

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE BLA MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: Spikevax TX, Inc.

Product: Spikevax COVID-19 mRNA vaccine

Application Type/Number: STN 125752/0

Proposed Indication: Active immunization against coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in persons 18 years of age and older.

Submission Date: September 17, 2021

Action Due Date: January 31, 2022

1. OBJECTIVE

The purpose of this review is to assess the adequacy of the Sponsor's proposed pharmacovigilance plan (PVP) submitted under the original BLA 125752/0 for post marketing safety monitoring for Spikevax COVID-19 mRNA vaccine, and to identify potential safety issues associated with the use of Spikevax that may need to be addressed through additional pharmacovigilance activities, such as safety-related studies, Post-Marketing Requirements (PMRs), and/or Post-Marketing Commitments (PMCs) or Risk Evaluation and Mitigation Strategy (REMS).

2. PRODUCT INFORMATION

2.1 Product Description

The Spikevax COVID-19 mRNA vaccine (formerly Moderna Covid-19 Vaccine) is a novel lipid nanoparticle (LNP) encapsulated messenger ribonucleic acid (mRNA) vaccine against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The vaccine contains mRNA-1273, which encodes for a modified full-length spike glycoprotein (S) of SARS-CoV-2 modified to introduce 2 proline residues that stabilize the S protein into a prefusion conformation (1). The mRNA is combined in a mixture of 4 lipids, 3 of which are commercially available: cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol (PEG2000-DMG), and SM-102, Spikevax's custom ionizable lipid.

The mRNA-1273 for injection is an off-white sterile suspension of 0.20 mg/mL mRNA + LNP in 20 mM Tris-hydroxymethyl-aminomethane buffer (87 mg/mL sucrose + (b) (4) acetate) at pH 7.5. The sterile drug product is packaged in preservative-free, multidose vials and stored at -50°C to -15°C.

The Spikevax COVID-19 Vaccine is a suspension for intramuscular injection administered as a primary series of two doses (0.5 mL each) 1 month apart.

A third dose of the Spikevax COVID-19 Vaccine (0.5 mL) administered at least 28 days following the second dose is authorized for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

A booster dose of the Spikevax COVID-19 Vaccine is administered intramuscularly as a single dose (0.25 mL) at least 6 months after completing a primary series.

2.2 Proposed Indication

For active immunization against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in persons 18 years of age and older, when administered as two 0.5-mL doses by intramuscular injection 1 month apart.

3. PERTINENT REGULATORY HISTORY

The Moderna Covid-19 Vaccine received an Emergency Use Authorization (EUA) on December 18, 2020, for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older in the US. A 2-dose primary vaccination series of 100µg mRNA-1273 administered 1 month apart demonstrated vaccine efficacy of 94.1% against confirmed COVID-19 at least 14 days post dose 2, when compared to placebo. On August 12, 2021 an EUA amendment authorized a third dose of 100 µg mRNA-1273 in immunocompromised persons. On October 19, 2021, an EUA amendment to include a 50 µg booster dose at least 6 months after completion of a 2 dose primary series of 100 µg in individuals was authorized in individuals aged 65 years and older, individuals aged 18 through 64 years at high risk of severe COVID-19, or those whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19. On November 19, 2021 an EUA amendment to include a 50 µg booster dose at least 6 months after completion of a 2 dose primary series of 100 µg in individuals was authorized in individuals 18 years of age and older.

As of October 31, 2021, Spikevax Covid-19 Vaccine (mRNA-1273) is authorized or approved in over 40 countries.

4. DESCRIPTION OF SAFETY DATABASE

4.1 Clinical Studies

All three clinical studies supporting the safety and efficacy of mRNA-1273 are ongoing as of the data lock point (DLP) which includes data submitted in support of this BLA.

Table 1 – Summary of Clinical Studies Supporting Safety and Efficacy

Type of Study	Study Identifier (CT Identifier)/ Study Status ^a	Primary Objective(s) of Study	Study Design	Dose, Test Product(s) Regimen Route of Administration	Number of Participants Exposed	Study Population	Type of Report Location of Study Reports
Phase 1							
Safety Immunogenicity	20-0003 (NCT04283461)/ Ongoing	To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 5 dosages in healthy adults	Open-label, dose-ranging	10 ⁶ , 25, 50, 100, and 250 µg IM injection mRNA-1273 2 doses, 28 days apart	Total (n= 120) 25 µg (n=35) 50 µg (n=35) 100 µg (n=35) 250 µg (n=15)	Men and nonpregnant women at least 18 years of age, in good health	<ul style="list-style-type: none"> • P101 Day 119 CSR (full) • P101 CSR Addendum 1 (Day 209) (addendum) Module 5.3.5.2
Phase 2							
Safety Immunogenicity	mRNA-1273-P201 (NCT04405076)/ Ongoing	<u>Primary Safety</u> To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart <u>Primary Immunogenicity</u> To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific bAb.	Part A Randomized, observer-blind, placebo-controlled	50 or 100 µg IM injection mRNA-1273 or placebo 2 doses, 28 days apart	Total (n=600) 50 µg (n=200) 100 µg (n=200) placebo (n=200)	Men and nonpregnant women at least 18 years of age, in good health	<ul style="list-style-type: none"> • P201 Primary Analysis CSR (full) • P201 CSR Addendum 1 (End of Part A) (addendum) Module 5.3.5.1

Type of Study	Study Identifier (CT Identifier)/ Study Status ^a	Primary Objective(s) of Study	Study Design	Dose, Test Product(s) Regimen Route of Administration	Number of Participants Exposed	Study Population	Type of Report Location of Study Reports
Phase 3							
Efficacy Safety	mRNA-1273-P301 (NCT04470427)/ Ongoing	<u>Primary Efficacy</u> To demonstrate the efficacy of mRNA-1273 to prevent COVID-19. <u>Primary Safety</u> To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.	Part A				
			Case-driven, randomized, stratified, observer-blind, placebo-controlled	100 µg of mRNA-1273 or placebo 2 doses, 28 days apart	Total (n=30,346) 100 µg (n=15,184) placebo (n=15,162)	Men and nonpregnant women at least 18 years of age, at appreciable risk of SARS-CoV-2 infection, with a negative history for SARS-CoV-2 infection	<ul style="list-style-type: none"> • P301 Part A CSR (full) Module 5.3.5.1
			Part B				
			Open-label, observational	100 µg of mRNA-1273 2 doses, 28 days apart ^c	Total (n=12,648) 100 µg (n=12,648)	Men and nonpregnant women at least 18 years of age Must have previously enrolled in mRNA-1273-P301 (Part A participants who had received 1 dose of 100 µg mRNA-1273 or placebo)	<ul style="list-style-type: none"> • P301 CSR Addendum 1 (Part B) (addendum) Module 5.3.5.1

Abbreviations: bAb = binding antibody; COVID-19 = coronavirus disease 2019; CSR = clinical study report; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

^a Participants remain in all studies to all protocol-specified assessments of efficacy, immunogenicity, and safety through the scheduled end of study.

^b The 10 µg cohort was not enrolled.

^c 1 dose in some participants: participants who were unblinded at the participant decision visit and who received ONLY 1 dose of mRNA-1273 100 µg in Part A, were eligible to receive a second dose of mRNA-1273 in Part B if they met certain criteria.

**From Table 1: Clinical Overview Module 2.5*

Study P301 – Pivotal Trial

Study 301 is a pivotal, phase 3, randomized, double blind, placebo-controlled study of the efficacy, safety, and immunogenicity of two 100 µg doses of mRNA-1273 given 28 days apart, when compared to placebo. Part A was the blinded phase, part B was open label and was initiated after authorization in the US. More than 30,000 participants 18 years of age and older were randomized 1:1 to mRNA-1273 100 µg or placebo, stratified into 3 groups: ≥ 65 years, 18 to < 65 years and at increased risk for complications of COVID-19, and 18 to < 65 years and not at risk for complications of COVID-19. Participants continue to be followed for efficacy and safety through 24 months after the second dose. Vaccine efficacy was demonstrated based on the prespecified efficacy success criterion at the interim analysis (data lock point (DLP) November 11, 2020) based on a total of 95 adjudicated COVID-19 cases. The subsequent primary analysis of efficacy was performed using the November 25th DLP, with 196 adjudicated COVID-19 cases and was consistent with the interim analysis. The Moderna Covid-19 Vaccine was granted EUA in the US on December 18, 2020, based on these data and conditional approvals worldwide. After EUA in the US was granted, Part B, the open label observational phase of the study, was initiated. All participants in Part A were invited to proceed to Part B, and unblinded participants who had received placebo in Part A had the choice to be vaccinated in Part B.

