HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPIKEVAX safely and effectively. See full prescribing information for SPIKEVAX.

SPIKEVAX (COVID-19 Vaccine, mRNA)
Suspension for injection, for intramuscular use. a~~Suspension for Intramuscular Injection~~
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
SPIKEVAX is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular injection only

~~Spikevax~~SPIKEVAX is administered intramuscularly as a series of two doses (0.5 mL each) one month apart. ~~Administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart.~~ (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension for injection. A single dose is 0.5 mL. ~~Suspension for injection supplied in two presentations:~~
~~• 5.5 mL multiple-dose vial (3)~~
~~• 7.5 mL multiple-dose vials (3)~~

----------CONTRAINDICATIONS----------
Severe allergic reaction (e.g., anaphylaxis) to any component of ~~the vaccine~~SPIKEVAX. (4)

----------WARNINGS AND PRECAUTIONS----------
- ~~Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.1)~~
- Postmarketing data demonstrate increased r~~R~~isks of myocarditis and/~~or~~ pericarditis, particularly within 7 days following the second dose.~~;~~ ~~consider individual's clinical history.~~ (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions were pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ModernaTX, Inc. at 1-866-663-3762 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION ~~and FDA-approved patient labeling.~~

Revised: 00/2021

Commented [A1]: Comment to Moderna:
Please revise this section of Highlights to include, for the most commonly reported adverse reactions, the percentage of subjects reporting. Please present the percentages separately for clinical trial participants 18-64 and >/= 65 yoa.

Commented [A2]: Comment to Moderna
Please revise as follows ".. or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIKEVAX is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 ~~2.1~~ Preparation for Administration

- SPIKEVAX is supplied in two presentations:
  - multiple-dose vial containing 5.5 mL
  - multiple-dose vial containing 7.5 mL
- SPIKEVAX multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- ~~Remove the required number of vial(s) from storage and~~ T~~t~~haw each vial before use following the instructions below.

Vial	Thaw in Refrigerator	Thaw at Room Temperature
5.5 mL ~~Vial~~	Thaw ~~in refrigerated conditions~~ between 2° to 8°C (36° to 46°F) for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw ~~at room temperature~~ between 15° to 25°C (59° to 77°F) for 1 hour.
7.5 mL ~~Vial~~	Thaw ~~in refrigerated conditions~~ between 2° to 8°C (36° to 46°F) for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw ~~at room temperature~~ between 15° to 25°C (59° to 77°F) for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.
- SPIKEVAX is a white to off-white suspension. It may contain white or translucent product-related particulates. ~~Visually inspect SPIKEVAX vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.~~
- Each dose is 0.5 mL.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the SPIKEVAX vial label. Discard vial after 12 hours. Do not refreeze.

2.2 Administration

~~Visually inspect each dose of SPIKEVAX in the dosing syringe prior to administration. The white to off-white suspension may contain white or translucent product-related particulates. During the visual inspection:~~

- ~~Verify the final dosing volume of 0.5 mL.~~
- ~~Confirm there are no other particulates discoloration is observed.~~
- ~~Do not administer if vaccine is discolored or contains other particulate matter.~~

Administer a single 0.5 mL dose. ~~SPIKEVAX intramuscularly.~~

2.3 Dosing and Schedule

SPIKEVAX is administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart.

There are no data available on the interchangeability of SPIKEVAX with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of SPIKEVAX should receive a second dose of SPIKEVAX to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

SPIKEVAX is a suspension for intramuscular injection. A single dose is 0.5 mL. ~~supplied in two presentations:~~

~~5.5 mL multiple dose vial~~

- ~~7.5 mL multiple dose vial~~

4 CONTRAINDICATIONS

Do not administer SPIKEVAX to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of SPIKEVAX *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of SPIKEVAX.

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with

conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).
~~Reports of adverse events following use of SPIKEVAX under Emergency Use Authorization use as Moderna COVID-19 Vaccine suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of SPIKEVAX. Available data from short-term follow-up suggest that most cases have been mild with resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer SPIKEVAX to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances.~~

5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines including SPIKEVAX. Procedures should be in place to avoid injury from fainting.

5.~~3~~4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished immune response to SPIKEVAX.

5.~~4~~5 Limitations of Vaccine Effectiveness

SPIKEVAX may not protect all vaccine recipients.

