Vaccines and Related Biological Products Advisory Committee Meeting

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U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety of Moderna COVID-19 Vaccine in Children 6 Months through 5 Years of Age *Emergency Use Authorization Amendment*

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June 15, 2022

Outline

Background

P204 Study Design

Immunogenicity Data

Descriptive Efficacy Data

Safety Data

Pharmacovigilance

Summary of Benefits and Risks

Background

Moderna COVID-19 vaccine

- SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA
- Formulated in lipid particles
- Licensed as Spikevax on January 31, 2022 for individuals 18 years of age and older

Data included in EUA Request
6 Months through 5 Years

Study	Description	Data cutoff dates
P204	Phase 2/3, three-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children 6 months to less than 12 years	Blinded follow-up through the data cutoff of February 21, 2022 for children 6 months through 5 years of age, or the date of a participant's unblinding (whichever is earlier).

Pediatric Studies

	6-23 months	2-5 years	6-11 years	12-17 years
Dose/regimen:	25 µg Two doses (0, 28 days)	25 µg Two doses (0, 28 days)	50 µg Two doses (0, 28 days)	100 µg Two doses (0, 28 days)
Pediatric Study	P204	P204	P204	P203
mRNA-1273 recipients	1,761	3,031	3,007	2,486
Immunobridging to 18-25-year-old participants in P301 (GMC and seroresponse)	✓	✓	✓	✓
Descriptive efficacy	✓	✓	✓	✓

P204 Study Design

Part 1: Open-label, dose-escalation, age de-escalation phase

6-23 months (n= 150)

mRNA-1273 **25 µg**

Dose 1 — 28 days — Dose 2

2-5 years (n= 224)

mRNA-1273 **25 µg** (n=75)

Dose 1 — 28 days — Dose 2

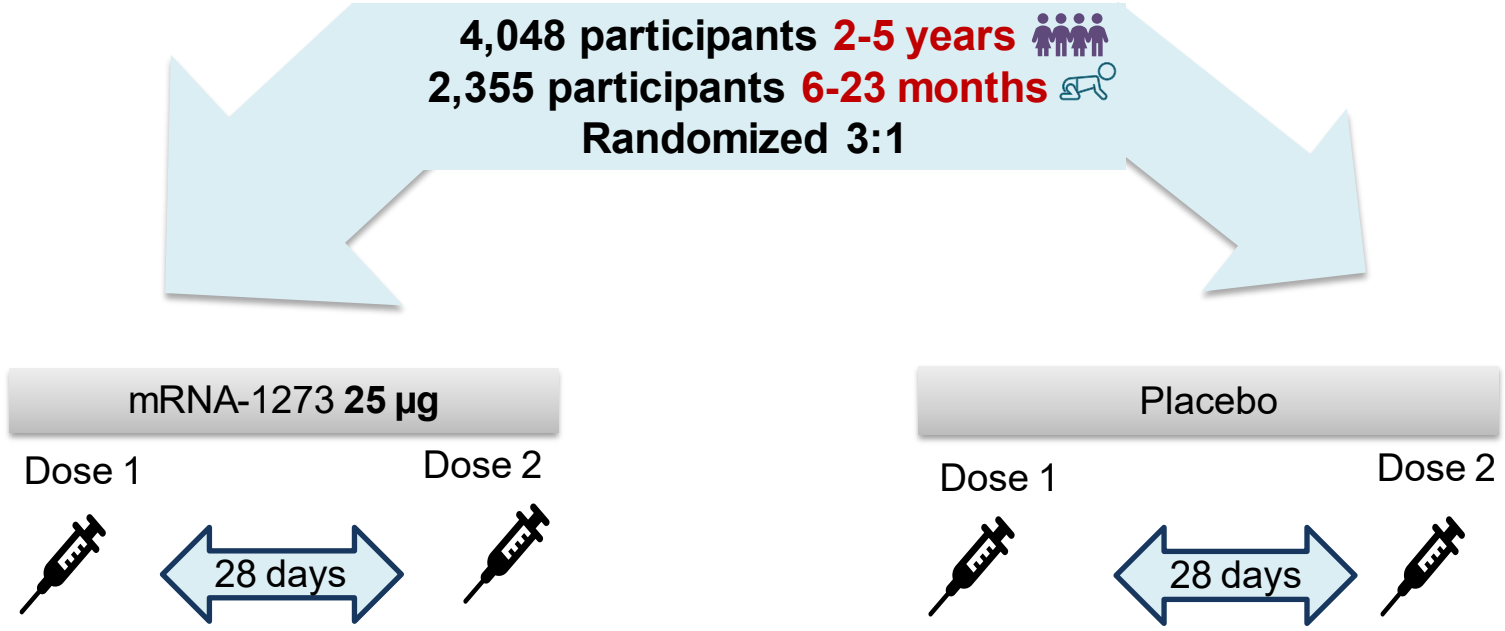
mRNA-1273 **50 µg** (n= 149)