Study P201

Study P201 is a blinded, randomized, placebo-controlled study designed to confirm the safety and immunogenicity of the 100 µg dose of mRNA 1273. This dose was then advanced into the pivotal Phase 3 study based on the safety and immunogenicity in healthy adults. The primary analysis of safety and immunogenicity through 28 days after the second injection for all participants was performed on November 6, 2020, and the study is ongoing for long-term safety follow-up and the evaluation of antibody persistence. After US authorization, an amendment to the study protocol adapted the study design to include open label interventional phases (Part B and Part C). Part B allowed unblinding of participants and offered 2 injections of mRNA-1273 in an open-label manner, 28 days apart, to all participants who received placebo in Part A. Part B also offered a single booster dose of mRNA-1273 (50 µg) to participants who received 1 or 2 doses of mRNA-1273 (50 µg or 100 µg) in Part A.

Study 20-0003 (P101)

This is a phase 1 open-label, dose-ranging study to identify candidate doses for later-phase clinical studies. Immune responses were measured through 3 months post second injection, in 120 participants aged 18 to 55 years, 56 to 70 years, and ≥ 71 years who received 25 µg, 100 µg (target dose), and 250 µg doses. Safety data with a DLP of October 7, 2020 were included in the safety database to support the initial EUA.

Table 2: Ongoing Clinical Studies

Study and Period	Clinical Study Reports and Summary of Clinical Safety		
	Data Included	Data Cutoff/Data Freeze	Database Lock
301 Part A	Safety data for participants across each age cohort through the PDV if completed, or through the data cutoff (blinded and placebo-controlled portion of the study)	26 Mar 2021 Note: Safety data presented in the EUA used a cutoff date of 25 Nov 2020, which corresponded to the analysis of efficacy performed based on 196 cases of COVID-19.	04 May 2021
301 Part B	Safety data for participants in the open-label observational phase from the PDV to the data cutoff	26 Mar 2021	04 May 2021
201 Day 57	Data collected through Day 57 (28 days after most recent injection)	05 Nov 2020	06 Nov 2020 (data extraction)
201 Part A	Data collected through Day 209 (180 days [6 months] after most recent injection)	Date of PDV for each participant	10 Jun 2021
101 Day 119	Data collected through Day 119 (3 months after second injection) for Cohorts 1-5, 7, and 8 and through Day 57 for Cohorts 10-12	07 Oct 2020	07 Oct 2020
101 Day 209	Data collected through Day 209 for Cohorts 1-5, 7, 8, and 10-12	17 Mar 2021	17 Mar 2021

From Module 2.7.4, Summary of Clinical Safety.

4.2 Adverse Events (AE) and Reactions (AR)

Safety Dataset

Data from the 3 ongoing clinical studies were not integrated by the Sponsor for this submission. The focus of safety data was the pivotal study data in P301 Part A, which provides safety data from the blinded portion of the study for 30,346 participants with data lock point (DLP) of May 4, 2021.

The Solicited Safety Set was defined as all randomized participants who received any study injection and contributed solicited adverse reactions (AR) data. The First Injection Solicited Safety Set and Second Injection Solicited Safety Set each included participants within the Solicited Safety Set who received a first or a second study injection and contributed any solicited AR data within 7 days. A Safety Set was defined for all other analyses of safety and included all participants who received any study injection. Participants were categorized for the analysis according to the treatment received (even if treatment was different from randomization). In Study 101, the Safety Analysis Population was used for analyses of solicited ARs and for all other analyses of safety and included all participants who received any study injection.

Table 3: Summary of Participants with Solicited Adverse Reactions Starting Within 7 Days After First Injection

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Solicited adverse reactions - N1	15151	15166	30317
Any solicited adverse reactions	7285 (48.1)	13317 (87.8)	20602 (68.0)
95% CI	47.3, 48.9	87.3, 88.3	67.4, 68.5
Grade 1	5134 (33.9)	9329 (61.5)	14463 (47.7)
Grade 2	1782 (11.8)	3134 (20.7)	4916 (16.2)
Grade 3	363 (2.4)	849 (5.6)	1212 (4.0)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	369 (2.4)	854 (5.6)	1223 (4.0)
Solicited local adverse reactions - N1	15147	15162	30309
Any solicited local adverse reactions	3009 (19.9)	12765 (84.2)	15774 (52.0)
95% CI	19.2, 20.5	83.6, 84.8	51.5, 52.6
Grade 1	2842 (18.8)	10725 (70.7)	13567 (44.8)
Grade 2	89 (0.6)	1511 (10.0)	1600 (5.3)
Grade 3	78 (0.5)	529 (3.5)	607 (2.0)
Grade 4	0	0	0
Grade 3 or above	78 (0.5)	529 (3.5)	607 (2.0)

Solicited systemic adverse reactions - N1	15151	15166	30317
Any solicited systemic adverse reactions	6397 (42.2)	8316 (54.8)	14713 (48.5)
95% CI	41.4, 43.0	54.0, 55.6	48.0, 49.1
Grade 1	4334 (28.6)	5358 (35.3)	9692 (32.0)
Grade 2	1746 (11.5)	2504 (16.5)	4250 (14.0)
Grade 3	311 (2.1)	449 (3.0)	760 (2.5)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	317 (2.1)	454 (3.0)	771 (2.5)

Table 4: Summary of Participants with Solicited Adverse Reactions Starting Within 7 Days After Second Injection

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Solicited adverse reactions - N1	14578	14691	29269
Any solicited adverse reactions	6255 (42.9)	13556 (92.3)	19811 (67.7)
95% CI	42.1, 43.7	91.8, 92.7	67.1, 68.2
Grade 1	4346 (29.8)	4847 (33.0)	9193 (31.4)
Grade 2	1558 (10.7)	5800 (39.5)	7358 (25.1)
Grade 3	348 (2.4)	2895 (19.7)	3243 (11.1)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	351 (2.4)	2909 (19.8)	3260 (11.1)
Solicited local adverse reactions - N1	14577	14688	29265
Any solicited local adverse reactions	2757 (18.9)	13029 (88.7)	15786 (53.9)
95% CI	18.3, 19.6	88.2, 89.2	53.4, 54.5
Grade 1	2594 (17.8)	8789 (59.8)	11383 (38.9)
Grade 2	88 (0.6)	3217 (21.9)	3305 (11.3)
Grade 3	75 (0.5)	1023 (7.0)	1098 (3.8)
Grade 4	0	0	0
Grade 3 or above	75 (0.5)	1023 (7.0)	1098 (3.8)
Solicited systemic adverse reactions - N1	14577	14690	29267
Any solicited systemic adverse reactions	5343 (36.7)	11678 (79.5)	17021 (58.2)
95% CI	35.9, 37.4	78.8, 80.1	57.6, 58.7
Grade 1	3519 (24.1)	3717 (25.3)	7236 (24.7)
Grade 2	1535 (10.5)	5611 (38.2)	7146 (24.4)
Grade 3	286 (2.0)	2336 (15.9)	2622 (9.0)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	289 (2.0)	2350 (16.0)	2639 (9.0)

Solicited Local AR

Solicited local AR (pain, erythema, swelling, axillary lymphadenopathy) were more common in participants who received vaccine (84.2% first dose, 88.7% second dose) compared with placebo (19.9% first dose, 18.9% second dose). The most common solicited local AR was pain (83.7% first dose, 88.3% second dose) with an overall slight increase in participants reporting pain between the first and second injections of vaccine. The second most commonly reported solicited AR was axillary lymphadenopathy; 10.2% vaccine vs 4.8% placebo after dose 1 and 14.2% vs 3.9% after dose 2 respectively. The majority of local AR were Grade 1 or 2, with no reported Grade 4 local AR. A minority of participants (3.5%) experienced a Grade 3 AR on the first dose, with the percentage of reported Grade 3 AR doubling (7.0%) after the second dose. Grade 3 pain was reported at a frequency > 2% after either injection (2.7% first dose vs 4.1% second dose).