6 ADVERSE REACTIONS

~~The most common adverse reactions in participants 18 years of age and older were pain at the injection site (92.0%), fatigue (70.1%), headache (64.9%), myalgia (61.6%), arthralgia (46.5%), chills (45.5%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.9%), fever (15.5%), swelling at the injection site (14.8%), and erythema at the injection site (10.2%).~~
In clinical studies, the most commonly reported (>10%) adverse reactions in participants 18 through 64 years of age following any dose were pain at injection site (93.3%), fatigue (71.9%), headache (68.7%), myalgia (64.8%), chills (49.7%), arthralgia (48.6%), nausea/vomiting (25.7%), axillary swelling/tenderness (22.2%), fever (17.3%), swelling at the injection site (15.4%), and erythema at the injection site (10.5%).

In clinical studies, the most commonly reported (>10%) adverse reactions in participants 65 years of age and older following any dose were pain at injection site (88.3%), fatigue (64.8%), headache (53.3%), myalgia (51.8%), arthralgia (40.2%), chills (32.7%), nausea/vomiting (15.0%), swelling at the injection site (13.0%), and axillary swelling/tenderness (12.7%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of SPIKEVAX was evaluated in a Phase 3 randomized, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,346 participants 18 years of age and older who received at least one dose of SPIKEVAX (n=15,184~~0~~) or placebo (n=15,162~~6~~) (Study 1, NCT04470427). Upon issuance of the Emergency Use Authorization (December 18, 2020) for SPIKEVAX, participants were unblinded in a phased manner over a period of months to offer placebo participants SPIKEVAX. The median duration of follow up for safety after the second injection during the blinded phase was 4 months. The median duration of follow up for safety after the second injection including both the blinded phase and the open-label phase was 6 months.

In Study 1, ~~T~~the median age of the population was 52 years (range 18-95); 22,826 (75.2%) participants were 18 to 64 years of age and 7,520 (24.8%) participants were 65 years of age and older. Overall, 52.6% of the participants were male, 47.4% were female, 20.5% were Hispanic or Latino, 79.2% were White, 10.2% were African American, 4.6% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Pacific Islander, 2.0% were other races, and 2.1% were Multiracial. Demographic characteristics were similar between participants who received SPIKEVAX and those who received placebo.

Solicited Adverse Reactions

Local and systemic adverse reactions and use of antipyretic medication were solicited in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among participants receiving SPIKEVAX (n=15,179) and participants receiving placebo (n=15,159) with at least 1 documented dose. Events that persisted for more than 7 days were followed until resolution. Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants.

The reported number and percentage of the solicited local and systemic adverse reactions by age group and dose are presented in Table 1 and Table 2, respectively.

Table 1: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 18-64 Years (Solicited Safety Set, Dose 1 and Dose 2)

	SPIKEVAX		**Placebo[a]**	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=11,000) n (%)	**Dose 1** (N=11,402) n (%)	**Dose 2** (N=10,929) n (%)
Local Adverse Reactions				
Pain	9,908 (86.9)	9,893 (89.9)	2,183 (19.1)	2,048 (18.7)