Dose 1 — 28 days — Dose 2

25 µg dose level was selected for evaluation in Part 2

P204 Study Design

Part 2: Randomized, placebo-controlled, observer-blind evaluation of the selected dose for each age cohort



P204 Study Objectives/Endpoints

Objectives/endpoints
Safety Endpoints: Solicited local and systemic events: 7 days after each vaccination in an e-diary Unsolicited adverse events: 28 days after each dose Medically attended adverse events, serious adverse events, and adverse events of special interest: Dose 1 to the end of the study Active monitoring for myocarditis/pericarditis: Dose 1 to the end of the study
Immunobridging approach: GMC ratio and seroresponse rate difference 1 month post dose 2 compared to young adults 18-25 years of age in P301 with demonstrated efficacy
Efficacy Endpoints: Secondary descriptive

Immunobridging Analyses

P204

6-23 Months of Age (n= 230)

2-5 Years of Age (n= 264)

25 µg

1 month

Comparisons of neutralizing antibody responses to USA-WA1/2020 Wuhan strain with D614G mutation*

P301

(Efficacy study n~44,000)
18-25 Years of Age
(n= random subset of 291)

100 µg

1 month

Vaccine Efficacy= 93.2%

n= evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection
* neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein

Immunobridging Analysis: Geometric Mean Concentration Ratio

Endpoint: Geometric mean neutralizing antibody concentration (GMC) 1 Month Post-Primary Series based on pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

$$\frac{\text{GMC pediatric age group}}{\text{GMC 18-25 years}}$$

Immunobridging success criteria:

- Lower limit of the 2-sided 95% CI for GMC ratio ≥0.67
- Point estimate of GMC ratio ≥0.8

Immunobridging Analysis: Seroresponse Rate Difference

Endpoint: Geometric mean neutralizing antibody concentration (GMC) 1 Month Post-Primary Series based on pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

% (pediatric age group) with ≥4-fold rise from baseline GMC to 1-month post-Dose 2

MINUS

% (18-25 years) with ≥4-fold rise from baseline GMC to 1-month post-Dose 2

Immunobridging success criteria:

- Lower limit of the 95% CI for the difference in % of participants with seroresponse is ≥-10%
- Point estimate of difference in seroresponse rates ≥ -5%.

*Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ.

Descriptive Efficacy Analysis: Case definitions

Endpoint	Definition
CDC case definition for COVID-19	At least one of the following systemic symptoms : • Fever (temperature > 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours), cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite or poor feeding, **AND** • At least 1 nasal swab (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR
P301 case definition for COVID-19	A positive RT-PCR test result (by NP swab, nasal swab, or saliva sample [or respiratory sample, if hospitalized]) together with eligible symptoms as follows: • At least 2 systemic symptoms: Fever (≥ 38° C/≥ 100.4° F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** • At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia

P204 Pediatric Analysis Populations

Population	Description
Per-protocol (PP) Immunogenicity Subset	A subset of participants selected for immunogenicity testing who received planned doses of study vaccination per schedule, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, complied with immunogenicity testing schedule, and had no major protocol deviations that impact key or critical data. Participants seropositive at baseline were excluded. The PP Immunogenicity Subset was used for analyses of immunogenicity unless otherwise specified.
Per Protocol (PP) Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, and had no major protocol deviations that impact key or critical efficacy data.
Safety Set	All enrolled participants (in Part 1) and all randomized participants (in Part 2) who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

P204 Follow-Up Time
6-23 Months and 2-5 Years

Duration of Follow-Up	6-23 Months mRNA-1273 25 µg N=1761	6-23 Months Placebo N=589	6-23 Months Total N=2350
Blinded follow-up	--	--	--
≥28 days since Dose 2, n (%)	1470 (83.5)	482 (81.8)	1952 (83.1)
≥56 days since Dose 2, n (%)	1138 (64.6)	368 (62.5)	1506 (64.1)
Median follow-up from Dose 2, days (min, max)	68 (0, 99)	68 (0, 99)	68 (0, 99)