The majority of ARs occurred within the first 1 to 2 days after administration of vaccine and generally persisted for a median of 1 to 3 days but solicited local AR that persisted beyond 7 days after any dose were reported by both vaccine (2.4%) and placebo (0.9%) recipients. Grade 3 persistent local ARs were reported by 22 participants (0.1%) in the mRNA-1273 group and 4 participants (<0.1%) in the placebo group after the first injection. The incidence of persistent local ARs was higher in the mRNA-1273 group (67 participants [0.5%]) after the second injection. Axillary swelling/tenderness and pain were the most commonly reported persistent local ARs; axillary swelling/tenderness was more common after the first injection and pain was more common after the second.

In the vaccine group, the incidence of local AR with delayed onset (starting on Day 8 or later) was higher after the first injection (80 participants [0.5%]) than after the second injection (10 participants [<0.1%]). The most common AR first reported on Day 8 or later was erythema (68 participants [0.4%]) in the vaccine group after the first injection and 6 participants (<0.1%) in the vaccine group after the second injection.

Solicited Systemic AR

Solicited systemic AR (fever, headache, fatigue, myalgia) were more common in participants who received vaccine compared with placebo, and the majority were Grade 1/2. The percentages of vaccine versus placebo recipients who reported systemic AR are described in Tables 3 and 4 above.

The median duration of solicited systemic ARs ranged from 1 to 2 days in both the vaccine and placebo groups after the first and the second injections. The median duration of grade 3 nausea/vomiting was 1 day after the first dose and 3 days after the second in the vaccine group. The duration of other solicited systemic ARs was similar after the first and second injections, and any Grade 4 solicited systemic ARs in both groups resolved within 7 days after injection. Persistent systemic ARs that were grade 3 or above were reported for 97 (0.6%) participants in the vaccine group and 91 (0.6%) in the placebo group, and the incidence was higher after the second dose in the vaccine group (231 participants [1.6%]). Fatigue and headache were the most commonly reported persistent systemic ARs after either injection in both groups. Persistent fever was reported in 4 participants in the vaccine group and 3 participants in the

placebo group after the first injection and for 2 and 1 participant(s), respectively, after the second injection.

Unsolicited AE

Unsolicited AEs were defined as any AE reported by the participant that was not specified as a solicited AR, or if specified, started beyond 7 days post vaccination. A treatment-emergent AE (TEAE) was defined as any event that was not present before receipt of vaccine, or any event already present that worsened in intensity or frequency after exposure. Otherwise, unsolicited AEs were those observed or reported with onset during the 28 days following each injection (i.e., the day of injection and 27 subsequent days). Deaths, serious adverse events (SAE), and medically attended adverse events (MAAE) were collected at least through one year after the second injection or participant withdrawal from the study.

At least one TEAE assessed by the investigator to be treatment related was reported in 13.6% and 8.2% of participants in the vaccine and placebo groups respectively. The percentages of participants who had severe TEAEs assessed as treatment related were 0.5% and 0.2%, respectively; and 20 (0.1%) and 14 (<0.1%) participants, respectively, discontinued treatment in response to an event.

Commonly reported unsolicited AEs were consistent with solicited ARs. Unsolicited TEAEs that were reported for $\geq 1\%$ of participants in the vaccine group and showed higher incidence compared with placebo were lymphadenopathy (1.7% vs. 0.8%), injection site pain (1.7% vs. 0.8%), and injection site erythema (1.0% vs. 0.3%). TEAEs reported for $\geq 1\%$ of participants in the vaccine group that were equal in incidence rate with the placebo group were arthralgia, myalgia, diarrhea, cough, nausea, oropharyngeal pain, nasal congestion, and hypertension.

Pericarditis and Myocarditis Review

In Part A of P301, there were 4 cases of pericarditis and 0 cases of myocarditis reported. For pericarditis, 2 of the cases were in the vaccine group and 2 in the placebo group. The cases of pericarditis in the vaccine group were as follows:

- (i) 59-year-old female had non-serious chest pain, dyspnea, and fatigue on Day 4 after the second dose that resolved within 2 days and subsequently presented with chest pain and syncope 68 days after the second dose leading to hospitalization and a diagnosis of pericarditis and pericardial effusion, both of which resolved. Of note, the participant had also received an influenza vaccination 1 month prior.
- (ii) 65-year-old male hospitalized with a diagnosis of pericarditis 73 days after the second dose and 19 days after an SAE of myocardial infarction which resolved the following day.

Non-fatal Serious Adverse Events (SAE)

There was no difference in the rates of SAEs within 28 days after vaccination between vaccine (401 events, 1.8%) and placebo (439 events, 1.9%) groups. COVID-19 was reported as a serious TEAE by 2 (< 0.1%) participants in the vaccine group and 40 (0.3%) participants in the

placebo group. A total of 16 participants reported at least 1 SAE assessed by the investigator as related. Of those, 12 (<0.1%) were in the vaccine arm, and 4 were in the placebo arm. Facial swelling was reported as a related SAE for 2 participants in the vaccine group, and 1 participant in the placebo group. Other related SAEs were B-cell small lymphocytic lymphoma, Basedow's (Grave's) disease, autonomic nervous system imbalance, cerebrovascular accident, multiple sclerosis, facial swelling, nausea, vomiting, alopecia areata, angioedema, rheumatoid arthritis, pericardial effusion, pericarditis and pleural effusion in the vaccine group, and polymyalgia rheumatica, acute myocardial infarction, hypomagnesemia, acute kidney injury, atrial fibrillation, organizing pneumonia, respiratory failure, facial swelling, immunization anxiety related reaction, feeling hot, paresthesia, and procedural hemorrhage in the placebo group. There were no reports of idiopathic thrombocytopenic purpura or thrombosis with thrombocytopenia, and there were no reports of cerebral venous sinus thrombosis or dural venous thrombosis.

Deaths

There were a total of 32 deaths, 16 deaths occurring in the vaccine group, and 16 in the placebo group. Baseline age of participants was ≥ 65 years for 9 of the participants in the vaccine group and 6 in the placebo group. In the vaccine group, SAEs leading to death included cardiac PTs (cardiac failure congestive, cardiac arrest, MI, cardiopulmonary arrest), Covid-19, and cancer (hepatocellular, pulmonary). In the placebo group, PTs included cardiac (MI, cardiopulmonary arrest, Covid-19, cancer (pancreatic). None of the unsolicited TEAEs leading to death were considered to be vaccine related. COVID-19 was reported as the event leading to death for 1 participant in the vaccine group and 3 in the placebo group.

Pregnancies

Pregnant participants were excluded from all three studies, however, pregnancies occurring in the study were followed for outcomes after discontinuation from study vaccination. There were 16 pregnancies reported in the mRNA-1273 group and 11 reported in the placebo group. Of the outcomes known as of 04 May 2021, 1 participant in the placebo group was induced at 37 weeks due to polyhydramnios and gestational diabetes and the child was noted as having congenital anomalies of bilateral talipes equinovarus and hydronephrosis. Five participants (2 vaccine group and 3 placebo) experienced spontaneous abortion/miscarriage. These events were reported as SAEs for 4 of the participants (2 participants in each group) and were considered not related. For 1 participant in the placebo group, the event was considered non-serious, and causality was not reported. Two participants (1 in each group) underwent elective termination of pregnancy without reported pregnancy complications for either participant. An observational pregnancy outcome study and an on-going clinical trial in pregnant women will evaluate the outcomes of these pregnancies in females exposed to the vaccine during pregnancy.

5. POST AUTHORIZATION SAFETY SURVEILLANCE

From December 18, 2020 (date of EUA) to November 30, 2021, a total of 348,505 Moderna COVID-19 Vaccine adverse event (AE) reports were received and processed (coded, redacted, and quality assurance performed) by the Vaccine Adverse Event Reporting System (VAERS). Of these, 18% (61,474) were SAEs, which include deaths, life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions (OMIC). The most common PTs among serious VAERS reports were pyrexia (n=10,606, 3.0%), headache (n=9,410, 2.7%), fatigue (n=8,387, 2.4%), dyspnea (n=6,612, 1.9%), nausea (n=6,387, 1.8%), chills (5,849, 1.7%), myalgia (n=4,993, 1.4%), dizziness (n=4,948, 1.4%), pain in extremity (n=4,487, 1.3%), and Covid-19 (n=4,461, 1.3%).