	SPIKEVAX		Placebo[a]	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=11,000) n (%)	**Dose 1** (N=11,402) n (%)	**Dose 2** (N=10,929) n (%)
Pain, Grade 3[b]	366 (3.2)	506 (4.6)	23 (0.2)	22 (0.2)
Axillary swelling/tenderness	1,322 (11.6)	1,777 (16.2)	567 (5.0)	474 (4.3)
Axillary swelling/tenderness, Grade 3[b]	37 (0.3)	47 (0.4)	13 (0.1)	12 (0.1)
Swelling (hardness) ≥25 mm	766 (6.7)	1,399 (12.7)	42 (0.4)	46 (0.4)
Swelling (hardness), Grade 3[c]	62 (0.5)	183 (1.7)	3 (<0.1)	5 (<0.1)
Erythema (redness) ≥25 mm	354 (3.1)	989 (9.0)	54 (0.5)	53 (0.5)
Erythema (redness), Grade 3[c]	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)
Systemic Adverse Reactions				
Fatigue	4,385 (38.5)	7,453 (67.8)	3,281 (28.8)	2,701 (24.7)
Fatigue, Grade 3[d]	121 (1.1)	1,178 (10.7)	83 (0.7)	88 (0.8)
Fatigue, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache	4,028 (35.3)	6,929 (63.0)	3,303 (29.0)	2,775 (25.4)
Headache, Grade 3[f]	220 (1.9)	559 (5.1)	163 (1.4)	132 (1.2)
Myalgia	2,700 (23.7)	6,789 (61.7)	1,625 (14.3)	1,425 (13.0)
Myalgia, Grade 3[d]	74 (0.6)	1,116 (10.1)	38 (0.3)	42 (0.4)
Arthralgia	1,892 (16.6)	5,010 (45.6)	1,327 (11.6)	1,180 (10.8)
Arthralgia, Grade 3[d]	47 (0.4)	650 (5.9)	30 (0.3)	37 (0.3)
Arthralgia, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills	1,050 (9.2)	5,357 (48.7)	730 (6.4)	662 (6.1)
Chills, Grade 3[g]	17 (0.1)	164 (1.5)	8 (<0.1)	15 (0.1)
Nausea/vomiting	1,068 (9.4)	2,355 (21.4)	908 (8.0)	807 (7.4)
Nausea/vomiting, Grade 3[h]	6 (<0.1)	11 (0.1)	8 (<0.1)	8 (<0.1)
Fever	102 (0.9)	1,909 (17.4)	37 (0.3)	38 (0.3)
Fever, Grade 3[i]	10 (<0.1)	185 (1.7)	1 (<0.1)	2 (<0.1)

	SPIKEVAX		Placebo[a]	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=11,000) n (%)	**Dose 1** (N=11,402) n (%)	**Dose 2** (N=10,929) n (%)
Fever, Grade 4[j]	4 (<0.1)	12 (0.1)	4 (<0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	6,307 (57.3)	1,523 (13.4)	1,254 (11.5)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).
[a] Placebo was a saline solution.
[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[e] Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.
[f] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[g] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[h] Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.
[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Table 2: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 65 Years and Older (Solicited Safety Set, Dose 1 and Dose 2)

	SPIKEVAX		Placebo[a]	
	Dose 1 (N=3,760) n (%)	**Dose 2** (N=3,691) n (%)	**Dose 1** (N=3,749) n (%)	**Dose 2** (N=3,649) n (%)
Local Adverse Reactions				
Pain	2,780 (73.9)	3,071 (83.2)	482 (12.9)	438 (12.0)
Pain, Grade 3[b]	50 (1.3)	100 (2.7)	32 (0.9)	19 (0.5)
Axillary swelling/tenderness	231 (6.1)	315 (8.5)	155 (4.1)	97 (2.7)
Axillary swelling/tenderness, Grade 3[b]	12 (0.3)	21 (0.6)	14 (0.4)	8 (0.2)
Swelling (hardness) ≥25 mm	169 (4.5)	408 (11.1)	23 (0.6)	14 (0.4)
Swelling (hardness), Grade 3[c]	20 (0.5)	72 (2.0)	3 (<0.1)	7 (0.2)
Erythema (redness) ≥25 mm	91 (2.4)	285 (7.7)	23 (0.6)	15 (0.4)
Erythema (redness), Grade 3[c]	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
Systemic Adverse Reactions				

	SPIKEVAX		Placebo[a]	
	Dose 1 (N=3,760) n (%)	**Dose 2** (N=3,691) n (%)	**Dose 1** (N=3,749) n (%)	**Dose 2** (N=3,649) n (%)
Fatigue	1,251 (33.3)	2,154 (58.4)	852 (22.7)	717 (19.6)
Fatigue, Grade 3[d]	30 (0.8)	255 (6.9)	22 (0.6)	20 (0.5)
Headache	922 (24.5)	1,708 (46.3)	723 (19.3)	652 (17.9)
Headache, Grade 3[e]	53 (1.4)	107 (2.9)	34 (0.9)	33 (0.9)
Myalgia	742 (19.7)	1,740 (47.2)	444 (11.9)	399 (10.9)
Myalgia, Grade 3[d]	17 (0.5)	205 (5.6)	9 (0.2)	10 (0.3)
Arthralgia	618 (16.4)	1,293 (35.1)	457 (12.2)	399 (10.9)
Arthralgia, Grade 3[d]	13 (0.3)	125 (3.4)	8 (0.2)	7 (0.2)
Chills	201 (5.3)	1,143 (31.0)	148 (4.0)	151 (4.1)
Chills, Grade 3[f]	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194 (5.2)	439 (11.9)	167 (4.5)	134 (3.7)
Nausea/vomiting, Grade 3[g]	~~45~~ (0.1)	10 (0.3)	~~54~~ (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4[h]	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever	10 (0.3)	367 (9.9)	7 (0.2)	5 (0.1)
Fever, Grade 3[i]	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4[j]	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	1,548 (41.9)	477 (12.7)	331 (9.1)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).

