

**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  
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 is administered intramuscularly as a series of two doses (0.5 mL each) one month apart. (2.3)

**DOSAGE FORMS AND STRENGTHS**  
Suspension for injection. A single dose is 0.5 mL.

**CONTRAINDICATIONS**  
Severe allergic reaction (e.g., anaphylaxis) to any component of SPIKEVAX. (4)

**WARNINGS AND PRECAUTIONS**

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. (5.2)

**ADVERSE REACTIONS**  
• In clinical studies of participants 18 through 64 years, the most commonly reported (>10%) adverse reactions 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%). (6.1)  
• In clinical studies of participants 65 years of age and older, the most commonly reported (>10%) adverse reactions 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)

To report SUSPECTED ADVERSE REACTIONS, contact ModernaTX, Inc. at 1-866-663-3762 or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.

See 17 for PATIENT COUNSELING INFORMATION

4412/2021

Revised:

**Commented [A1]:** SPONSOR COMMENT: Moderna has accepted CBER's comments received by email Dec. 9, 2021, and responded as noted in the document with tracked changes and comments.

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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 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.
- Thaw each vial before use following the instructions below.

Vial	Thaw in Refrigerator	Thaw at Room Temperature
<b>5.5 mL</b>	Thaw between 2°C to 8°C (36°F to 46°F) for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw between 15°C to 25°C (59°F to 77°F) for 1 hour.
<b>7.5 mL</b>	Thaw between 2°C to 8°C (36°F to 46°F) for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw between 15°C to 25°C (59°F 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.
- SPIKEVAX is a white to off-white suspension. It may contain white or translucent product-related particulates. Do not administer if vaccine is discolored or contains other particulate matter.
- 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°C to 25°C (36°F 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

Administer a single 0.5 mL dose.

## 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 injection. A single dose is 0.5 mL.

## 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>).

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### 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.

### 5.4 Altered Immunocompetence

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

### 5.5 Limitations of Vaccine Effectiveness

SPIKEVAX may not protect all vaccine recipients.

## 6 ADVERSE REACTIONS

In clinical studies, the most commonly reported ( $\geq 10\%$ ) 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 ( $\geq 10\%$ ) 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 an ongoing 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) or placebo (n=15,162) (Study 1, NCT04470427). Upon issuance of the Emergency Use Authorization (December 18, 2020) for Moderna COVID-19 Vaccine (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, 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 <sup>a</sup>	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=11,000) n (%)	Dose 1 (N=11,402) n (%)	Dose 2 (N=10,929) n (%)
<b>Local Adverse Reactions</b>				
Pain	9,908 (86.9)	9,893 (89.9)	2,183 (19.1)	2,048 (18.7)
Pain, Grade 3 <sup>b</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>c</sup>	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)
<b>Systemic Adverse Reactions</b>				
Fatigue	4,385	7,453	3,281	2,701

	SPIKEVAX		Placebo <sup>a</sup>	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=11,000) n (%)	Dose 1 (N=11,402) n (%)	Dose 2 (N=10,929) n (%)
	(38.5)	(67.8)	(28.8)	(24.7)
Fatigue, Grade 3 <sup>d</sup>	121 (1.1)	1,178 (10.7)	83 (0.7)	88 (0.8)
Fatigue, Grade 4 <sup>e</sup>	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 <sup>f</sup>	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 <sup>d</sup>	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 <sup>d</sup>	47 (0.4)	650 (5.9)	30 (0.3)	37 (0.3)
Arthralgia, Grade 4 <sup>e</sup>	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 <sup>g</sup>	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 <sup>h</sup>	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 <sup>i</sup>	10 (<0.1)	185 (1.7)	1 (<0.1)	2 (<0.1)
Fever, Grade 4 <sup>j</sup>	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).

<sup>a</sup> Placebo was a saline solution.

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

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

<sup>d</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>e</sup> Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.

<sup>f</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>g</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>h</sup> Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

<sup>i</sup> Grade 3 fever: Defined as  $\geq 39.0^{\circ} - \leq 40.0^{\circ}C / \geq 102.1^{\circ} - \leq 104.0^{\circ}F$ .

<sup>j</sup> Grade 4 fever: Defined as  $>40.0^{\circ}C / >104.0^{\circ}F$ .