VAERS received 5,203 reports of death (1.5% of all AE reports for Moderna Covid-19 Vaccine), of which 4020 were US reports. Of note, FDA requires vaccination providers to report any deaths after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. Manual review of all US death reports, including review of available medical records and/or autopsy reports, has not identified any new safety concerns.

FDA review of VAERS reports, including non-fatal serious and death reports, identified anaphylaxis and myocarditis and pericarditis as safety concerns, to which the Sponsor revised their Pharmacovigilance Plan (PVP) and included anaphylaxis, myocarditis, and pericarditis as important identified risks. The Warnings section of the label also includes subsections on the Management of Acute Allergic Reactions and Myocarditis and Pericarditis.

5.2 Anaphylaxis

For the important identified risk of anaphylaxis, VAERS was queried from the date of authorization (December 18, 2020) to November 30, 2021 using the PTs "*anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, or anaphylactoid shock*". The search returned 1,718 reports (887 (52%) were US reports), and 1,262 (73%) serious reports, including 11 death reports. There were 173,215,703 doses of Moderna Covid-19 vaccine administered as of 11/28/2021 (*CDC Internal Communication*). This equates to an anaphylaxis crude reporting rate of approximately 5.1 cases per million doses. Among the 11 death reports, 4 were foreign, and 7 were US reports. There were 6 reports of anaphylaxis in males, 4 in females, and 1 in an individual of unknown sex. The median age was 71 years (range=33-85 years; 1 individual of unknown age), and the median onset as calculated by VAERS dates was 0 days post-vaccination (range = 0-61 days). Three of the 11 death reports state PT terms consistent with anaphylaxis without further descriptive information. Five reports described deaths in patients with chronic underlying conditions including hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, diabetes mellitus, brain aneurism, and sleep apnea. None of the death reports specified a history of hypersensitivity or food allergy, or a history of COVID-19 disease.

Limitations to interpreting VAERS data are based on the important limitations of passive surveillance data including missing/inaccurate data, unconfirmed diagnoses, potential under-reporting, lack of comparator group, and variable or incomplete reporting. The methodology for calculating crude reporting rates was based on reports retrieved from automated queries, which may include duplicate cases. Additionally, all cases were not manually reviewed nor adjudicated to apply the Brighton Collaboration case definition criteria for anaphylaxis. (Note that this is a key difference in the above methodology compared to previous publications²⁻⁴ which calculated reporting rates based only on adjudicated cases that were confirmed through medical record review or contact with the provider). The occurrence of anaphylaxis after receipt of the Moderna COVID-19 vaccine during the review period is comparable with those reported after the receipt of other vaccines.

5.3 Myocarditis/Pericarditis

On June 25, 2021, Moderna EUA Fact Sheets were revised to add Warnings for myocarditis and pericarditis. For this important identified risk, FDA performs ongoing safety reviews. A VAERS query on November 30, 2021 found there were 3,065 reports of myocarditis or pericarditis following vaccination with the Moderna COVID-19 Vaccine, of which 312 (10%) reports were in individuals under 30 years of age. Overall, there were 2,737 (89%) serious reports, including 44 (1.6%) deaths. Of these 44 deaths, 23 were foreign reports and 21 were US reports; the median age was 56 years (range 17-89 years) and the median days to onset as calculated by VAERS dates was 4.5 days post-vaccination (range = 0-187 days). The majority of these death reports were in individuals over 40 years of age who had comorbidities and alternate etiologies for myocarditis, or other possible causes of death listed, notably STEMI/NSTEMI, cardiovascular disease, atherosclerosis, substance abuse and respiratory failure. A minority of the death reports (12, 27%) were in individuals under 40 years of age; of those, 7 were US reports. All 7 US reports in individuals under age 40 were manually reviewed; there were no deaths without an alternate plausible etiology for myocarditis and these reports were assessed as unrelated to vaccination.

Observed to Expected Analysis (See Tables A2 and A3 in Appendix)

Prior to the first authorization of the Moderna booster dose on October 20, 2021, observed to expected (O/E) analyses were performed for a risk window of 7 days for reports indicating dose 1 or dose 2. Reports were retrieved from automated queries of the VAERS database with DLP 9/27/21, using the following PTs: *Autoimmune Myocarditis; Autoimmune Pericarditis; Eosinophilic Myocarditis; Hypersensitivity Myocarditis; Immune-Mediated Myocarditis; Myocarditis; Pericarditis; Pericarditis Adhesive; Pericarditis Constrictive; Pleuropericarditis.*

Of the 830 myocarditis reports with vaccine dose number reported, 562 (67.7%) describe AEs in males and 255 (30.7%) in females. The median age of individuals with events post dose 1 is 37 years (range 18-94 years), and 31 years (range 15-87 years) post dose 2. The median time from vaccination to symptom onset post dose 1 is 4 days (ranged from 0 to 210 days) and post dose 2 is 3 days (range 0 to 253 days).

The O/E analysis, stratified by age and dose number, indicated that the observed numbers of cases exceeded the expected number of cases for multiple age groups and genders (based on pre-COVID19 pandemic U.S. population-based background incidence rates)

with higher relative risk (RR) in younger age groups. The RR of myocarditis was higher in males than in females for almost all age groups. A recent analysis of VAERS data from passive surveillance found that the rates of myocarditis were highest after the second vaccination dose, and in adolescent males aged 18 to 24 years of age, with a reporting rate of ranging from 40-56 per million doses (6,7).

5.4 Herpes Zoster (HZ)

In Study mRNA-1273 P301, Herpes Zoster was reported in more participants in the vaccine arm compared to the placebo arm. Overall, in Part A, there were 73 participants with herpes zoster (50 vaccine recipients, 23 placebo). Within 28 days of vaccination, there were 22 cases in the vaccine arm and 15 in the placebo arm. Most cases were of moderate severity, however, one 61-year-old male participant in the mRNA-1273 arm developed herpes zoster 9 days after dose 1 that was reported as severe and two participants in the mRNA-1273 arm developed post-herpetic neuralgia. Among vaccine recipients with onset of herpes zoster within 28 days of any vaccination, the Sponsor assessed 2 cases as vaccine-related.

Given this imbalance in the clinical trial data, an O/E analysis was performed using US VAERS data for a risk window of 28 days, stratified by vaccine dose (dose 1 or dose 2). Reports were retrieved from automated queries of the VAERS database with DLP 12/16/21, using the following PTs: *Herpes Zoster Cutaneous Disseminated; Varicella Zoster Pneumonia; Herpes Zoster Meningoencephalitis; Herpes Zoster Oticus; Herpes Zoster Multi-Dermatomal; Herpes Zoster Disseminated; Herpes Zoster Meningomyelitis; Disseminated Varicella Zoster Virus Infection; Herpes Zoster; Herpes Zoster Pharyngitis; Varicella Zoster Virus Infection; Herpes Zoster Reactivation; Herpes Zoster Ophthalmic; Ophthalmic Herpes Zoster; Herpes Zoster Meningitis; Varicella Zoster Virus Serology Positive; Varicella Zoster Oesophagitis; Herpes Zoster Necrotising Retinopathy; Genital Herpes Zoster; Herpes Zoster Infection Neurological.*

Of the 2035 US reports with onset ≤ 28 days, the median age was 57 years (range 18-96 years), and the median time from vaccination to symptom onset was 6 days (range 0 to 28 days). Vaccine dose number was reported for 1,710 (84%) reports.

