

DRAFT Template for Full EUA Prescribing Information for COVID-19 Vaccines (Contents section list based on Remdesivir Full EUA Prescribing Information)

Commented [A1]: Moderna: We request that you use Section numbers as specified in the template provided by FDA on November 10, 2020. Please do not reassign section numbers to account for omitted sections

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

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11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Moderna COVID-19 Vaccine during pregnancy. Women who are vaccinated with Moderna COVID-19 Vaccine 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 US 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. No adequate and well-controlled studies of Moderna COVID-19 Vaccine use in pregnant women have been conducted. There are no completed developmental toxicity studies of Moderna COVID-19 Vaccine in animals. Therefore, use of Moderna COVID-19 Vaccine is not recommended in pregnant women. Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

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11.2 Lactation

Risk Summary

~~It is not known whether Moderna COVID-19 Vaccine is excreted in human milk. Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion. Therefore, use of Moderna COVID-19 Vaccine is not recommended in breastfeeding mothers.~~

11.3 Pediatric Use

~~Emergency Use Authorization of Moderna COVID-19 Vaccine does not include use in individuals younger than 18 years of age. Safety and effectiveness have not been assessed in persons less than 18 years of age.~~

11.4 Geriatric Use

~~Clinical studies of Moderna COVID-19 Vaccine included participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. In an ongoing Phase 3 clinical study, xx% (n=xxxx) of participants were 65 years of age and older and xx% (n=xxxx) of participants were 75 years of age and older. the safety and efficacy of Moderna COVID-19 Vaccine was assessed in individuals 18 years of age and older, including 3527 subjects 65 years of age and older. In an interim analysis, no overall differences in safety or effectiveness were observed between these subjects and younger subjects. [see Clinical Trials Experience (6.1, Clinical Trial Results and Supporting Data for EUA (13))]. In an interim analysis, the efficacy of Moderna COVID-19 Vaccine was consistent between older subjects (≥65 years) and younger subjects (18-64 years). [see Full EUA Prescribing Information, Clinical Trial Results and Supporting Data for EUA (13)] [Section 2.5.4.2.3] Subjects 65 years of age and older reported solicited local and systemic adverse reactions at a lower rate than subjects 18-64 years of age. [see Full EUA Prescribing Information, Clinical Trials Experience (6.1)]~~

Commented [A2]: Moderna, please insert percentages and number of subjects for these 2 age groups.

13 ~~PRODUCT DESCRIPTION~~

Moderna COVID-19 Vaccine is a ~~sterile~~ lipid nanoparticle (LNP) suspension for intramuscular injection comprised of a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized Spike glycoprotein(S) of SARS-CoV-2 virus and four lipids. The synthetic mRNA is manufactured in a cell-free, in vitro transcription reaction and formulated with SM-102 (a proprietary ionizable lipid), PEG2000-DMG, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) to form the mRNA/lipid nanoparticles.

Moderna COVID-19 Vaccine is provided as a ~~sterile~~ suspension for intramuscular injection and is white to off-white in appearance. Each 0.5 mL dose contains 100 mcg RNA and a total lipid content of 1.93 mg in tris buffer (0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride), 0.043 mg acetic acid, 0.12 mg sodium acetate, and 43.5 mg sucrose.

Moderna COVID-19 Vaccine does not contain any preservatives, ~~antibiotics, adjuvants, or human or animal derived materials.~~ The vial stopper does not contain natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Moderna COVID-19 Vaccine encodes for the pre-fusion stabilized Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection.

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T cell and B cell responses. The immune response to the Spike protein results in functional Ab and T cell responses and in the generation of memory immune cell populations.

The mRNA in the Moderna COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which may contribute to protection against COVID-19.

The specific mechanism of protection for the SARS-CoV-2 virus remains under investigation.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Moderna COVID-19 Vaccine is being evaluated in an ongoing ^A Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older is ongoing conducted in the United States in subjects aged 18 years and older who were at increased risk of COVID-19 disease (NCT04470427). Randomization was stratified by age and health risk: 18 to <65 years of age not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and 65 years of age and older. In addition, pre-specified cohorts of subjects who were either ≥65 years of age or 18 to <65 years of age with comorbid medical conditions were included. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. 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 30,418 participants 18 years of age and older were randomized equally to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 24 months after the second dose. A total of 30,350 subjects were followed for a median of 78 days (range: 0-108) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per-Protocol Set), included 27,817 subjects who received two doses (at 0 and 1 month) of either Moderna COVID-19 Vaccine
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(n=13,934) or placebo (n=13,883), had a negative baseline SARS-CoV-2 status, and did not develop confirmed COVID-19 within 14 days after the second dose. In the Per-Protocol Set, 47.4% were female, 20% were Hispanic or Latino; 79.4% were white, 9.7% were African American, 4.7% were Asian, and 3.1% other races. The study population was 52.6% male, 20% Hispanic or Latino, and 9.7% African American. The median age of subjects was 53 years (range 18-95) and 25.3% of participants were 65 years of age and older. Of the study participants in the Per Protocol Set, 26.322.3% 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). There were no notable differences in demographics or pre-existing medical conditions between participants who received Moderna COVID-19 Vaccine or placebo.

