP.8.1 paediatric PFS, removal of completed Studies mRNA-1273-P901 and mRNA-1273-P910, and updates related to completed Study mRNA-1273-P206.

The following updates were included in this consolidated RMP:

- EU RMP v11.0 (EMA/VR/0000264109): removed use in pregnancy and while breast-feeding as missing information. This version is the base RMP used for this consolidation.
- EU RMP v12.0 (EMA/VR/0000278795): added Spikevax LP.8.1 that contains SARS-CoV-2 LP.8.1 mRNA.
- Spikevax LP.8.1 paediatric PFS (EMA/VR/0000291533): added Spikevax LP.8.1 paediatric PFS.
- Study mRNA-1273-P901 (EMA/VR/0000266225): removed completed Study mRNA-1273-P901 as an additional pharmacovigilance activity.
- Study mRNA-1273-P910 (EMA/VR/0000282182): removed completed Study mRNA-1273-P910 as an additional pharmacovigilance activity.
- Study mRNA-1273-P206 (EMA/VR/0000272245): updated paediatric population information due to completion of Study mRNA-1273-P206.

Summary of significant changes in this RMP:

Compared to the previously approved Spikevax, Spikevax bivalent Original/Omicron BA.1, Spikevax bivalent Original/Omicron BA.4-5, Spikevax XBB.1.5, Spikevax JN.1, European Union (EU) RMP version 11.0, this RMP version 13.0 has been updated:

To update the Products Overview table in Part I to add Spikevax LP.8.1 in line with the current status of the vaccines.

To update the Products Overview table in Part I to add Spikevax LP.8.1 paediatric PFS in line with the SmPC.

To update the paediatric population information in the Products Overview table in Part I in line with the SmPC.

To update the epidemiology section to add the Spikevax LP.8.1 indication and with current data up to 07 Mar 2025 in Module SI.

To update the nonclinical section for vaccine associated disease enhancement in Module SII.

To update the clinical trial exposure in Module SIII to include data from completed Study mRNA-1273-P203 (Part 1A, Part 1B, Part IC-1, Part 1C-2, Part 2, and Part 3).

To update the clinical trial exposure in Module SIII to include data from completed Study mRNA-1273-P204 (Part 1, Part 2, and Part 3).

To update the clinical trial exposure in Module SIII to include data from completed Study mRNA-1273-P205 (Part A.1, Part A.2, Part B, Part C, Part D, Part E, Part F, Part G, Part H, and Part J).

To update the clinical trial exposure in Module SIII to include data from completed Study mRNA-1273-P304 (Part A and Part B).

To update the clinical trial exposure in Module SIII to include data from ongoing Study mRNA-1273-P306 (Part 1, Part 2, Part 4A, and Part 4B).

To update the paediatric population information in Module SIV.1 due to completion of study mRNA-1273-P206.

To update the paediatric exposure in Module SIV.3 to include data from completed studies mRNA-1273-P203 and mRNA-1273-P204, ongoing Study mRNA-1273-P306, and from the cumulative post-authorisation exposure as of 17 Dec 2024.

To update the pregnancy exposure in Module SIV.3 to include data from completed studies mRNA-1273-P203, mRNA-1273-P905, and Study mRNA-1273-P919, and with cumulative post-authorisation exposure data up to 17 Dec 2024.

To update cumulative post-authorisation breastfeeding exposure data in Module SIV.3 up to 17 Dec 2024.

To update participants with relevant comorbidities exposure in Module SIV.3 to include data from completed Study mRNA-1273-P304 and with cumulative post-authorisation exposure data up to 17 Dec 2024.

To update the cumulative post-authorisation exposure in Module SV.1.2 as of 17 Dec 2024.

To include information in Module SVII from studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P306, and mRNA-1273-P904 relating to myocarditis, pericarditis and long-term safety.

To provide justification for removing use in pregnancy and while breast-feeding as missing information in Module SVII.2 and to consequently update Modules SVII.3 and SVIII, Part V (Parts V.1 and V.3), Part VI (Parts II.A and II.B), and Annex 2.

To update the studies characterising long-term safety in Module SVII.3.

To update the routine pharmacovigilance practices in Part III.2 in line with current practices.

To remove completed studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P304, mRNA-1273-P920, mRNA-1273-P904, mRNA-1273-P905, mRNA-1273-P919, and

mRNA-1273-P910 in Parts III.2, III.3, and V.3, and in the Summary of the RMP (Parts II.B and II.C.2), and to move the studies from the table of planned and ongoing studies to the table of completed studies in Annex 2.

To remove completed study mRNA-1273-P901 in Parts III.2, III.3, and the Summary of the RMP (Part II.C.2), and to move the study from the table of planned and ongoing studies to the table of completed studies in Annex 2.