Table 5: O/E Analysis Results for US Reports of HZ following Moderna Vaccination, VAERS (DLP 12/16/2021)

Population	Vaccines administered (n)	Observed cases (n)	Reporting Rate/1000 00 doses	Expected cases (n)	Observed rate per 1000 PY	Expected rate per 1000 PY	Incidence rate ratio (O/E)	95% CI Lower Limit	95% CI Upper Limit
All ≤ 28 days	160,109,359	2035	1.271	56460	0.166	4.6	0.036	0.03	0.04
Dose 1	86231855	1057	1.226	30408	0.160	4.6	0.035	0.03	0.04
Dose 2	73877504	653	0.884	26052	0.115	4.6	0.025	0.02	0.03
18-64 yrs	122,914,447	1298	1.056	25441	0.138	2.7	0.051	0.05	0.05
≥ 65 yrs	62,240,445	735	1.181	50576	0.154	10.6	0.015	0.01	0.02

The O/E analysis, stratified by age and dose number, indicated that the observed numbers of cases did not exceed the expected number of cases for by age (18-64 years, ≥ 65 years) or by dose number (based on pre-COVID19 pandemic U.S. population based background incidence rates).⁷ The results of this analysis are consistent with analyses performed by the Sponsor in November 2021 when FDA requested the Sponsor to perform an analysis to determine the risk

of HZ after administration of Moderna vaccination (see Appendix Table A4 for Sponsor O/E Analysis results).

5.5 Thrombosis with Thrombocytopenia Syndrome (TTS)

An increased risk for thrombosis with thrombocytopenia syndrome (TTS) has been identified following administration of adenovirus-vectored COVID-19 vaccines, including the Janssen COVID-19 Vaccine. This prompted the VAERS analyses for reports of TTS that occurred following administration of mRNA-1273 vaccines. To date, 3 confirmed cases of TTS following vaccination with the Moderna COVID-19 Vaccine have been reported to VAERS:

- VAERS ID 1205036: 65-year-old male with a history of hypertension, hyperlipidemia, obesity, found to have acute pulmonary embolism, cerebral venous sinus thrombosis (CVST), upper and lower extremity deep vein thromboses, and thrombocytopenia (platelets 14,000) 11 days post dose 2.
- VAERS ID 1407622: 54-year-old male with a history of Type 2 diabetes, hypertension, and hyperlipidemia, found to have CVST and thrombocytopenia (platelets 67,000) 2 days post dose 2, with positive PF4 antibody but no heparin exposure.
- VAERS ID 1126935: 50-year-old female, presented with abdominal pain and an initially normal platelet count 10 days post vaccination, which rapidly dropped to 34,000. Patient was subsequently diagnosed with multiple arterial thrombi in the aorta, pulmonary artery, superior mesenteric arteries; splenic artery, left kidney requiring procedural interventions, and potentially cerebellar infarctions. Initially treated with heparin and tPA and switched to steroids and argatroban, and found to have positive PF4 antibodies, and no recent heparin exposure.

The low reporting rate suggests that these cases represent the background rate of thrombosis with thrombocytopenia rather than signaling a risk of TTS attributable to the Moderna COVID-19 vaccine.

5.4 Data Mining

Data mining was performed to evaluate whether any reported events following the use of Moderna COVID-19 Vaccine were disproportionately reported compared to other vaccines in the VAERS database, which contains VAERS reports since 1990. Disproportionality alerts do not by themselves demonstrate causal associations, rather, they may serve as a signal for further investigation. Data mining query with the Empirica Signal tool was performed on 12/3/21 for each of the four Main Views (All Signals from Age Groups, All Signals from Gender, All Signals from Serious/Fatal, and All Signals from US/All VAERS). The alert score for disproportional reporting is the lower bound of the 90% confidence interval of the Empirical Bayesian Geometric Mean, which is denoted as an EB05 of >2.0. There were two preferred terms (PTs) with a disproportional reporting alert:

‘Product dose omission issue’ – EB05 2.40

‘Product administered to patient of inappropriate age’ - EB05 2.05

Of note, these PTs are not mutually exclusive, as a single report can include multiple PTs. The above PTs reflect product use issues and medication errors that are not associated with a clinical adverse event. There were no new safety concerns from review of the data mining results

6. SPONSOR'S PHARMACOVIGILANCE PLAN

The Sponsor submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with use of the Spikevax COVID-19 Vaccine. The Sponsor includes anaphylaxis, myocarditis, and pericarditis as Important Identified Risks, and vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as an Important Potential Risk. Use in pregnancy and while breastfeeding, long term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects and in subjects with unstable health conditions and comorbidities, use in the pediatric population, and use in subjects with autoimmune or inflammatory disorders are areas the Sponsor identified as missing information. The Sponsor's Pharmacovigilance Plan (PVP) is summarized in Table 7 below.

Table 6: Sponsor's Proposed Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risks	<i>Anaphylaxis</i>	<ul style="list-style-type: none"> *Routine and Enhanced Pharmacovigilance Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years following dose 2 Post-authorization safety studies (P903, P904) to perform long-term active surveillance for safety events of interest among vaccinees. <p><i>Risk communication:</i> Prescribing Information Section 5: Warnings and Precautions 5.1 Management of Acute Allergic Reactions</p>
	<i>Myocarditis</i> <i>Pericarditis</i>	<ul style="list-style-type: none"> *Routine and Enhanced Pharmacovigilance Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years following dose 2 Post-authorization safety studies (P903, P904) to perform long-term active surveillance for safety events of interest among vaccinees. <p><i>Risk communication:</i> Prescribing Information Section 5: Warnings and Precautions 5.2 Myocarditis and Pericarditis</p>
Important Potential Risks	Vaccine-associated enhanced disease (VAED) and Vaccine-associated enhanced respiratory disease (VAERD)	<ul style="list-style-type: none"> *Routine and Enhanced Pharmacovigilance Mandatory reporting of cases of COVID-19 resulting in hospitalization or death Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years following dose 2 Post-authorization safety studies (P903, P904) to perform long-term active surveillance for safety events of interest among vaccinees.
Missing Information	Use in pregnancy and lactation	<ul style="list-style-type: none"> *Routine Pharmacovigilance

		<ul style="list-style-type: none"> Planned pregnancy registry to monitor vaccine-exposed pregnancies within the U.S. <p><i>Risk communication:</i> Prescribing Information, Sections 11.1 and 11.2: Use in Specific Populations: Pregnancy and Lactation.</p>
	Vaccine effectiveness Long term safety Long term effectiveness Use with concomitant vaccines	<ul style="list-style-type: none"> Routine pharmacovigilance Mandatory reporting of cases of COVID-19 resulting in hospitalization or death Real World Effectiveness (RWE) study (P901) <p><i>Risk communication:</i> Prescribing Information, Section 5.5: Limitations of Vaccine Effectiveness</p>
	Use in immunocompromised patients	<ul style="list-style-type: none"> Routine pharmacovigilance Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years Post authorization RWE study (P901) <p><i>Risk communication:</i> Prescribing Information, Section 5.4 Warnings and Precautions: Altered Immunocompetence</p>
	Interaction with other vaccines	<ul style="list-style-type: none"> Post-authorization RWE and safety studies (P901, P904) to perform long-term active surveillance for safety events of interest among vaccinees
	Use in frail subjects with unstable health conditions and comorbidities (COPD, T2DM, CVD, chronic neurological disease)	<ul style="list-style-type: none"> Routine pharmacovigilance Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years following dose 2 Post-authorization RWE and safety studies (P901, P904)
	Use in subjects with autoimmune or inflammatory disorders.	<ul style="list-style-type: none"> Routine pharmacovigilance Completion of ongoing clinical studies evaluating safety and efficacy with surveillance for two years following dose 2 Post-authorization RWE and safety studies (P901, P904)
	Use in pediatric individuals < 18 years of age	<p>Ongoing phase 2/3 randomized, observer-blind, placebo-controlled safety and efficacy studies.</p> <ul style="list-style-type: none"> -Study P203 – adolescents 12 to 17 -Study P204 – children/infants <6 months. <p><i>Risk communication:</i> Prescribing information Section 11.3: Use in Specific Populations; Pediatric Use</p>

**Adapted Pharmacovigilance Plan, Module 1.16.1*

6.1 Post marketing studies

In addition to characterizing subclinical myocarditis in the ongoing clinical trials (P301, 203, 204), Moderna proposes to conduct post-authorization observational studies for safety to evaluate the association between Spikevax COVID-19 mRNA vaccine and a pre-specified list of adverse events of special interest (AESI) along with deaths and hospitalizations, and severe COVID-19 disease. The Sponsor has proposed the following planned surveillance studies; OBE will provide feedback on the pending protocols (mRNA-1273-P911 and mRNA-1273-P902) after reviewing the final protocols once they are submitted by the Sponsor.