Duration of Follow-Up	2-5 Years mRNA-1273 25 µg N=3031	2-5 Years Placebo N=1007	2-5 Years Total N=4038
Blinded follow-up	--	--	--
≥28 days since Dose 2, n (%)	2713 (89.5)	892 (88.6)	3605 (89.3)
≥56 days since Dose 2, n (%)	2180 (71.9)	710 (70.5)	2890 (71.6)
Median follow-up from Dose 2, days (min, max)	71 (0, 99)	70 (0, 99)	71 (0, 99)
Including both blinded and open-label phases	--	--	--
≥56 days since Dose 2, n (%)	2248 (74.2)	--	--
Median follow-up from Dose 2, days (min, max)	74 (0, 99)	--	--

P204 Demographics and Baseline Characteristics 6-23 Months, Safety Set

Characteristic	6-23 months mRNA-1273 25 µg N= 1761	Placebo N= 589
Sex	48% female	51% female
Race	79% White 11% Multiracial 3% Black/African American 5% Asian	79% White 11% Multiracial 3% Black/African American 6% Asian
Ethnicity	13% Hispanic or Latino	14% Hispanic or Latino
Country	94% US 6% Canada	94% US 6% Canada
Obesity	22%	22%
Positive baseline SARS-CoV-2 status	6%	7%

P204 Demographics and Baseline Characteristics 2-5 Years, Safety Set

Characteristic	mRNA-1273 25 µg N= 3031	Placebo N= 1007
Sex	49% female	49% female
Race	76% White 11% Multiracial 5% Black/African American 6% Asian	79% White 10% Multiracial 4% Black/African American 5% Asian
Ethnicity	14% Hispanic or Latino	14% Hispanic or Latino
Country	94.6% US 5.4% Canada	94.5% US 5.5% Canada
Obesity	11%	11%
Positive baseline SARS-CoV-2 status	9%	8%

Immunogenicity Data

P204 Immunobridging Based on GMC Ratio 6-23 Months

Geometric Mean SARS-CoV-2 Neutralizing Concentration as Measured by Pseudovirus nAb Assay* at Day 57
6-23 Months of Age, Per-Protocol Immunogenicity Subsets

6-23 Months mRNA-1273 25 µg GMC (95% CI) N=230	18-25 Years mRNA-1273 100 µg GMC (95% CI) N=291	GMC Ratio (6-23 Months/18-25 Years) (95% CI)
1780.7 (1606.4, 1973.8)	1390.8 (1269.1, 1524.2)	**1.3 (1.1, 1.5)**

Success criteria met

1. Lower bound of the 2-sided 95% CI for the GMC ratio ≥0.67
2. Point estimate of the GMC ratio ≥0.8

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

P204 Immunobridging Based on Seroresponse 6-23 Months

Seroresponse Rates as Measured by Pseudovirus nAb Assay* at Day 57, 6-23 Months of Age, Per-Protocol Immunogenicity Subsets

6-23 Months mRNA-1273 25 µg Seroresponse n (%) (95% CI) N=230	**18-25 Years mRNA-1273 100 µg Seroresponse n (%) (95% CI) N=291**	**Difference in Seroresponse Rate % (6-23 Months−18-25 Years) (95% CI)**
230 (100) (98.4, 100)	289 (99.3) (97.5, 99.9)	**0.7 (−1.0, 2.5)**

Success criteria met

1. Lower bound of the 95% CI for the difference in seroresponse rate ≥ -10%
2. Seroresponse rate difference point estimate ≥ -5%

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

P204 Subgroup Analyses of GMC by Baseline SARS-CoV-2 Status, 6-23 Months

Geometric Mean SARS-CoV-2 Neutralizing Concentrations as Measured by Pseudovirus nAb Assay* at Day 57 by Baseline SARS-CoV-2 Status, Immunogenicity Subsets

Baseline SARS-CoV-2 Status	6-23 Months Study P204 GMC (n)	18-25 Years of Age Study P301 GMC (n)
Positive	6733.8 (12)	3850.1 (15)
Negative	1760.8 (234)	1358.7 (296)

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

P204 Immunobridging Based on GMC Ratio 2-5 Years

Geometric Mean SARS-CoV-2 Neutralizing Concentration as Measured by Pseudovirus nAb Assay* at Day 57
2-5 Years of Age, Per-Protocol Immunogenicity Subsets