**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 <sup>a</sup>	
	Dose 1 (N=3,760) n (%)	Dose 2 (N=3,691) n (%)	Dose 1 (N=3,749) n (%)	Dose 2 (N=3,649) n (%)
<b>Local Adverse Reactions</b>				
Pain	2,780 (73.9)	3,071 (83.2)	482 (12.9)	438 (12.0)
Pain, Grade 3 <sup>b</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>c</sup>	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
<b>Systemic Adverse Reactions</b>				
Fatigue	1,251 (33.3)	2,154 (58.4)	852 (22.7)	717 (19.6)
Fatigue, Grade 3 <sup>d</sup>	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 <sup>e</sup>	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 <sup>d</sup>	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 <sup>d</sup>	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 <sup>f</sup>	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194	439	167	134

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	SPIKEVAX		Placebo <sup>a</sup>	
	Dose 1 (N=3,760) n (%)	Dose 2 (N=3,691) n (%)	Dose 1 (N=3,749) n (%)	Dose 2 (N=3,649) n (%)
	(5.2)	(11.9)	(4.5)	(3.7)
Nausea/vomiting, Grade 3 <sup>e</sup>	4 (0.1)	10 (0.3)	5 (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4 <sup>h</sup>	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 <sup>i</sup>	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4 <sup>j</sup>	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).

<sup>a</sup> Placebo was a saline solution.

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

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

<sup>d</sup> Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

<sup>e</sup> Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

<sup>f</sup> Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

<sup>g</sup> Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

<sup>h</sup> Grade 4 nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.

<sup>i</sup> Grade 3 fever: Defined as  $\geq 39.0^{\circ}$  –  $\leq 40.0^{\circ}$ C /  $\geq 102.1^{\circ}$  –  $\leq 104.0^{\circ}$ F.

<sup>j</sup> Grade 4 fever: Defined as  $>40.0^{\circ}$ C /  $>104.0^{\circ}$ 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) had evidence of prior SARS-CoV-2 infection at baseline (immunologic or virologic evidence of prior SARS-CoV-2 infection [defined as positive RT-PCR test and/or positive Elecsys immunoassay result at Day 1]). Overall, among the 347 vaccine participants, there were no notable differences in reactogenicity compared to the 14,750 vaccine participants who had no evidence of prior SARS-CoV-2 infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1).

#### Unsolicited Adverse Events

Participants were monitored for unsolicited adverse events for 28 days following each dose. 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 any 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.

During the 28-day follow up period following any dose, 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.

In the blinded portion of the study, 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.

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, serious adverse events were reported by 1.8% (n=268) of participants who received SPIKEVAX and 1.9% (n=292) of participants who received placebo.

There were three serious adverse events of angioedema/facial swelling in the vaccine group in recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1-2 days after the second dose and was likely related to 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

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**Commented [A2]:** FDA COMMENT: **CBER COMMENT (12/10/2021):**

This section may be revised pending review of your response to IR #30 regarding unsolicited adverse events.

SPONSOR RESPONSE: Moderna acknowledges that additional changes could be forthcoming.

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

Nervous System Disorders: syncope

## **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 was performed in female rats administered the equivalent of a single human dose of SPIKEVAX twice prior to mating and twice during gestation. The study revealed no evidence of harm to the fetus due to the vaccine (*see Animal Data*).

#### Data

##### *Animal Data*

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients that are included in a 0.5 mL 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.

### **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. The

developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPIKEVAX and any potential adverse effects on the breastfed infant from SPIKEVAX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

#### **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 a Phase 3 clinical study, 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,398) 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 compared to participants 18-64 years of age [see *Adverse Reactions (6.1)*].

### **11 DESCRIPTION**

SPIKEVAX (COVID-19 Vaccine, mRNA) is 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 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 SPIKEVAX is encapsulated in lipid 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, mutagenic potential, or impairment of male fertility in animals. A developmental toxicity study was conducted in female rats that received a vaccine formulation containing 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 Use in Specific Populations [8.1]*).

## 14 CLINICAL STUDIES

Study 1 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, 22.8% 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.

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~~-follow-up for participants in the blinded placebo-controlled phase of the study was 4 months following Dose 2.

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 ( $\geq 38^{\circ}\text{C}$  /  $\geq 100.4^{\circ}\text{F}$ ), 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.

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).

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

**Commented [A3]:** SPONSOR COMMENT: Moderna has combined Tables 3 and 4 and added the symptoms in the footnote, per CBER's request.

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	
$\geq 18$	14,287	55	9.6	14,164	744	136.6	93.2 (91.0, 94.8)
18 to <65	10,661	46	10.7	10,569	644	159.0	93.4 (91.1, 95.1)
$\geq 65$	3,626	9	6.2	3,595	100	71.7	91.5 (83.2, 95.7)

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	
14,287	55	9.6	14,164	744	136.6	93.2 (91.0, 94.8)

\* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms (fever [ $\geq 38^{\circ}\text{C}$  /  $\geq 100.4^{\circ}\text{F}$ ], chills, myalgia, headache, sore throat, new olfactory and taste disorder[s]) or one respiratory symptom (cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia). Cases starting 14 days after Dose 2.

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

SARS-CoV-2 identified in the majority of 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). Representation of identified variants among cases in the vaccine versus placebo recipients did not suggest decreased vaccine effectiveness against these variants.

