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U.S. FOOD & DRUG ADMINISTRATION

FDA

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety of Moderna COVID-19 Vaccine in Children 6 through 17 Years of Age *Emergency Use Authorization Amendment*

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June 14, 2022

Outline

Background

P203 (12-17 Years)

Study Design

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P204 (6- 11 Years)

Study Design

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Descriptive Efficacy Data

Safety Data

Pharmacovigilance

Summary of Benefits and Risks

Background

Moderna COVID-19 vaccine, mRNA

- 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

Study	Description	Data cutoff dates
P203	Phase 2/3 randomized, placebo-controlled study to evaluate safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents ages 12-17 years	Blinded follow-up through the data cutoff of May 8, 2021 (with a subsequent second data cutoff for safety of January 31, 2022)
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 November 10, 2021 (with a subsequent second data cutoff for safety of February 21, 2022), for participants 6-11 years

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 (GMT and seroresponse)	✓	✓	✓	✓
Descriptive efficacy	✓	✓	✓	✓

P203 and P204 Study Objectives/Endpoints

	P203	P204
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:		
GMT 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 6-11 Years of Age (n= 319)

P203 12-17 Years of Age (n=340)

1 month

50 µg (6-11 Years)
100 µg (12-17 Years)

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

P301 18-25 Years of Age
(Efficacy study n~44,000)
Random subset of ~300

1 month

100 µg

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 Titer Ratio

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

$$\frac{\text{GMT (pediatric age group)}}{\text{GMT 18-25 years (P301)}}$$

Immunobridging success criteria:

- Lower limit of the 2-sided 95% CI for GMT ratio >0.67 AND
- Point estimate of GMT ratio >0.8

Immunobridging Analysis: Seroresponse Rate Difference

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

% (pediatric age group) with seroresponse from baseline GMT to 1-month post-Dose 2

MINUS

% (18-25 years) with seroresponse from baseline GMT 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% AND
- A point estimate of difference in seroresponse rates >-5%.

*P203 ONLY: Pre-specified protocol definition of seroresponse: change from below lower limit of quantification (LLOQ) to greater than or equal to the LLOQ, or at least a 3.3-fold rise in participants ≥LLOQ at baseline.
Post-hoc analysis conducted using FDA definition: ≥4-fold rise in titer from baseline; if the baseline titer was <LLOQ, then it was set to LLOQ for the analysis

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

P203 and 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.
PP Set for Efficacy	All participants 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 randomized participants 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.

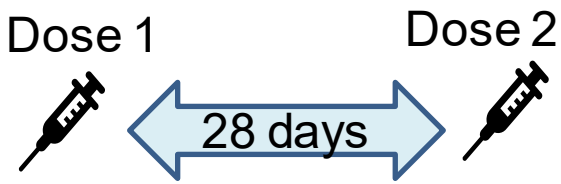
P203 Study Design

P203 Study Design

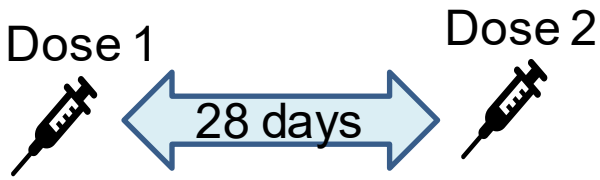
Study P203 is an ongoing randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents ages **12-17 years**

3,732 participants randomized 2:1

mRNA-1273 (100 µg)



Placebo



P203 Follow-Up Time

Length of Follow-Up	mRNA-1273 100 µg N=2486	Placebo N=1240	Total N=3726
Blinded follow-up (May 8, 2021 cutoff)			
Median follow-up post-Dose 2 (min, max)	53 days (0, 121)	51 days (0, 121)	53 days (0, 121)
≥1 month post-Dose 2, n (%)	2452 (98.6%)	1173 (94.6%)	3625 (97.3%)
≥2 months post-Dose 2, n (%)	1087 (43.7%)	474 (38.2%)	1561 (41.9%)
Blinded + open-label follow-up (January 31, 2022 cutoff)			
Median follow-up post-Dose 2 (min, max)	312 days (0, 389)	--	--
≥6 months post-Dose 2, n (%)	2376 (95.6%)	--	--