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 ($\geq 38^{\circ}\text{C}$), 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 ~~confirmed-adjudicated~~ by ~~Polymerase Chain Reaction (PCR)~~ and ~~by~~ a Clinical Adjudication Committee.

At the time of the interim analysis, the median length of follow up for efficacy for participants in the study was 7 weeks post dose 2. There were 5 COVID-19 cases in the Moderna COVID-19 Vaccine group and 90 cases in the placebo group, with a vaccine efficacy of 94.5% (95% confidence interval of 86.5% to 97.8%).

~~An interim analysis was conducted on confirmed COVID-19 cases starting 14 days after Dose 2 of Moderna COVID-19 Vaccine or placebo (Table 2).~~

Table 2: Interim Primary Efficacy Analysis: ~~Confirmed COVID-19*~~ ~~Regardless of Severity~~ Starting 14 Days After Dose 2 ~~per Adjudication Committee Assessments~~– Per-Protocol Set

Age Group (Years)	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI) [†]
	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall (≥ 18)	13,934	5	1.840	13,883	90	33.365	94.5 (86.5, 97.8) [‡]
18 to <65	10,407	5	2.504	10,384	75	37.788	93.4 (83.7, 97.3)
≥ 65	3,527	0	--	3,499	15	21.046	100

* 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

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‡ The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0049 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

The subgroup analyses of vaccine efficacy are presented in Table 3.

Table 3: Interim Subgroup Analyses of Vaccine Efficacy: COVID-19 Cases Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per- Protocol Set

Subgroup	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)†
	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall	3,116	1	1.604	3,075	24	39.177	95.9 (69.7, 99.4)
High risk*							
High risk* 18 to <65	2,098	1	2.428	2,061	18	44.673	94.6 (59.4, 99.3)
Not high risk* 18 to <65	8,309	4	2.524	8,323	57	36.034	93.0 (80.8, 97.5)
Females	6,661	3	2.271	6,514	45	34.991	93.5 (79.2, 98.0)
Males	7,273	2	1.433	7,369	45	31.883	95.5 (81.5, 98.9)

* Subjects 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

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

Commented [A4]: Moderna please include only analyses of age groups 18-65 and 65 and above and delete the other information.

Efficacy Against Severe COVID-19

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 subjects in the Per-Protocol Set interim analysis, no cases of severe COVID-19 were reported in the Moderna COVID-19 Vaccine group compared with 11 cases reported in the placebo group (incidence rate 4.072 per 1,000 person-years). ~~Vaccine efficacy against severe~~

COVID-19 was 100%.

Additional Efficacy Analyses

An interim subgroup analysis was conducted on confirmed COVID-19 cases starting 14 days after Dose 2 of Moderna COVID-19 Vaccine or placebo in high-risk subjects, females, and males (Table 3).

Table 3: Interim Subgroup Analyses of Vaccine Efficacy: COVID-19 Cases 14 Days After Dose 2 per Adjudication Committee Assessments (Primary Efficacy Analysis Set) Per Protocol Set

Subgroup	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI) [†]
	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall high-risk [‡]	3,116	1	1.604	3,075	24	39.177	95.9 (69.7, 99.4)
High-risk [‡] 18 to <65	2,098	1	2.428	2,061	18	44.673	94.6 (59.4, 99.3)
Not high-risk [‡] 18 to <65	8,309	4	2.524	8,323	57	36.034	93.0 (80.8, 97.5)
Females	6,661	3	2.271	6,514	45	34.991	93.5 (79.2, 98.0)
Males	7,273	2	1.433	7,369	45	31.883	95.5 (81.5, 98.9)

[‡] Subjects 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

[†] VE and 95% CI from the stratified Cox proportional-hazard model

19 HOW SUPPLIED/STORAGE AND HANDLING

Moderna COVID-19 Vaccine is supplied as a multiple-dose vial containing ~~a maximum of~~ 10 doses of 0.5 mL each.

Each carton of Moderna COVID-19 Vaccine contains 10 multiple-dose vials (NDC 80777-273-99).

Store frozen between -25° to -15°C (-13° to 5°F). Store in the original carton to protect from light. Do not store on dry ice or below -40°C (-40°F).

Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Do not refreeze.

Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. Do not

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refreeze.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Discard vial after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the ~~See~~ Fact Sheet for Recipients and Caregivers.

21 CONTACT INFORMATION

If you have questions, please contact:

Moderna

1-866-MODERNA (1-866-663-3762)

medinfo@modernatx.com

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

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