1. Post Marketing Requirements

a) PMR #1: mRNA-1273-P903 – US Active Surveillance Using Health-Verity Database to assess myocarditis and pericarditis:

This active surveillance study is conducting retrospective analyses of medical and pharmacy claims data to address three objectives: estimation of background rates of 26 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. A sample of pediatric, adolescent, and adult individuals enrolled in health plans contributing data to Health-Verity will be used for calculation of background rates. Patients from this dataset as well as additional patients with evidence of SARS-CoV-2 vaccination will be included as vaccine uptake increases. Secondary database analyses will be completed using retrospective analyses of pre-vaccination data as well as prospectively updated data during the vaccination period. A sample of pediatric, adolescent, and adult individuals enrolled in health plans contributing data to Health Verity will be used for calculation of background rates. Patients from this dataset as well as additional patients with evidence of SARS-CoV-2 vaccination will be included as vaccine uptake increases.

- Final Protocol Submission: 01/31/2022
- Study Completion: 12/31/2022
- Final Study Report: 06/30/2023

b) PMR #2: mRNA-1273-P904 – EU Active Surveillance using Electronic Healthcare Databases to assess myocarditis and pericarditis:

This is a Post-Authorization active surveillance safety study using secondary data to monitor Real-World safety of the Spikevax mRNA-1273 Covid-19 Vaccine in the EU. The primary objectives are to estimate the incidence rates of AESI among persons receiving Spikevax Covid-19 vaccine overall and in subgroups of interest and to assess whether vaccination is associated with an increased rate of AESI and with increased rates of AESI compared with the expected rates in subpopulations of interest. Secondary objectives are to estimate incidence rates of AESI among vaccinated individuals using real-world data, in the following specific subpopulations; women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and morbidities, patients with autoimmune or inflammatory disorders, and in age specific populations (children, adolescents, adults).

- Final Protocol Submission: 11/04/2021
- Study Completion: 3/31/2023
- Final Study Report: 12/31/2023

**Please refer to the OBE Sentinel Team review memo for details on review of Real World Effectiveness study protocol:*

c) *PMR #3: mRNA-1273-P911 – Observational prospective cohort study using hospital-based network, for long term sequelae of myocarditis with 5-year follow-up*

This is an observational prospective cohort study using hospital-based network for long term outcomes of myocarditis with 5-year follow-up; to characterize the presentation, clinical course of acute postvaccine myocarditis, and potential long-term sequelae and functional outcomes in children and young adults.

- Final Protocol Submission: 04/30/2022
- Study Completion: 10/31/2027
- Final Study Report: 10/31/2028

2. Ongoing Clinical trial PMRs: to characterize subclinical myocarditis in the ongoing clinical trials.

a) *PMR #4: mRNA-1273-P301*

Title: Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Adults Aged 18 Years and Older.

- Final Protocol Submission: 09/14/2021
- Study Completion date: 12/31/2022
- Final study report: 06/30/2023

b) *PMR #5: mRNA-1273-P203*

Title: Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS CoV- 2 Vaccine in Healthy Adolescents 12 to < 18 years of age.

- Final Protocol Submission: 11/12/2021
- Study Completion: 04/30/2024
- Final Study Report: 07/31/2024

c) *PMR #6: mRNA-1273-P204*

Title: A Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age.

- Final Protocol Submission: 10/06/2021
- Study Completion: 12/31/2023
- Final Study Report: 03/31/2024

3. Post Marketing Commitments

a) *PMC#1: mRNA-1273-P901- Real World Effectiveness Study:*

This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California (KPSC) to evaluate the real-world effectiveness (RWE) and long-term effectiveness of Spikevax COVID-19 mRNA vaccine in preventing COVID-19 and severe COVID-19 disease. Effectiveness will be stratified by age, sex, race/ethnicity, and comorbid conditions. Effectiveness of two doses of vaccine in preventing COVID-19 among immunocompromised patients will be studied. Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Durability of one or two doses of against COVID-19 and severe COVID-19 disease will also be assessed. Vaccinated participants

will receive Spikevax COVID-19 mRNA vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members.

- Protocol submission: 12/20/2021
- Study Completion: 01/31/2024
- Final Study Report: 04/14/2025

b) PMC#2: mRNA-1273-P902 – Observational Pregnancy Registry (EU/Canada/US):

The Sponsor has established a passive pregnancy registry with an internal unvaccinated comparator cohort to monitor vaccination during pregnancy within populations expected to receive the Spikevax Covid-19 vaccine. The study will evaluate outcomes of pregnancies and infant births in females exposed to vaccine during pregnancy. Pregnant women from Germany, Italy, Finland, Canada, and the United States exposed to Spikevax COVID-19 mRNA vaccine are being recruited from the general population and followed, along with their live-born infants. European Surveillance of Congenital Anomalies (EUROCAT) network data, Metropolitan Atlanta Congenital Defects Program (MACDP) data, and other published data will provide an external comparator.

- Final Protocol Submission: 07/31/2022
- Study Completion: 9/30/2023
- Final Study Report: 06/30/2024

c) PMC#3: mRNA-1273-P905 – EU Pregnancy Study using Electronic Databases: (UK/Denmark/Norway/Italy/Spain)

This is a secondary electronic database analysis study comparing birth prevalence of study outcomes for pregnancies with and without Spikevax mRNA-1273 Covid-19 Vaccine exposure. The study plans to monitor the safety of Spikevax COVID-19 Vaccine use during pregnancy in the EU, using routinely collected health data in five European countries. Characterizing and evaluating outcomes of pregnancies in women exposed to Spikevax COVID-19 Vaccine during pregnancy, the study objectives are to describe vaccine utilization during pregnancy, and to determine whether exposure to vaccine during pregnancy is associated with an increased risk of pregnancy complications, adverse pregnancy outcomes, and adverse neonatal outcomes. The study population will encompass all pregnancies identified in the databases and ending in a live or still birth; a spontaneous abortion; or an induced abortion.

- Final Protocol Submission: 11/04/2021
- Study Completion: 3/31/2023
- Final Study Report: 12/31/2023

7. ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1: Important Identified Risks

7.1.1: Anaphylactic Reactions

Anaphylactic reactions (including anaphylaxis) to vaccination can occur with any injectable vaccine. Reported rates of anaphylaxis after vaccination range from 1-2 cases per million doses in adults and children⁵. A majority of patients have a history of atopy, but reactions can also occur in persons with no known history of hypersensitivity. Reports of anaphylactic reactions have occurred in association with Spikevax COVID-19 vaccination, thus, this is an important

identified risk. The sponsor proposes enhanced pharmacovigilance, expedited reporting of cases, and further study in current ongoing clinical trials and in post marketing safety studies.

Reviewer Comment:

Anaphylaxis is a labeled event for Spikevax mRNA-1273 Covid-19 Vaccine vaccination. The risk of anaphylactic reactions exists for each dose, and should be monitored after each dose of vaccine, including the booster dose. The Sponsor's proposed PV plan is acceptable.

7.1.2: Myocarditis and Pericarditis

Monitoring for myocarditis and pericarditis is ongoing and includes the following activities:

- Continued passive surveillance using VAERS
- Benefit/Risk analyses using different data sources
- Continued active surveillance using the Vaccine Safety Datalink (VSD)
- Ongoing Sponsor passive surveillance using worldwide adverse events data
- Ongoing Sponsor active surveillance studies as detailed in Section 6.1

In addition to these surveillance activities, the Sponsor has updated their pharmacovigilance plan (PVP) to include myocarditis and pericarditis as important identified risks, and also updated the proposed Spikevax fact sheets to describe myocarditis and pericarditis under the Warnings section. This label change was made under EUA for both of the two mRNA COVID-19 vaccines that are currently authorized/approved for emergency use.

Reviewer Comment:

In the setting of ongoing vaccinations after authorization and during the ongoing COVID-19 pandemic, the risk of myocarditis and pericarditis should be monitored. The Sponsor's proposed PV plan is acceptable.