P203 Demographics and Baseline Characteristics Safety Set 12-17 Years

Characteristic	mRNA-1273 100 µg N=2486	Placebo N=1240
Sex	48% female	49% female
Median age	14 years	14 years
Race	84% White, 3% Black or African American, 6% Asian, 5% Multiracial,	84% White, 3% Black or African American, 6% Asian, 4% Multiracial
Ethnicity	11% Hispanic	12% Hispanic
Countries	US 100%	US 100%
BMI ≥30 kg/m^2	7%	8%
Positive baseline SARS-CoV-2 status	6%	6%

P203 Immunogenicity Data

P203 Immunobridging Based on GMT Ratio 12-17 Years

Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57
Per-Protocol Immunogenicity Subsets

12-17 Years P203 100 µg GMT (95% CI) N=340	**18-25 Years P301 100 µg GMT (95% CI) N=296**	**GMT Ratio (12-17 Years/18-25 Years) (95% CI)**
1401.7 (1276.3,1539.4)	1301.3 (1177.0, 1438.8)	**1.1 (0.9, 1.2)**

Success criteria met

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

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

P203 Immunobridging Based on Seroresponse 12-17 Years

Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57, Per-Protocol Immunogenicity Subsets

12-17 Years P203 100 µg Seroresponse n (%) (95% CI) N=340	**18-25 Years P301 100 µg Seroresponse n (%) (95% CI) N=296**	**Difference in Seroresponse Rate% ([12-17y]−[18-25y]) (95% CI)**
336 (98.8) (97.0, 99.7)	292 (98.6) (96.6, 99.6)	**0.2 (-1.8, 2.4)**

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)

Subgroup Analyses of GMT by Baseline SARS-CoV-2 Status

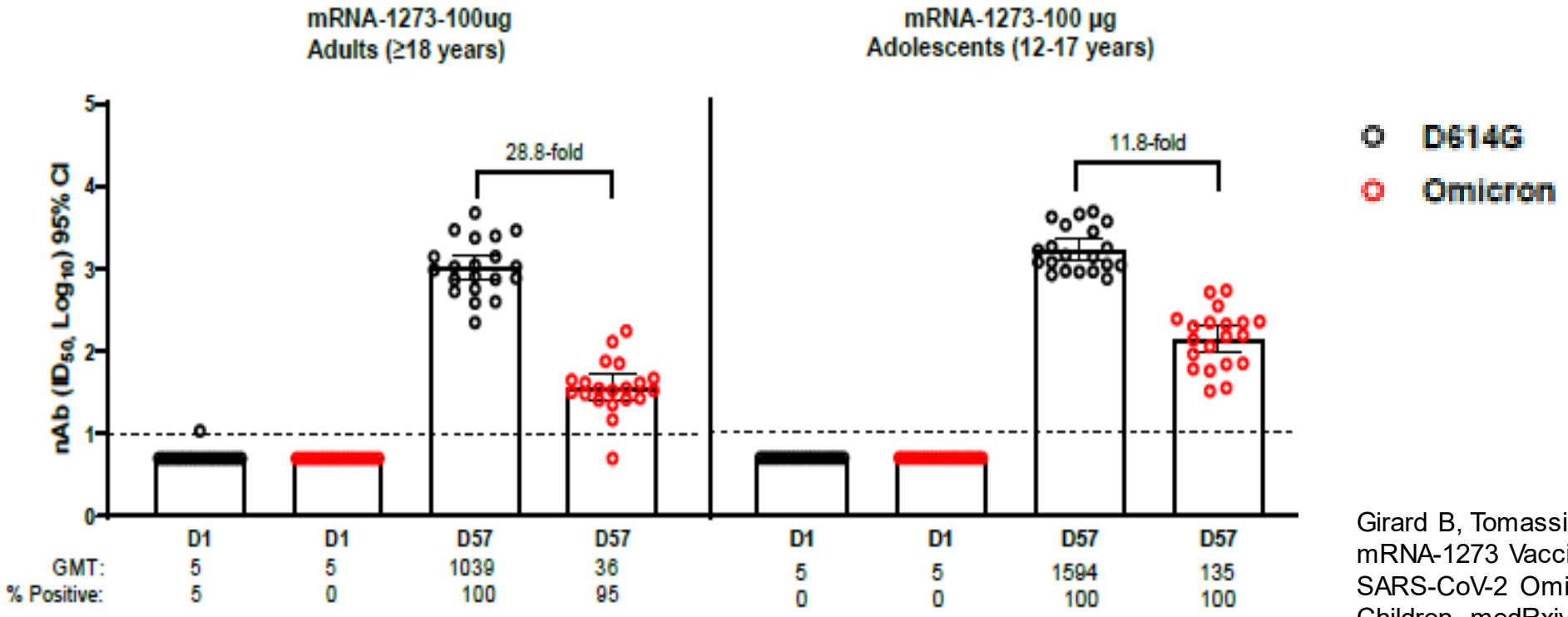
Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57 by Baseline SARS-CoV-2 Status, Immunogenicity Subsets