[a] Placebo was a saline solution.

[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.

[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.

[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

[e] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

[f] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

[g] Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

[h] Grade 4 nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.

[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.

[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Solicited local and systemic adverse reactions reported following administration of SPIKEVAX had a median duration of 1 to 3 days.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

In Study 1, 2.3% of participants (vaccine=347, placebo=337~~n=684~~) ~~were positive for~~had evidence of prior SARS-CoV-2 infection at baseline (immunologic or virologic evidence of prior COVID-19 infection [defined as positive RT-PCR test and/or positive Elecsys immunoassay result at Day 1]). Overall, ~~A~~among the ~~those 684~~347 vaccine- participants ~~s (vaccine=347, placebo=337)~~, there were no notable differences in reactogenicity compared to ~~rates of solicited ARs were comparable to~~ the ~~29,491~~14750- vaccine participants who had no evidence of prior SARS-CoV-2 infection at ~~were~~ baseline ~~negative~~ (negative RT-PCR test and negative Elecsys immunoassay result at Day 1).
~~The median duration of follow up after the second injection was 6 months.~~

Unsolicited Adverse Events communicated

Participants were monitored for unsolicited adverse events for up to 28 days following each dose and follow up is ongoing. Serious adverse events and medically attended adverse events will be recorded for the entire study duration (2 years). Among the 30,346 participants who had received at least 1 dose of vaccine or placebo (vaccine=15,184, placebo=15,162), unsolicited adverse events that occurred within 28 days following each vaccination were reported by 31.3% of participants (n=4,752) who received SPIKEVAX and 28.6% of participants (n=4,338) who received placebo.

Lymphadenopathy-related events were reported by 1.7% of vaccine recipients and 0.8% of placebo recipients. These events included lymphadenopathy, lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness at the injected arm.

Hypersensitivity adverse events were reported in 2.2% of vaccine recipients and 1.8% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. Delayed injection site reactions that began >7 days after vaccination were reported in 2.4% of vaccine recipients and 1.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

There were 8 reports of facial paralysis (including Bell's palsy) in the SPIKEVAX group, and 3 in the placebo group. In the 28-day period after vaccination, there were two cases of facial paralysis in the SPIKEVAX group, which occurred on 8 and 22 days, respectively, after vaccination, and one in the placebo group, which occurred 17 days after vaccination. Currently available information on facial paralysis is insufficient to determine a causal relationship with the vaccine.

Commented [A3]: Note to Moderna:
This section is still under review and our comments on this section will be communicated at a later time.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

Serious Adverse Events

During the blinded phase of the study, s~~S~~erious adverse events were reported by ~~1.8~~2.6% (n=~~268~~392) of participants who received SPIKEVAX and ~~1.9~~2.8% (n=~~292~~427) of participants who received placebo.

Commented [A4]: Moderna: Please confirm these are correct: SAEs in participants (n and %) who received SPIKEVAX vs placebo in Part A (blinded safety phase).

There were three serious adverse events of facial swelling in vaccine and placebo recipients with a history of injection of dermatological fillers. Two cases occurred in the vaccine group with onset of swelling reported 1 and 3 days, respectively, after vaccination, and one case in the placebo group with onset of swelling reported at 7 days after vaccination.

There were no other notable patterns or imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

6.2 Emergency Use Authorization Experience

The following adverse reactions have been identified during emergency use authorization of SPIKEVAX (Moderna COVID-19 Vaccine). Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis
Immune System Disorders: anaphylaxis

~~7 DRUG INTERACTIONS~~

~~There are no data to assess the concomitant administration of SPIKEVAX with other vaccines.~~

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPIKEVAX during pregnancy. Women who are vaccinated with SPIKEVAX during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general

population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on SPIKEVAX administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered ~~a~~ the equivalent of a single human dose of SPIKEVAX ~~(100 mcg)~~ twice prior to mating and twice during gestation. The study revealed no evidence of harm~~s~~ to the fetus due to the vaccine ~~es~~ (*see ~~8.1 Animal Data~~*).