7.2: Important Potential Risks

7.2.1: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

The potential for vaccination against SARS-CoV-2 to be associated with disease enhancement is a theoretical concern based on similar observations with other respiratory viruses, in preclinical studies of SARS-CoV and MERS-CoV vaccines, and in the clinical experience with RSV, measles, and dengue vaccines in humans⁶. Non-clinical studies of mRNA-1273 to evaluate this theoretical concern did not show immune signatures predictive of VAED (5), nor vaccine-enhanced viral replication or pulmonary pathology after challenge with SARS-CoV-2 in relevant animal species. In addition, the pivotal phase 3 P301 trial was designed to assess the risk of enhanced disease with prespecified rules for harm.

No safety concerns for VAED have been identified to date in post marketing surveillance. To further characterize the potential risk of VAED/VAERD, the Sponsor proposes analyses of the results of ongoing clinical trials through study completion (two years after the second dose), ongoing active surveillance studies and AE reporting required under EUA. The Sponsor also proposes post-authorization safety studies that include active surveillance for safety events of interest, including severe or atypical COVID-19 among vaccinated subjects and will continue to follow this outcome post vaccination.

Reviewer comment:

Distinguishing between VAED/VAERD and vaccine failure is difficult because of the overlap between clinical symptoms of VAED/VAERD and COVID-19. Although there has been no signal to date, given the limitations of monitoring this important potential risk in clinical trials, the Sponsor's plan for evaluating the risk of VAED/VAERD through post authorization active surveillance studies is acceptable.

7.3: Important Missing Information

7.3.1 Use in Pregnancy and Lactation

Pregnancy was an exclusionary condition in the clinical trials, and to date, there have been no post authorization safety signals associated with receipt of Moderna Covid-19 Vaccine in pregnant women. The Sponsor is conducting a pregnancy registry with an unvaccinated internal comparator cohort to study the safety of the Spikevax COVID-19 Vaccine in pregnant women. Lack of data regarding use in pregnant women is labeled in the current EUA provider prescribing information insert and patient fact sheet and in the proposed Spikevax PI.

Reviewer comment: *The Sponsor's plan to address this missing information post receipt in pregnancy and lactation through routine pharmacovigilance, labeling, and the ongoing pregnancy registry is acceptable.*

7.3.2 Long term safety / immunosuppression

The Sponsor proposes to study and characterize long term safety with continued follow up from the clinical trial, active surveillance for safety, and routine pharmacovigilance. Immunosuppressed participants were excluded from the vaccine clinical trials due to the expectation that they may not acquire the protective antibody level achieved in healthy individuals. Currently, a third 100 µg dose is authorized in immunocompromised patients, and the Sponsor is monitoring safety of this third dose in patients via routine pharmacovigilance and post authorization safety studies.

Reviewer comment: *The Sponsor's plan to address long term safety and safety in the immunosuppressed through routine pharmacovigilance and ongoing active surveillance studies for safety is acceptable.*

7.3.3 Vaccine Effectiveness/Concomitant administration

Real-world vaccine effectiveness studies for the primary series, assessing the duration of protective immunity, and the generalizability of the clinical trial results when used in the general population are ongoing. Characterization of this efficacy profile through continued trial follow up, in addition to the ongoing non-interventional study for long term effectiveness and coadministration with influenza vaccine is ongoing.

Reviewer comment: *The Sponsor's proposal to continue to study vaccine effectiveness in the ongoing pivotal trial, ongoing non-interventional studies, and with regard to concomitant administration with non-COVID vaccines is acceptable.*

7.3.4 Use in Pediatric Individuals

Participants younger than 18 years of age were excluded from the Spikevax clinical trials submitted in support of this BLA; there are no clinical data in the pediatric population. The Sponsor has ongoing clinical trials of safety, efficacy, and immunogenicity of the primary series in participants <18 years of age in a separate pediatric clinical development plan. The safety and efficacy of in children is unknown at this time. The proposed label notes that no data are available for use in pediatric subjects.

Reviewer comment: The indications for use do not include pediatric subjects younger than age 18 at this time. Lack of data regarding use in the pediatric age group is labeled in the current EUA provider prescribing information insert and patient fact sheet and in the proposed Spikevax PI. The proposed PVP is adequate to monitor use in individuals <18 years of age.

8. DE Conclusions

Based on review of available data, there is a safety signal for myocarditis and pericarditis from post-authorization safety surveillance which warrants a FDAAA Title IX post-marketing requirement (PMR) safety study to assess the important identified risks of myocarditis and pericarditis. The sponsor's proposed Pregnancy Registry observational study will be a post-marketing commitment (PMC). In addition, the safety of Spikevax can be monitored through routine PV activities, risk communication through labeling, and the additional post-authorization safety studies proposed by the sponsor.

9. DE Recommendations

Based on the review of the clinical trial and post-authorization safety data, OBE/DE recommends the following actions should Spikevax be approved:

1. Routine pharmacovigilance: in accordance with adverse event reporting regulations under 21 CFR 600.80, as per the sponsor's proposed PVP.

2. Three Post-marketing requirements (PMRs) safety studies: under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to assess the serious risk of myocarditis and pericarditis, including a study of long-term sequelae of myocarditis.

a) PMR #1: mRNA-1273-P903

Title: Post-Authorization Safety of SARSCoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity.

Objective: This study aims to augment ongoing active and passive safety signal detection through signal refinement and, where warranted, evaluation of potential safety signals associated with exposure to the SARS-CoV-2 mRNA-1273 vaccine. It will monitor both AESI (including myocarditis and pericarditis) and emerging validated safety signals.

b) *PMR #2: mRNA-1273-P904*

Title: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273Vaccine in the EU.

Objective: To determine whether the occurrence of adverse events of special interest (AESI) among persons vaccinated with COVID-19Vaccine Moderna in Europe is higher than expected.

c) *PMR #3: mRNA-1273-P911*

Title: Long-term outcomes of myocarditis following administration of Spikevax (Moderna COVID-19, mRNA-1273)

Objective: Observational prospective cohort study using hospital-based network for long term outcomes of myocarditis with 5-year follow-up; to characterize the presentation, clinical course of acute postvaccine myocarditis, and potential long-term sequelae and functional outcomes in children and young adults.

Ongoing Clinical trial PMRs: to characterize subclinical myocarditis in the ongoing clinical trials.

d) *PMR #4: mRNA-1273-P301*

Title: Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS CoV-2 Vaccine in Adults Aged 18 Years and Older.

e) *PMR #5: mRNA-1273-P203*

Title: Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age.

f) *PMR #6: mRNA-1273-P204*

Title: A Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age.

Three Post-marketing commitment safety studies: PMCs for a pregnancy registry, an EU pregnancy study to assess whether pregnant women receiving the Spikevax are at increased risk of pregnancy related adverse events and infant safety outcomes, and a PMC to study vaccine effectiveness in the KPSC system.

g) *PMC #1: Study mRNA-1273-P901*

Title: Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S.

Objective: To evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis and severe COVID-19 disease at KPSC

h) *PMC #2: Study mRNA-1273-P902*

Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study

Objective: To evaluate pregnancy and birth outcomes in women exposed to mRNA-1273 vaccine during pregnancy, recruited from the general population (US, Canada, Germany, Italy, Finland).

i) *PMC #3: Study mRNA-1273-P905*

Title: Safety of Moderna Covid019 Vaccine in pregnancy

Objective: Monitoring safety in pregnancy: an observational study using routinely collected health data in five European countries.

The available safety data do not suggest a safety concern that would require a REMS at this time. Please see the final version of the package insert submitted by the Sponsor for the final agreed-upon language for the label.