2-5 Years mRNA-1273 25 µg GMC (95% CI) N=264	**18-25 Years mRNA-1273 100 µg GMC (95% CI) N=291**	**GMC Ratio (2-5 Years/18-25 Years) (95% CI)**
1410.0 (1273.8, 1560.8)	1390.8 (1262.5, 1532.1)	**1.0 (0.9, 1.2)**

Success criteria met

1. Lower bound of the 2-sided 95% CI for the GMC ratio ≥0.67
2. Point estimate of the GMC ratio ≥0.8

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

P204 Immunobridging Based on Seroresponse 2-5 Years

Seroresponse Rates as Measured by Pseudovirus nAb Assay* at Day 57, 2-5 Years of Age, Per-Protocol Immunogenicity Subsets

2-5 Years mRNA-1273 25 µg Seroresponse n (%) (95% CI) N=264	18-25 Years mRNA-1273 100 µg Seroresponse n (%) (95% CI) N=291	Difference in Seroresponse Rate % (2-5 Years−18-25 Years) (95% CI)
261 (98.9) (96.7, 99.8)	289 (99.3) (97.5, 99.9)	**-0.4 (-2.7, 1.5)**

Success criteria met

1. Lower bound of the 95% CI for the difference in seroresponse rate ≥ -10%
2. Seroresponse rate difference point estimate ≥ -5%

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

P204 Subgroup Analyses of GMC by Baseline SARS-CoV-2 Status, 2-5 Years

Geometric Mean SARS-CoV-2 Neutralizing Concentrations as Measured by Pseudovirus nAb Assay* at Day 57 by Baseline SARS-CoV-2 Status, Immunogenicity Subsets

Baseline SARS-CoV-2 Status	2-5 Years of Age Study P204 GMC (n)	18-25 Years of Age Study P301 GMC (n)
Positive	4791.3 (20)	3930.0 (15)
Negative	1425.2 (268)	1358.7 (296)

*Assay: pseudotype virus neutralization assay (USA-WA1/2020 Wuhan strain with D614G mutation)

Descriptive Efficacy Data

P204 Descriptive Efficacy Analysis 6-23 Months

Vaccine Efficacy, First Occurrence COVID-19 Starting 14 Days After Dose 2
6-23 Months of Age, Study P204 (Part 2), Per-Protocol Set for Efficacy

Data accrued through February 21, 2022 **(Omicron variant predominant period)**

Endpoint	6-23 months mRNA-1273 25 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=1511	6-23 months Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=513	Vaccine Efficacy (95% CI)
CDC definition	51 (3.4) 138.2 (102.9, 181.8)	34 (6.6) 279.8 (193.8, 391.0)	**50.6%** **(21.4, 68.6)**
P301 definition	37 (2.4) 100.0 (70.4, 137.8)	18 (3.5) 146.0 (86.6, 230.8)	**31.5%** **(-27.7, 62.0)**

Person-years= total years from randomization date to the first date of COVID-19 (P301 primary definition or CDC definition, as applicable), last date of study participation, or efficacy data cutoff date, whichever is the earliest.
Incidence rate= the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group.
Vaccine efficacy (VE), defined as 1 — ratio of incidence rate (mRNA-1273 vs placebo).

P204 Descriptive Efficacy Analysis 2-5 Years

Vaccine Efficacy, First Occurrence COVID-19 Starting 14 Days After Dose 2
2-5 Years of Age, Study P204 (Part 2), Per-Protocol Set for Efficacy
Data accrued through February 21, 2022 **(Omicron variant dominant period)**

Endpoint	2-5y mRNA-1273 25 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=2594	2-5y Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=858	Vaccine Efficacy (95% CI)
CDC definition	119 (4.6) 175.0 (145.0, 209.4)	61 (7.1) 277.0 (211.9, 355.8)	**36.8%** **(12.5, 54.0)**
P301 definition	71 (2.7) 103.8 (81.0, 130.9)	43 (5.0) 193.5 (140.1, 260.7)	**46.4%** **(19.8, 63.8)**

Person-years= total years from randomization date to the first date of COVID-19, last date of study participation, efficacy data cutoff/extraction date, or unblinding point, whichever is earlier
Incidence rate= number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group
Vaccine efficacy (VE), defined as 1 — ratio of incidence rate (mRNA-1273 vs placebo).