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Data

Animal Data

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing ~~the same quantity of~~ nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of SPIKEVAX was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effect on postnatal development were observed in the study.

Commented [A5]: Comment to Moderna:
Please provide values for the quantity of mRNA-1273 as well as individual/total lipid components used in the 0.2 mL vaccine formulation administered in the developmental toxicity study.

8.2 Lactation

Risk Summary

It is not known whether SPIKEVAX is excreted in human milk. Data are not available to assess the effects of SPIKEVAX on the breastfed infant or on milk production/excretion. ~~Data are not sufficient to assess the effects of SPIKEVAX on the breastfed infant or on milk production/excretion.~~ The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breastfed infant from (name of drug) or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.~~Data~~

~~*Animal Data*~~

~~In a developmental toxicity study of female rats that received a single human dose of SPIKEVAX (100 mcg), transfer of IgG antibodies was observed in pups at lactation day 21.~~

8.4 Pediatric Use

Safety and effectiveness have not been established in persons less than 18 years of age.

8.5 Geriatric Use

Clinical studies of SPIKEVAX included participants 65 years of age and older receiving vaccine

or placebo, and their data contribute to the overall assessment of safety and efficacy. In an ongoing Phase 3 clinical study, 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 91.5% (95% CI 83.2, 95.7) compared to 93.4% (95% CI 91.1, 95.1) in participants 18 to <65 years of age *[see Clinical Studies (14)]*. A lower proportion of participants 65 years of age and older reported solicited local and systemic adverse reactions ~~at a lower rate than~~ compared to ~~subjects~~ participants 18-64 years of age *[*see *Adverse Reactions (6.1)]*.

Commented [A6]: **Comment to Moderna:**
FAS indicates **n=1,398** participants 75 years of age and older. Please reconcile this discrepancy.

11 DESCRIPTION

SPIKEVAX (COVID-19 Vaccine, mRNA) is ~~provided as~~ a sterile white to off-white suspension for intramuscular injection. Each 0.5 mL dose of SPIKEVAX contains 100 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each 0.5 mL dose of ~~the~~ SPIKEVAX also contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose.

SPIKEVAX does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The nucleoside-modified mRNA in the SPIKEVAX is encapsulated ~~formulated~~ in lipid ~~nano~~ particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SPIKEVAX has not been evaluated for carcinogenic, ~~or~~ mutagenic potential, or impairment of male ~~in~~fertility in animals. A developmental toxicity study was conducted in female rats that received a vaccine formulation containing ~~the same quantity of~~ nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of SPIKEVAX. No impact on female fertility was reported ~~-~~ *(see ~~Pregnancy~~ Use in Specific Populations [8.1])*.

14 CLINICAL STUDIES

Study 1 ~~was~~ is an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of SPIKEVAX in participants 18 years of age and older in the United States. Randomization was stratified by age and health risk: 18 to <65 years of age without comorbidities (not at risk for progression to severe COVID-19), 18 to <65 years of age with comorbidities (at risk for progression to severe COVID-19), and 65 years of age and older with or without comorbidities. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable human immunodeficiency virus (HIV) infection. A total of 30,415 participants were randomized equally to receive 2 doses of SPIKEVAX or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 2 years after the second dose.

The primary efficacy analysis population (referred to as the Per-Protocol Set) included 28,451 participants who received two doses (at 0 and 1 month) of either SPIKEVAX (n=14,287) or placebo (n=14,164), and had a negative baseline SARS-CoV-2 status. In the Per-Protocol Set, 47.5% of participants were female, 19.7% were Hispanic or Latino; 79.7% were White, 9.7% were African American, 4.7% were Asian, and 2.0% other races. The median age of participants was 53 years (range 18-95) and 25.4% of participants were 65 years of age and older. Of the study participants in the Per-Protocol Set, 18.5% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection) regardless of age. There were no notable differences in demographics or pre-existing medical conditions between participants who received SPIKEVAX and those who received placebo.