**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	10,569	644	159.0	93.4 (91.1, 95.1)
≥65	3,626	9	6.2	3,595	100	71.7	91.5 (83.2, 95.7)

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  $\geq 30$  per minute, heart rate  $\geq 125$  beats per minute, SpO<sub>2</sub>  $\leq 93\%$  on room air at sea level or PaO<sub>2</sub>/FIO<sub>2</sub>  $< 300$  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 54).

**Table 54: Vaccine Efficacy 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			% Vaccine Efficacy (95% CI)†
Participants (N)	Severe COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	Severe COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
14,287	2	0.3	14,164	106	19.1	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  $\geq 30$  per minute, heart rate  $\geq 125$  beats per minute, SpO<sub>2</sub>  $\leq 93\%$  on room air at sea level or PaO<sub>2</sub>/FIO<sub>2</sub>  $< 300$  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.

In an exploratory analysis, occurrence of asymptomatic SARS-CoV-2 infection was assessed using the Per-Protocol Set. Asymptomatic SARS-CoV-2 infection was defined as having a positive scheduled serology test based on binding antibody against SARS-CoV-2 nucleocapsid protein as measured by the Roche Elecsys immunoassay (N-serology) and/or a positive RT-PCR test for SARS-CoV-2, in the absence of any reported COVID-19 symptoms included as part of the primary efficacy endpoint case definition (described above) or symptoms included in the secondary COVID-19 endpoint case definition (fever  $\geq 38^{\circ}\text{C}$  /  $\geq 100.4^{\circ}\text{F}$ , chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, or diarrhea) at any time during the study. To assess for asymptomatic infection starting 14 days after Dose 2, all participants had scheduled blood draws for N-serology collected at the 1 month post-Dose 2 visit and the 6 months post-Dose 2 visit (if still blinded to treatment arm), and scheduled N-serology and nasopharyngeal swab for RT-PCR collection at the Participant Decision Visit for treatment unblinding.

In the Per-Protocol Set, [#14,287](#) participants in the SPIKEVAX group and [#14,164](#) participants in the placebo group had N-serology and/or RT-PCR results available from one or more of the pre-specified timepoints listed above. Among these participants, there were [180-210](#) cases of asymptomatic SARS-CoV-2 infection in the SPIKEVAX group compared with [399-487](#) cases in the placebo group, [with a vaccine efficacy of 62.9% \(95% confidence interval of 56.4% to 68.5%\)](#). Limitations of this analysis include the [infrequent](#) scheduled assessments for serology and PCR testing, which may not have captured all cases of asymptomatic infections which occurred during the study.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

SPIKEVAX is supplied in multiple-dose vials as follows:  
Draft Dec. 14, 2021

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**Commented [A4]:** SPONSOR COMMENT: Moderna proposes to use the analysis provided in IR#27 Table 1-3, submitted Dec. 9, 2021. The definition of asymptomatic infections per protocol was that a microbiological or immunological endpoint was met (Elecsys seropositivity or positive RT-PCR) in the absence of any COVID-19 symptoms 14 days prior to or 14 days subsequent to the test date. Moderna proposes to retain the pre-planned per protocol definition and analysis of asymptomatic cases since it retains a defined association of symptoms with the laboratory endpoint. Various sensitivity analyses were performed and resulted in consistent efficacy estimates. Seroreconversion by Elecsys occurs within one or two weeks after infection – any infection detected by that methodology is antecedent. For RT-PCR positivity, it is Moderna’s opinion that the +/- 14-day window is conservative. The problem with including further respiratory symptoms is that the case definition becomes increasingly unspecific. Over an observation period extending to two years, there is a high probability that most participants would at some point show respiratory symptoms without necessarily being associated with a specific SARS-CoV-2 infection. Moderna furthermore proposes to retain an efficacy statement for asymptomatic infection since it was a pre-specified endpoint, and it provides important information on the benefit and limitations of vaccination.

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.

#### Frozen Storage

Store frozen between -50°C to -15°C (-58°F to 5°F).

#### 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.**

Thawed vials can be handled in room light conditions.

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

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

## **17 PATIENT COUNSELING INFORMATION**

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling.

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

Inform the vaccine recipient or caregiver of the importance of completing the two dose vaccination series.

Instruct the vaccine recipient or caregiver to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

Draft Dec. 14, 2021

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

Prior to administering the vaccine, provide the vaccine recipient the Vaccine Information Fact Sheet for Recipients and Caregivers 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. The Vaccine Information Fact Sheet for Recipients and Caregivers is available at <https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-recipients.pdf>.

This product's labeling may have been updated. For the most recent prescribing information, please visit <https://dailymed.nlm.nih.gov/dailymed/>.

Manufactured for:  
Moderna US, Inc.  
Cambridge, MA 02139

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SPIKEVAX is a trademark of ModernaTX, Inc.  
Patent(s): [www.modernatx.com/patents](http://www.modernatx.com/patents)

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