Baseline SARS-CoV-2 Status	12-17 Years Study P203 GMT (n)	18-25 Years of Age Study P301 GMT (n)
Positive	2866.6 (27)	1216.2 (15)
Negative	1413.1 (347)	1263.3 (300)

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

Exploratory Immunogenicity Analyses Omicron Variant

Immunogenicity against the B.1.1.529 (Omicron) variant was assessed by ID50 titers (GMT) using a non-validated pseudovirus neutralization assay at Day 1 and Day 57 following Dose 2 of mRNA-1273 in a subgroup of adults ≥18 years from P301 (n= 20) and adolescents 12-17 years from P203 (n= 20).



Girard B, Tomassini JE, Deng W, et al. mRNA-1273 Vaccine-elicited Neutralization of SARS-CoV-2 Omicron in Adolescents and Children. medRxiv 2022.01.24.22269666. https://www.medrxiv.org/content/10.1101/2022.01.24.22269666v1

*Not verified from datasets (published report)

P203 Descriptive Efficacy Data

P203 Descriptive Efficacy Analysis 12-17 Years

Vaccine Efficacy, First Occurrence COVID-19 Starting 14 Days After Dose 2
Participants 12 Through 17 Years of Age, Study P203, Per-Protocol Set for Efficacy

Data accrued through May 8, 2021 **(Ancestral strain with D614G mutation-, and then Alpha variant- predominant period)**

Endpoint	mRNA-1273 100 µg n (%) Incidence Rate per 1,000 person-years (95% CI) N=2,139	Placebo n (%) Incidence Rate per 1,000 person-years (95% CI) N=1,042	Vaccine Efficacy % (95% CI)
P301 definition	0 0 (NE, 7.1)	4 (0.4) 16.5 (4.5, 42.3)	**100.0 (28.9, NE)**
CDC definition	1 (<0.1) 1.9 (0, 10.8)	7 (0.7) 29.0 (11.7, 59.7)	**93.3 (47.9, 99.9)**

Updated analysis including cases through May 31, 2021 was comparable:
P301 definition VE= 100% (95% CI: 61.2, NE); CDC definition VE= 89.9% (95% CI: 51.0, 98.9)

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). NE=non-evaluable

P203 Safety Data

P203 Safety Analyses: Local Reactions 12-17 Years

Frequency of Solicited Local Reactions Within 7 Days After Each Dose
P203 12-17 Years, Solicited Safety Set

Event	mRNA-1273 100 µg Dose 1 N=2481-2482	Placebo Dose 1 N=1238	mRNA-1273 100 µg Dose 2 N=2477-2478	Placebo Dose 2 N=1220
Any local adverse reaction (%)				
Any	94.2	36.8	93.4	32.6
Grade 3	6.8	>0.1	8.9	0.2
Pain (%)				
Any	93.1	34.8	92.4	30.3
Grade 3	5.4	<0.1	5.1	0.2
Erythema (redness) (%)				
Any >25 mm	13.5	0.6	19.5	0.9
Grade 3	0.8	0	2.9	0
Swelling (hardness) (%)				
Any >25 mm	16.2	1.0	20.5	1.0
Grade 3	1.1	0	2.3	0
Axillary swelling or tenderness (%)				
Any	23.3	8.2	21.0	5.0
Grade 3	0.4	0	0.3	0

Pain and axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity
Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm

P203 Safety Analyses: Systemic Reactions 12-17 Years (1)

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P203 12-17 Years, Solicited Safety Set