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APPENDIX

Table A1: Materials Reviewed in Support of this Review

Date	Source	Document Type	Document(s) Reviewed
08/24/2021	SpikevaxTX, Inc	BLA 125752/0003	Module 1.16.1 EU Risk Management Plan for COVID-19 Vaccine Spikevax – v2.2
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 5.3.5.1 Study Reports of Controlled Clinical Studies
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 5.3.6 Reports of Post-marketing Experience
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 1.14.1 Draft Labeling Text
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 2.5 Clinical Overview
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 2.7.4 Summary of Clinical Safety
08/24/2021	SpikevaxTX, Inc.	BLA 125752/0003	Module 2.7.3 Summary of Clinical Efficacy
Various	Spikevax TX Inc.	IR	Sponsor IR responses
n/a	VAERS	Reports	VAERS database and data mining

Table A2: VAERS Reporting Rates and Relative Risk of Myocarditis & Pericarditis Post Vaccination in Males, 7-Day Risk Window

SPIKEVAX COVID-19 vaccine DOSE 1: Observed-to-Expected (O/E) Analysis: 7-day Risk Window								
MALES								
Age Group	Doses Administered	Background Rate/ 100,000	Observed* Cases	Expected† Cases	Relative Risk	95% CI		p. Value
						Lower	Upper	
18 – 24	2712541	2.16	34	1.122892	30.27897	20.96906	42.31182	<0.001
25 – 29	2181962	2.16	19	0.903252	21.03511	12.66451	32.84893	<0.001
30 – 39	4788947	2.16	17	1.982447	8.575261	4.995405	13.72982	<0.001
40 – 49	4830137	2.16	7	1.999498	3.500878	1.407535	7.213147	<0.001
50 – 64	9115645	2.16	11	3.77354	2.915035	1.455175	5.215802	0.002
>65 yrs	10458519	2.16	5	4.32944	1.154884	0.374988	2.695113	0.63
30 – 39	4788947	4.4	17	4.038318	4.209673	2.45229	6.740095	<0.001
40 – 49	4830137	4.4	7	4.073052	1.718613	0.690972	3.541	0.14
50 – 64	9115645	4.4	11	7.686841	1.431017	0.714359	2.560485	0.21
>65 yrs	10458519	4.4	5	8.81923	0.566943	0.184085	1.323056	0.24
12 – 94	34136257	2.16	93	14.13115	6.581206	5.311883	8.062422	<0.001

Sources for background rates: Gubernot et al. U.S. Population-based Background Incidence Rates of Medical Conditions for Use in Safety Assessment of COVID-19 Vaccines. *Vaccine*. 2021 Jun 23;39(28):3666-3677. Roth et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. *J Am Coll Cardiol*. 2020 Dec 22; 76(25): 2982-3021.

^a Background rates are rates per 100,000 persons per year.

^b Reporting rates are per 100,000 doses of vaccine

^c Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021

Table A3: VAERS Reporting Rates and Relative Risk of Myocarditis and Pericarditis Post Vaccination in Females, 7-Day Risk Window

SPIKEVAX COVID-19 vaccine DOSE 1: Observed-to-Expected (O/E) Analysis: 7-day Risk Window FEMALES								
Age Group	Doses Administered	Background Rate/ 100,000	Observed* Cases	Expected† Cases	Relative Risk	95% CI		p. Value
						Lower	Upper	
18 - 24	3006756	2.16	5	1.244686	4.017078	1.304334	9.37452	0.01
25 - 29	2316707	2.16	3	0.959031	3.128157	0.645101	9.141803	0.07
30 - 39	5101819	2.16	5	2.111964	2.367464	0.768709	5.524871	0.06
40 - 49	5302541	2.16	7	2.195056	3.188985	1.282137	6.570527	0.01
50 - 64	10116505	2.16	22	4.187859	5.253281	3.292203	7.95353	<0.001
>65 yrs	12351599	2.16	5	5.113105	0.977879	0.317515	2.282044	1
30 - 39	5101819	4.4	5	4.30215	1.16221	0.377366	2.71221	0.63
40 - 49	5302541	4.4	7	4.47141	1.565502	0.629413	3.225532	0.23
50 - 64	10116505	4.4	22	8.530824	2.578883	1.616172	3.90446	<0.001
>65 yrs	12351599	4.4	5	10.41559	0.48005	0.155871	1.120276	0.12
12 - 94	38249547	2.16	47	15.8339	2.968315	2.181006	3.94723	<0.001

Sources for background rates: Gubernot et al. U.S. Population-based Background Incidence Rates of Medical Conditions for Use in Safety Assessment of COVID-19 Vaccines. *Vaccine*. 2021 Jun 23;39(28):3666-3677. Roth et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. *J Am Coll Cardiol*. 2020 Dec 22; 76(25): 2982-3021.

^a Background rates are rates per 100,000 persons per year.

^b Reporting rates are per 100,000 doses of vaccine

^c Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021.

Table A4: Observed/Expected Analyses Stratified by Age, Herpes Zoster Expected Rates from the United States

	Person-years	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	18,264,867	2786	0.15	81644	4.5	0.03 (0.03, 0.04)	0.07 (0.07, 0.07)	0.14 (0.13, 0.14)
By age								
<18	547,946	6	0.01	471	0.9	0.01 (0.01, 0.03)	0.03 (0.01, 0.05)	0.05 (0.03, 0.08)
18-24	1,643,838	50	0.03	4504	2.7	0.01 (0.01, 0.01)	0.02 (0.02, 0.03)	0.04 (0.04, 0.05)
25-39	4,018,271	381	0.09	14627	3.6	0.03 (0.02, 0.03)	0.05 (0.05, 0.06)	0.1 (0.1, 0.11)
40-49	2,739,730	389	0.14	12384	4.5	0.03 (0.03, 0.03)	0.06 (0.06, 0.07)	0.13 (0.12, 0.13)
50-64	4,748,865	684	0.14	32007	6.7	0.02 (0.02, 0.02)	0.04 (0.04, 0.05)	0.09 (0.08, 0.09)
65-74	2,739,730	591	0.22	25534	9.3	0.02 (0.02, 0.03)	0.05 (0.04, 0.05)	0.09 (0.09, 0.1)
75+	1,826,487	476	0.26	21954	12.0	0.02 (0.02, 0.02)	0.04 (0.04, 0.05)	0.09 (0.08, 0.09)
By gender								
Male	8,675,812	860	0.10	31753	3.7	0.03 (0.03, 0.03)	0.05 (0.05, 0.06)	0.11 (0.1, 0.11)
Female	9,589,055	1856	0.19	50343	5.3	0.04 (0.04, 0.04)	0.07 (0.07, 0.08)	0.15 (0.14, 0.15)
By age and gender								
Male								
<18	260,274	2	0.01	216	0.8	0.01 (0, 0.04)	0.02 (0.01, 0.05)	0.04 (0.02, 0.07)
18-24	780,823	14	0.02	1890	2.4	0.01 (0, 0.01)	0.01 (0.01, 0.02)	0.03 (0.02, 0.04)
25-39	1,908,679	123	0.06	6108	3.2	0.02 (0.02, 0.02)	0.04 (0.04, 0.05)	0.08 (0.07, 0.09)
40-49	1,301,372	127	0.10	5088	3.9	0.02 (0.02, 0.03)	0.05 (0.04, 0.06)	0.1 (0.09, 0.11)
50-64	2,255,711	184	0.08	11301	5.0	0.02 (0.01, 0.02)	0.03 (0.03, 0.04)	0.07 (0.06, 0.07)
65-74	1,301,372	204	0.16	9825	7.6	0.02 (0.02, 0.02)	0.04 (0.04, 0.05)	0.08 (0.08, 0.09)
75+	867,581	170	0.20	9162	10.6	0.02 (0.02, 0.02)	0.04 (0.03, 0.04)	0.07 (0.07, 0.08)
Female								
<18	287,672	4	0.01	256	0.9	0.02 (0.01, 0.04)	0.03 (0.02, 0.06)	0.06 (0.04, 0.1)
18-24	863,015	35	0.04	2624	3.0	0.01 (0.01, 0.02)	0.03 (0.02, 0.03)	0.05 (0.05, 0.06)
25-39	2,109,592	253	0.12	8544	4.1	0.03 (0.03, 0.03)	0.06 (0.05, 0.06)	0.12 (0.11, 0.13)
40-49	1,438,358	260	0.18	7336	5.1	0.04 (0.03, 0.04)	0.07 (0.06, 0.08)	0.14 (0.13, 0.15)
50-64	2,493,154	499	0.20	20818	8.4	0.02 (0.02, 0.03)	0.05 (0.04, 0.05)	0.1 (0.09, 0.1)
65-74	1,438,358	385	0.27	15879	11.0	0.02 (0.02, 0.03)	0.05 (0.05, 0.05)	0.1 (0.09, 0.1)
75+	958,905	303	0.32	12773	13.3	0.02 (0.02, 0.03)	0.05 (0.04, 0.05)	0.09 (0.09, 0.1)

* Rates presented per 1,000 person-years. Rates from [Johnson 2015](#)