Safety Data

P204 Safety Analyses: Local Reactions 6-23 Months

Frequency of Solicited Local Reactions Within 7 Days After Each Dose, P204 6-23 Months, Solicited Safety Set

Event	6-23 Months mRNA-1273 25µg Dose 1 N=1743-1745 %	6-23 Months Placebo Dose 1 N=582 %	6-23 Months mRNA-1273 25µg Dose 2 N=1596 %	6-23 Months Placebo Dose 2 N=526 %
Any local adverse reaction	44.4	33.2	54.4	30.2
Grade 3	0.5	0.3	1.4	0
Any pain at injection site	37.4	30.1	46.2	25.7
Grade 3	0	0	0	0
Any erythema (redness)	8.6	4.1	13.5	3.8
Grade 3	0.3	0.3	0.9	0
Any swelling (hardness)	8.4	2.6	15.3	2.1
Grade 3	0.3	0	0.9	0
Any axillary (or groin) swelling or tenderness	5.9	4.5	9.3	5.3
Grade 3	0	0	0	0

Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=5-20mm (participants aged 6 to ≤36 months); Grade 2=>20-50mm (participants aged 6 to ≤36 months); Grade 3=>50mm (participants aged 6 to ≤36 months) .
Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=some swelling or tenderness but no interference with normal daily activities for participants aged 6 to ≤36; Grade 2=swelling or tenderness that interferes with normal daily activities for participants aged 6 to ≤36 months; Grade 3=swelling or tenderness that prevents normal daily activities for participants aged 6 to ≤36.

P204 Safety Analyses: Systemic Reactions 6-23 Months

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P204 6-23 Months, Solicited Safety Set

Adverse Reaction	6-23 Months mRNA-1273 25 µg Dose 1 N= 1737-1746 %	6-23 Months Placebo Dose 1 N=581-582 %	6-23 Months mRNA-1273 25 µg Dose 2 N=1589-1596 %	6-23 Months Placebo Dose 2 N=525-526 %
Any systemic adverse reaction	76.4	72.3	73.6	66.5
Grade 3	2.6	1.7	2.8	2.3
Grade 4	<0.1	0.2	0.2	0
Any fever: ≥38.0° C	11.0	8.4	14.6	8.4
Grade 3: 39.6° C to 40.0° C	0.6	0.5	0.4	1.1
Grade 4: >40.0° C	<0.1	0.2	0.2	0
Any irritability/crying	67.6	62.1	64.3	58.5
Grade 3	1.4	1.0	1.6	1.0
Grade 4	0	0	0	0
Any sleepiness	37.1	37.3	35.1	33.3
Grade 3	0.2	0.2	0.7	1.1
Grade 4	0	0	0	0
Any loss of appetite	30.2	26.2	32.1	25.1
Grade 3	0.6	0.2	1.0	0.4
Grade 4	0	0	0	0
Any use of antipyretic or pain medication	27.6	24.2	34.0	21.1

Toxicity grade for irritability/crying, sleepiness, and loss of appetite is defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization.

P204 Safety Analyses: Local Reactions 2-5 Years

Frequency of Solicited Local Reactions Within 7 Days After Each Dose, P204 2-5 Years, Solicited Safety Set

Event	2-5 years mRNA-1273 25µg Dose 1 N=2954-2957 %	2-5 years Placebo Dose 1 N=970 %	2-5 years mRNA-1273 25µg Dose 2 N=2938 %	2-5 years Placebo Dose 2 N=959 %
Any local adverse reaction	63.4	42.0	73.4	42.1
Grade 3	0.8	0.4	1.2	0
Any pain at injection site	61.4	39.4	71.4	41.2
Grade 3	0.1	0	0.4	0
Any erythema (redness)	5.5	1.4	8.8	1.6
Grade 3	0.4	0.3	0.4	0
Any Swelling (hardness)	4.5	1.8	8.2	1.1
Grade 3	0.3	0.2	0.4	0
Any Axillary (or groin) swelling or tenderness	6.9	5.8	9.1	3.2
Grade 3	0	0	<0.1	0

Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants ages 24-36 months is defined as: G1 = 5-20 mm; G2 = >20-50 mm; G3 = >50 mm
Toxicity grade for injection site erythema (redness) or swelling (hardness) for participants 37 months-5 years is defined as: G1 = 25 — 50 mm; G2 = 51-100 mm; G3 = >100 mm
Toxicity grade for Groin or underarm swelling or tenderness for subject age 6 to ≤36 months, or for Axillary swelling or tenderness for subject age 37 months to <12 years is defined as: G1 = Some swelling or tenderness but no interference with normal daily activities/No interference with activity; G2 = Swelling or tenderness that interferes with normal daily activities/Some interference with activity; G3 = Swelling or tenderness that prevents normal daily activities/Prevents daily activity