To update study title and objectives for Study mRNA-1273-P306 in Parts III.2 and III.3, in the Summary of the RMP (Part II.C.2), and Annex 2.

To update the Summary of the RMP in Part VI to add Spikevax LP.8.1.

To remove the completed studies in Annex 3.

To update the references in line with the updated sections of the RMP in Annex 7.

RMP Module:	**Significant Changes:**
Part I Products Overview	Added Spikevax LP.8.1 in line with the SmPC. Added Spikevax LP.8.1 paediatric PFS in line with the SmPC. Updated paediatric population information in line with the SmPC. Updated in line with the current SmPCs.
Part II Safety Specification	
Module SI Epidemiology of the indication(s) and target population(s)	Added the Spikevax LP.8.1 indication. Updated with current data up to 07 Mar 2025.
Module SII Non-clinical part of the safety specification	Updated vaccine associated disease enhancement.
Module SIII Clinical trial exposure	Updated clinical trial exposure for completed Study mRNA-1273-P203 (Part 1A, Part 1B, Part IC-1, Part 1C-2, Part 2, and Part 3). Updated clinical trial exposure for completed Study mRNA-1273-P204 (Part 1, Part 2, and Part 3). Updated clinical trial exposure for completed Study mRNA-1273-P205 (Part A.1, Part A.2, Part B, Part C, Part D, Part E, Part F, Part G, Part H, and Part J). Updated clinical trial exposure for completed Study mRNA-1273-P304 (Part A and Part B). Updated clinical trial exposure for ongoing Study mRNA-1273-P306 (Part 1, Part 2, Part 4A, and Part 4B).
Module SIV Populations not studied in clinical trials	Updated the status of study mRNA-1273-P206 from ongoing to completed in Module SIV.1. Updated the paediatric exposure to include data from completed studies mRNA-1273-P203 and mRNA-1273-P204, ongoing Study mRNA-1273-P306, and with cumulative post-authorisation exposure up to 17 Dec 2024. Updated pregnancy exposure to include data from completed studies mRNA-1273-P203, mRNA-1273-P905, and mRNA-1273-P919, and with cumulative data up to 17 Dec 2024.

RMP Module:	Significant Changes:
	Updated breastfeeding exposure to include cumulative data up to 17 Dec 2024. Updated participants with relevant comorbidities exposure to include data from completed Study mRNA-1273-P304 and with cumulative post-authorisation exposure data up to 17 Dec 2024.
Module SV Post-authorisation experience	Updated the post-authorisation exposure with cumulative data up to 17 Dec 2024.
Module SVI Additional EU requirements for the safety specification	No changes.
Module SVII Identified and potential risks	Provided justification for removing use in pregnancy and while breast-feeding as missing information. Included information from studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P306, and mRNA-1273-P904 relating to myocarditis, pericarditis and long-term safety. Updated the studies characterising long-term safety in Module SVII.3.
Module SVIII Summary of the safety concerns	Removed use in pregnancy and while breast-feeding as missing information.
Part III Pharmacovigilance plan	Updated the routine pharmacovigilance practices in Part III.2 in line with current practices. Removed completed studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P304, mRNA-1273-P920, mRNA-1273-P904, mRNA-1273-P905, mRNA-1273-P919, mRNA-1273-P901, and mRNA-1273-P910 from Parts III.2 and III.3. Updated study title and objectives for Study mRNA-1273-P306 in Parts III.2 and III.3.
Part IV Plans for post-authorisation efficacy studies	No changes.
Part V Risk minimisation measures	Removed use in pregnancy and while breast-feeding as missing information in Parts V.1 and V.3. Removed completed studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P304, mRNA-1273-P920, mRNA-1273-P904, mRNA-1273-P905, mRNA-1273-P919, and mRNA-1273-P910 from Part V.3.
Part VI Summary of the risk management plan	Added Spikevax LP.8.1. Removed use in pregnancy and while breast-feeding as missing information in Parts II.A and II.B. Removed completed studies mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P304, mRNA-1273-P920, mRNA-1273-P904, mRNA-1273-P905, mRNA-1273-P919, and mRNA-1273-P910 from Parts II.B and II.C.2. Removed completed study mRNA-1273-P901 from Part II.C.2. Updated study title and objectives for Study mRNA-1273-P306 in Part II.C.2.
Part VII Annexes	Annex 2 – Moved completed studies from the table of planned and ongoing studies to the table of completed studies. Updated study title and objectives for Study mRNA-1273-P306. Annex 3 – Updated to remove the completed studies. Annex 7 – Updated references.