Commented [A7]: Comment to Moderna
CSR indicates **22.8%** of study participants in the PPS exhibit increased risk of severe COVID-19 due to at least 1 pre-existing condition (regardless of age). Please reconcile this discrepancy.

The population for the vaccine efficacy analysis included participants 18 years of age and older who were enrolled from July 27, 2020 and followed for the development of COVID-19 through the data cutoff of March 26, 2021 or the participant decision visit for treatment unblinding, whichever was earlier. The median length of follow up for participants in the blinded placebo-controlled phase of ~~in~~ the study was ~~6~~ 4 months following Dose 2.

SARS-CoV-2 identified in the majority COVID-19 cases in this study were sequenced to be the B.1.2 variant. Additional SARS CoV-2 variants identified in this study included B.1.427/B.1.429 (Epsilon), P.1 (Gamma), and P.2 (Zeta); the number of cases were too small to assess for vaccine efficacy against these variants.

Commented [A8]: Comment to Moderna
Please verify the terminology describing the sequencing data.

Efficacy Against COVID-19

COVID-19 was defined based on the following criteria: The participant must have experienced at least two of the following systemic symptoms: fever (≥38ºC / ≥100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have

experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

~~SPIKEVAX significantly reduced the risk of COVID-19 infection compared to placebo.~~ There were 55 COVID-19 cases in the SPIKEVAX group and 744 cases in the placebo group, with a vaccine efficacy of 93.2% (95% confidence interval of 91.0% to 94.8%) (Table 3). ~~Protection was demonstrated starting 14 days after Dose 2 with duration of protection through 6 months.~~

Table 3: ~~Primary~~ Vaccine Efficacy ~~Analysis:~~Against COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

SPIKEVAX			Placebo			
Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	% Vaccine Efficacy (95% CI)†
14,287	55	9.6~~599~~	14,164	744	136.6~~33~~	93.2 (91.0, 94.8)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

The subgroup analyses of vaccine efficacy are presented in Table 4.

Table 4: Subgroup Analyses of Vaccine Efficacy: COVID-19* Cases Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

Age Subgroup (Years)	SPIKEVAX			Placebo			% Vaccine Efficacy (95% CI)†
	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
18 to <65	10,661	46	10.7~~42~~	10,569	644	15~~98~~.0~~958~~	93.4 (91.1, 95.1)
≥65	3,626	9	6.2~~17~~	3,595	100	71.7~~44~~	91.5 (83.2, 95.7)

65 to <75	2,990	9	7.546	2,898	81	71.980	89.7 (79.6, 94.9)
≥75	636	0	0.000	697	19	70.755	100.0 (NE, 100.0)

NE = Not estimable
* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

Severe COVID-19 was defined based on confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or PaO2/FIO2 <300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death.

Among all participants in the Per-Protocol Set analysis, which included COVID-19 cases confirmed by an adjudication committee, 2 cases of severe COVID-19 were reported in the SPIKEVAX group compared with 106 cases reported in the placebo group, with a vaccine efficacy of 98.2% (95% confidence interval of 92.8% to 99.6%) (Table 5).

Table 5: Vaccine Efficacy ~~Analysis:~~Against Severe COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

SPIKEVAX			Placebo			
Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	% Vaccine Efficacy (95% CI)†
14,287	2	0.3~~49~~	14,164	106	19.1~~12~~	98.2 (92.8, 99.6)

* Severe COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or

PaO2/FIO2 <300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death. Cases starting 14 days after Dose 2.

† VE and 95% CI from the stratified Cox proportional hazard model.

Prevention of asymptomatic SARS-CoV-2 infection was analyzed using the Per-Protocol Set and identified by seroconversion against nucleocapsid protein (by the Elecsys immunoassay) and/or detection by RT-PCR in the absence of symptoms.

Among all participants in the Per-Protocol Set analysis, 214 cases of asymptomatic SARS-CoV-2 infection were reported in the SPIKEVAX group compared with 498 cases reported in the placebo group, with a vaccine efficacy of 63.0% (95% confidence interval of 56.6% to 68.5%) (Table 6).