P204 Safety Analyses: Systemic Reactions 24-36 Months

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P204 24-36 Months, Solicited Safety Set

Adverse Reaction	24-36m mRNA-1273 25 µg Dose 1 N=941-944 %	24-36m Placebo Dose 1 N=319-320 %	24-36m mRNA-1273 25 µg Dose 2 N=962-963 %	24-36m Placebo Dose 2 N=330 %
Any systemic adverse reaction	65.0	61.9	67.6	58.8
Grade 3	1.9	2.8	2.9	0.6
Grade 4	0.3	0.3	0.3	0
Any fever: ≥38.0° C	11.3	7.8	18.9	10.6
Grade 3: 39.6° C to 40.0° C	0.3	0.9	1.2	0
Grade 4: >40.0° C	0.3	0.3	0.3	0
Any irritability/crying	54.5	51.1	54.3	44.8
Grade 3	1.3	1.9	1.0	0.6
Grade 4	0	0	0	0
Any sleepiness	30.3	28.8	36.0	27.0
Grade 3	0.2	0	0.1	0
Grade 4	0	0	0	0
Any loss of appetite	23.9	22.3	30.5	20.9
Grade 3	0.7	0.3	0.8	0
Grade 4	0	0	0	0
Any use of antipyretic or pain medication	20.4	18.4	30.3	18.8

Toxicity grade for irritability/crying, sleepiness, and loss of appetite is defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization. Medications were collected on an eDiary

P204 Safety Analyses: Systemic Reactions 37 Months-5 Years (1)

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P204 37 Months-5 Years, Solicited Safety Set

Adverse Reaction	37m-5y mRNA-1273 25 µg Dose 1 N=2013 %	37m-5y Placebo Dose 1 N=650 %	37m-5y mRNA-1273 25 µg Dose 2 N=1974-1975 %	37m-5y Placebo Dose 2 N=627-629 %
Any systemic adverse reaction	48.8	44.6	58.9	37.2
Grade 3	2.3	2.2	5.1	1.7
Grade 4	<0.1	0.2	0.2	0
Any fever: ≥38.0° C	7.7	5.1	16.0	4.5
Grade 3: 39.0° C to 40.0° C	1.1	0.6	2.9	0.3
Grade 4: >40.0° C	0	0.2	0.2	0
Any headache	11.5	12.0	15.7	8.1
Grade 3	0.2	0.3	0.4	0.2
Grade 4	0	0	0	0
Any fatigue	40.1	36.3	48.4	29.4
Grade 3	1.0	1.7	2.3	1.3
Grade 4	0	0	0	0
Any myalgia	9.9	9.2	15.7	7.5
Grade 3	0.2	0.3	0.5	0.5
Grade 4	0	0	0	0

Toxicity grade for headache, fatigue, and myalgia defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization.

P204 Safety Analyses: Systemic Reactions 37 Months-5 Years (2)

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P204 37 Months-5 Years, Solicited Safety Set

Adverse Reaction	37m-5y mRNA-1273 25 µg Dose 1 N=2013 %	37m-5y Placebo Dose 1 N=650 %	37m-5y mRNA-1273 25 µg Dose 2 N=1975 %	37m-5y Placebo Dose 2 N=629 %
Any arthralgia	6.2	4.9	8.5	4.5
Grade 3	<0.1	0.2	0.2	0
Grade 4	0	0	0	0
Any nausea/vomiting	6.8	7.7	9.8	4.8
Grade 3	0.3	0.3	0.3	0
Grade 4	0	0	0	0
Any chills	6.4	6.2	12.4	4.9
Grade 3	<0.1	0	0.2	0.3
Grade 4	0	0	0	0
Any use of antipyretic or pain medication	15.2	9.5	25.7	6.8

Toxicity grade for arthralgia and chills is defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization.
Toxicity grade for nausea/vomiting is defined as Grade 1=1-2 episodes/ 24 hours; Grade 2=>2 episodes/24 hours; Grade 3=prevents daily activity; Grade 4=requires emergency room visit or hospitalization