RMP Module:	Significant Changes:
	Annex 8 – Updated to reflect the changes made to the RMP.

7.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

8. Changes to the Product Information

As a result of this variation, sections 4.6 and 4.8 of the SmPC are being amended to update the frequencies of the adverse reactions anaphylaxis and erythema multiforme from "not known" to rare, and to reflect updated data on pregnancy outcomes, respectively. The Package Leaflet (PL) is updated accordingly.

9. Request for supplementary information

9.1. Other concerns

Clinical aspects

1. The MAH is requested to clarify the rationale for proposing the frequency term 'rare' instead of 'very rare' for inclusion in the product information, given that the incidence proportions for erythema multiforme were classified as 'very rare' across all countries.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1
The MAH is requested to clarify the rationale for proposing the frequency term 'rare' instead of 'very rare' for inclusion in the product information, given that the incidence proportions for erythema multiforme were classified as 'very rare' across all countries.

Summary of the MAH's response
The MAH proposed the frequency term of "rare" for erythema multiforme based on the case counts at any time after vaccination (any dose) across the post-authorization safety studies (PASS) mRNA-1273-P903 and mRNA-1273-P904, used to assess the reporting incidence of erythema multiforme.

In the US PASS mRNA-1273-P903, we observed an overall population estimate of 1.02 cases per 10,000 vaccine recipients at any time after any dose of vaccine, which corresponded to a frequency of "rare" (≥1/10 000 to <1/1 000).

In Study mRNA-1273-P904, we observed overall population estimates between 0.28 and 0.96 cases per 10,000 vaccine recipients at any time after any dose of vaccine, which would correspond to a frequency of 'very rare' (<1/10 000) (unless rounding is applied to the highest estimate, which derived from Spain).

Given similarity of the US and Spanish estimates and the totality of data, the MAH proposed a more conservative frequency of 'rare.'

Assessment of the MAH's response

Although study mRNA-1273-P904, conducted in the EU (Norway, Denmark, UK, and Spain), indicated a frequency of erythema multiforme as "very rare" (0.28–0.96 cases per 10,000 vaccine recipients), the MAH proposes the term "rare" for inclusion in the product information. This proposal is based on the totality of evidence, including the US study mRNA-1273-P903, which estimated a frequency of 1.02 cases per 10,000 recipients, corresponding to "rare", and represents a more conservative approach.

One could argue that the frequency term in the EU product information should rely exclusively on EU data (mRNA-1273-P904). However, the PRAC Rapporteur considers that both studies (mRNA-1273-P904 and mRNA-1273-P903) are included in the RMP, are of high quality, and involve populations comparable with respect to risk factors for erythema multiforme. Therefore, it is considered appropriate that the frequency term is based on both studies, with the more conservative frequency term preferred.

In conclusion, the PRAC Rapporteur agrees with the MAH that the frequency term "rare" should be used for erythema multiforme in the EU product information.

Conclusion

☒ Overall conclusion has been updated accordingly.

☐ No need to update overall conclusion and impact on benefit-risk balance

11. 2nd Request for supplementary information

11.1. Other concerns

Clinical aspects

1. The PRAC agrees that an update of SmPC section 4.6 is warranted based on the data from pregnancy PAS studies and in line with the removal of this missing information from the RMP. However, the MAH's current proposal is too elaborate and not acceptable. The PRAC considers that the wording should be amended in line with the recommendations on the harmonisation of labelling with regards to section 4.6, as per EMEA/CHMP/203927/2005. The MAH is asked to implement the wording proposed in section 6.2. (Regulatory implications) in conjunction with the comments on the changes proposed by the MAH to the PI (Attachment 1).

12. Assessment of the responses to 2nd Request for supplementary information

Question 1

The PRAC agrees that an update of SmPC section 4.6 is warranted based on the data from pregnancy PAS studies and in line with the removal of this missing information from the RMP. However, the MAH's current proposal is too elaborate and not acceptable. The PRAC considers that the wording should be amended in line with the recommendations on the harmonisation of labelling with regards to section 4.6, as per EMEA/CHMP/203927/2005. The MAH is asked to implement the wording proposed in section 6.2. (Regulatory implications) in conjunction with the comments on the changes proposed by the MAH to the PI (Attachment 1).

Response

The MAH agrees with the PRAC recommendations to update the wording in line with the guideline on the harmonisation of labelling with regards to section 4.6, as per EMEA/CHMP/203927/2005. Accordingly, PIL section 2 has been updated in agreement with the PRAC proposal. The commented product information has been provided in the working documents folder, along with the response and agreement to each comment.

Assessor´s comment

The requested additional changes to SmPC section 4.6 and PIL 2 were fully implemented.

Issue resolved.