Table 6: Efficacy Analysis: Asymptomatic SARS-CoV-2 Infection* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 – Per-Protocol Set

SPIKEVAX		Placebo		
Participants (N)	**Asymptomatic SARS-CoV-2 Infection Cases (n)**	**Participants (N)**	**Asymptomatic SARS-CoV-2 Infection Cases (n)**	**% Vaccine Efficacy (95% CI)†**
14,287	214	14,164	498	63.0 (56.6, 68.5)

* Asymptomatic SARS-CoV-2 infection: Absence of COVID-19 symptoms from either the primary efficacy endpoint case definition or secondary definition of COVID-19. Primary endpoint case definition = at least two of the following symptom: fever (≥38ºC / ≥100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR). Secondary definition = presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea]) and at least one of either seroconversion at scheduled visits when blood samples for immunogenicity were collected or by RT-PCR at scheduled visits. Cases starting 14 days after Dose 2.

† VE and 95% CI from the Fine and Gray's sub-distribution hazard model.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIKEVAX ~~Suspension for Intramuscular Injection~~ is supplied in m~~M~~ultiple-d~~D~~ose v~~V~~ials ~~are supplied~~ as follows:

NDC 80777-100-99 Carton of 10 multiple-dose vials, each vial containing 5.5 mL
NDC 80777-100-98 Carton of 10 multiple-dose vials, each vial containing 7.5 mL

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Commented [A9]: Comment to Moderna
This section is still under review and our comments on this section will be communicated separately.

~~During storage, minimize exposure to room light.~~

Frozen Storage

Store frozen between -50°C to -15°C (-58°F to 5°F). ~~Store in the original carton to protect from light.~~

Storage after Thawing

- Storage at 2°C to 8°C (36°F to 46°F):
  - Vials may be stored refrigerated between 2°C to 8°C (36°F to 46°F) for up to 30 days prior to first use.
  - Vials should be discarded 12 hours after the first puncture.
- Storage at 8°C to 25°C (46°F to 77°F):
  - Vials may be stored between 8°C to 25°C (46°F to 77°F) for a total of 24 hours.
  - Vials should be discarded 12 hours after the first puncture.
  - Total storage at 8°C to 25°C (46°F to 77°F) must not exceed 24 hours.

Do not refreeze once thawed.

- ~~Vials may be stored refrigerated between 2°C to 8°C (36°F to 46°F) for up to 30 days prior to first use.~~
- ~~Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.~~

~~After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.~~

Thawed vials can be handled in room light conditions.

~~Do not refreeze once thawed.~~

Transportation of Thawed Vials at 2° to 8°C (36° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

17 PATIENT COUNSELING INFORMATION

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling. ~~(Information for Recipients and Caregivers).~~

Inform the vaccine recipient or caregiver of the potential benefits and risks of vaccination~~immunization~~ with SPIKEVAX.

~~Inform the vaccine recipient or caregiver that SPIKEVAX does not contain SARS-CoV-2 and~~

Commented [A10]: Comment to Moderna:
Please include Fahrenheit/Celsius designation for all values when listing temperature ranges and assure notation is consistent throughout the package insert.

~~cannot give them COVID-19. SPIKEVAX stimulates the immune system to produce antibodies that protect against COVID-19.~~

Inform the vaccine recipient or caregiver of the importance of completing the two dose vaccination series. ~~need for two doses administered 1 month apart. The full effect of the vaccine is generally achieved approximately 2 weeks after vaccination.~~

Instruct the vaccine recipient or caregiver to report any ~~severe or unusual~~ adverse events~~reactions~~ to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers.hhs.gov.

There is a pregnancy exposure registry for SPIKEVAX. Encourage individuals~~women~~ who receive SPIKEVAX around the time of conception or while pregnant to enroll in the pregnancy exposure registry. Pregnant individuals ~~women~~ can enroll in the pregnancy exposure registry by calling 1-866-MODERNA (1-866-663-3762).

Prior to administering the vaccine, p~~P~~rovide the vaccine recipient the Vaccine Information Fact Sheet for Recipients and Caregivers ~~Statements~~ about SPIKEVAX (COVID-19 Vaccine, mRNA) and the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) for Use in Individuals 18 Years of Age and Older. ~~prior to immunization~~. The Vaccine Information Fact Sheet for Recipients and Caregivers is available at https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-recipients.pdf
~~These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).~~
This product's labeling may have been updated. For the most recent prescribing information, please visit https://dailymed.nlm.nih.gov/dailymed/

Manufactured for:
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Patent(s): www.modernatx.com/patents
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