P204 Safety Analyses: Unsolicited Adverse Events 6-23 Months

Unsolicited adverse events	**6-23 Months mRNA-1273 25 µg N= 1761 n (%)**	**6-23 Months Placebo N= 589 n (%)**
Unsolicited TEAE within 28 days after any injection	869/1761 (49.3)	284/589 (48.2)
Non-serious unsolicited TEAE	868/1761 (49.3)	284/589 (48.2)
Related non-serious unsolicited TEAE	292/1761 (16.6)	71/589 (12.1)
Severe non-serious unsolicited TEAE	18/1761 (1.0)	4/589 (0.7)
Related severe non-serious unsolicited TEAE	13/1761 (0.7)	3/589 (0.5)
Medically attended adverse event (MAAE) throughout study	678/1761 (38.5)	242/589 (41.1)
Related MAAE	26/1761 (1.5)	5/589 (0.8)

TEAE= Treatment emergent adverse event

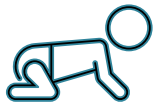
P204 Safety Analyses
Adverse Events of Clinical Interest – Cardiac
6-23 Months

Cardiac events 6-23 Months

- Symptoms of myocarditis and pericarditis were solicited for the duration of the study:
  - 7 days after each dose
  - Every 4 weeks thereafter

- A search strategy to identify potential cases of myocarditis/pericarditis after mRNA-1273 retrieved the following events: dyspnea, irritability, and vomiting.

- No events met CDC criteria for probable or confirmed myocarditis or pericarditis through data cutoff of February 21, 2022 (median 68 days follow-up after Dose 2).



P204 Safety Analyses
Adverse Events of Clinical Interest—General
6-23 Months

Events 6-23 Months*	mRNA-1273 N=1761	Placebo N= 589	Comments
Respiratory tract-related infections			Some respiratory events more common after placebo, and no imbalance in an aggregate comparison of all respiratory-tract infection events Frequency and clinical course of events as expected for the study population
Croup	1.3%	0.3%	
Respiratory syncytial virus (RSV)	0.8%	0.5%	
Pneumonia	0.2%	0%	
Lymphadenopathy-related	1.5%	0.2%	Plausibly related and consistent with solicited events of axillary (or groin) swelling/tenderness.

*February 21, 2022 data cutoff (median 68 days blinded follow-up after Dose 2)

P204 Safety Analyses: Unsolicited Adverse Events 2-5 Years

Unsolicited adverse events	**2-5 Years mRNA-1273 25 µg N= 3031 n (%)**	**2-5 Years Placebo N= 1007 n (%)**
Unsolicited TEAE within 28 days after any injection	1212 (40.0)	378 (37.5)
Non-serious unsolicited TEAE	1211 (40.0)	378 (37.5)
Related non-serious unsolicited TEAE	286 (9.4)	80 (7.9)
Severe non-serious unsolicited TEAE	21 (0.7)	9 (0.9)
Related severe non-serious unsolicited TEAE	18 (0.6)	8 (0.8)
Medically attended adverse event (MAAE) throughout study	1002 (33.1)	344 (34.2)
Related MAAE	31 (1.0)	3 (0.3)

TEAE= Treatment emergent adverse event

P204 Safety Analyses
Adverse Events of Clinical Interest – Cardiac
2-5 Years

Cardiac events 2-5 Years

• Symptoms of myocarditis and pericarditis were solicited for the duration of the study.
  • 7 days after each dose
  • Every 4 weeks thereafter
 	
• A search strategy to identify potential cases of myocarditis/pericarditis after mRNA-1273 retrieved the following events: chest pain/discomfort, dyspnea, palpitations, and mental status changes.
 	
• No events met CDC criteria for probable or confirmed myocarditis or pericarditis through data cutoff of February 21, 2022 (median 71 days follow-up after Dose 2).

P204 Safety Analyses
Adverse Events of Clinical Interest—General
2-5 Years

Events 2-5 Years*	mRNA-1273 N=3031	Placebo N= 1007	Comments
Respiratory tract-related infections			Some respiratory events more common after placebo, and no imbalance in an aggregate comparison of all respiratory-tract infection events Frequency and clinical course of events as expected for the study population
Respiratory syncytial virus (RSV)	0.4%	<0.1%	
Pneumonia	0.3%	0	
Abdominal pain	0.7%	0.4%	All mild to moderate in severity. Related events (n=2 in the mRNA-1273 group and n=1 in the placebo group) all within 2 days of vaccination. Likely manifestation of systemic reactogenicity.
Lymphadenopathy-related	0.9%	<0.1%	Plausibly related and consistent with solicited events of axillary (or groin) swelling/tenderness.

*February 21, 2022 data cutoff (median 71 days blinded follow-up after Dose 2)

P204 Safety Analyses: Serious Adverse Events 6-23 Months

SAEs 6-23 Months
• In Blinded Phase Part 2, from Dose 1 through the data cutoff, SAEs were reported in 15 mRNA-1273 recipients (0.9%) and 1 placebo recipient (0.2%). No deaths were reported. • In Part 1, 5 SAEs were reported by 3 participants in the mRNA-1273 group. • FDA has assessed events of pyrexia, febrile convulsion, and maculopapular rash in a 1-year-old child within 3 days following Dose 1 as potentially related to study vaccination, although a viral illness remains a plausible alternative etiology. FDA agrees with the Sponsor that none of the remaining SAEs were related to study vaccine.

P204 Safety Analyses: Serious Adverse Events 2-5 Years

SAEs 2-5 Years
• In Blinded Phase Part 2, from Dose 1 through the data cutoff, SAEs were reported in 9 mRNA-1273 recipients (0.3%) and 2 placebo recipients (0.2%). No deaths were reported. • In Part 1, no SAEs were reported. • FDA agrees with the investigator's assessments that none of the SAEs were related to study vaccine.

Pharmacovigilance

Pharmacovigilance Plan

Important identified risks	Anaphylaxis, myocarditis, pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and lactation, vaccine effectiveness, long-term safety, use in immunocompromised patients, interaction with other vaccines, use in frail subjects with unstable health conditions and comorbidities, use in subjects with autoimmune or inflammatory disorders, use in pediatric individuals <6 months of age

Surveillance activities	• Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days: Serious adverse events (irrespective of attribution to vaccination); Cases of Multisystem Inflammatory Syndrome; Cases of COVID-19 that result in hospitalization or death. Additionally, the sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.
	• The Sponsor will conduct:
	  • Passive and active surveillance activities for continued vaccine safety monitoring
	  • Periodic aggregate review of safety data and submit periodic safety reports
	  • Planned surveillance studies, including active follow-up studies for safety in the US and EU
	  • Post-authorization pregnancy studies

Surveillance Studies

Post-authorization surveillance studies including children 6 months- 5 years

To evaluate myocarditis/pericarditis	
mRNA-1273-P903	"Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity", to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
mRNA-1273-P904	"Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe," to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
mRNA-1273-P911	"Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273)," to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.
mRNA-1273-204 Substudy	To prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months through <12 years of age.
To evaluate effectiveness	
mRNA-1273-P901	"Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine."

Adverse Event (AE) Reporting Under the EUA

Reporter	Data provided	Provided To	Reviewed by
Vaccine recipients	Voluntary reports, either spontaneous or solicited through V-SAFE	VAERS	FDA and CDC
Vaccine providers and EUA Sponsor	Mandatory reporting of • Vaccination administration errors (providers only) • Serious adverse events (SAEs) • Multisystem Inflammatory Syndrome • Cases of COVID-19 that result in hospitalization or death	VAERS	FDA and CDC
Vaccine EUA Sponsor	Monthly Periodic Safety Reports, including analysis of aggregate AE data and newly identified safety concerns	FDA	FDA

CDC		FDA
• Review of AESI • Data Abstraction	Coordination Data Sharing	• Screening of all incoming SAEs • Literature review • Data Mining • Potential safety signals will be further evaluated

Summary of Benefits and Risks

Summary of Benefits and Risks
6 months- 5 years

Known and Potential Benefits	Uncertainties in Benefits	Known and Potential Risks	Uncertainties in Risks
Prevention of symptomatic COVID-19, based on: • Immunobridging analyses met pre-specified success criteria that allow for inference of vaccine effectiveness for individuals 6 months- 5 years of age • Supportive evidence of vaccine efficacy against symptomatic COVID-19 in descriptive analyses • Expectation of greater effectiveness against more severe COVID-19	• Effectiveness against: emerging SARS-CoV-2 variants, long term effects of COVID-19 disease • Effectiveness in: certain populations at higher risk of severe COVID-19, individuals previously infected with SARS-CoV-2 • Duration of protection	• Local and systemic reactogenicity • Lymphadenopathy • Myocarditis/pericarditis • Anaphylaxis and other hypersensitivity reactions	• Safety in certain subpopulations • Adverse reactions that are uncommon or that require longer follow-up to be detected

Voting Question for VRBPAC

Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine when administered as a 2-dose series (25 µg each dose) outweigh its risks for use in children 6 months through 5 years of age?

END