Event	mRNA-1273 100 µg N=2480-2482 Dose 1	Placebo N=1238 Dose 1	mRNA-1273 100 µg N=2477-2478 Dose 2	Placebo N=1219-1220 Dose 2
Any systemic adverse reaction (%)	68.5	55.5	86.1	46.0
Grade 3	4.4	2.9	13.7	2.0
Grade 4	0	0	0.1	<0.1
Fever (%)				
≥38.0°C	2.5	1.0	12.2	1.0
38.0°C to 38.4°C	1.5	0.7	6.5	0.5
38.5°C to 38.9°C	0.7	0.2	3.8	0.3
39°C to 40.0°C	0.4	0.1	1.9	<0.1
>40.0°C	0	0	<0.1	<0.1
Any Headache (%)	44.6	38.5	70.2	30.3
Grade 3	2.3	1.4	4.5	1.1
Grade 4	0	0	<0.1	0
Any Fatigue (%)	47.9	36.6	67.8	28.9
Grade 3	1.3	1.5	7.6	0.8
Grade 4	0	0	0	0

Fever is defined as: grade 1 = 38 to 38.4° C; grade 2 = 38.5 to 38.9° C; Grade 3 = 39 to 40° C; grade 4 = greater than 40° C.
Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
Fatigue: Grade 3 significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.

P203 Safety Analyses: Systemic Reactions 12-17 Years (2)

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P203 12-17 Years, Solicited Safety Set

Event	mRNA-1273 100 µg N=2480-2482 Dose 1 %	Placebo N=1238 Dose 1 %	mRNA-1273 100 µg N=2477-2478 Dose 2 n (%)	Placebo N=1220 Dose 2 n (%)
Any Myalgia	26.9	16.6	46.6	12.5
Grade 3	1.0	0.8	5.2	0.2
Grade 4	0	0	0	0
Any Arthralgia	15.0	11.6	28.9	9.3
Grade 3	0.6	0.4	2.3	0.2
Grade 4	0	0	0	0
Any Nausea/vomiting	11.3	8.9	23.9	8.7
Grade 3	<0.1	0	<0.1	0
Grade 4	0	0	<0.1	0
Any Chills	18.4	11.1	43.0	8.0
Grade 3	0.2	<0.1	0.4	0
Grade 4	0	0	0	0
Any use of antipyretic or pain medication	30.1	9.5	50.1	8.9

Myalgia, arthralgia: Grade 3 significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
Chills: Grade 3 prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.

P203 Safety Analyses: Solicited ARs by Baseline SARS-CoV-2 Status, 12-17 Years

Frequency of Solicited Systemic Reactions Within 7 Days After Dose 1 by Baseline SARS-CoV-2 Status, P203 12-17 Years, Solicited Safety Set (mRNA-1273 Recipients)

Event	Baseline SARS-CoV-2 Negative N=2161-2163 Dose 1 %	Baseline SARS-CoV-2 Positive N=147 Dose 1 %
Any Fever	1.5	19.7
≥39.0°C	0.2	2.7
Any Headache	43.4	70.1
Grade 3	2.0	7.5
Any Fatigue	46.4	70.1
Grade 3	1.2	2.7
Any Chills	16.8	49.0
Grade 3	0.2	0
Any Myalgia	25.8	42.9
Grade 3	0.9	2.0

- Rates of solicited ARs comparable between the two groups after Dose 2

Myalgia, fatigue, headache: Grade 3 significant, prevents daily activity.
Chills: Grade 3 prevents daily activity and requires medical intervention.

P203 Safety Analyses: Unsolicited Adverse Events 12-17 Years

Unsolicited adverse events	**mRNA-1273 50 µg N= 2486 n (%)**	**Placebo N= 1240 n (%)**
Unsolicited TEAE within 28 days after any injection	510 (20.5)	197 (15.8)
Non-serious unsolicited TEAE	509 (20.5)	196 (15.8)
Related non-serious unsolicited TEAE	312 (12.6)	72 (5.8)
Severe non-serious unsolicited TEAE	11 (0.4)	1 (<0.1)
Related severe non-serious unsolicited TEAE	9 (0.4)	1 (<0.1)
Medically attended adverse event (MAAE) throughout study	203 (8.2)	104 (8.4)
Related MAAE	20 (0.8)	6 (0.5)

TEAE= Treatment emergent adverse event

P203 Safety Analyses (12-17 Years)
Adverse Events of Clinical Interest—Cardiac

Cardiac events

- A search strategy to identify potential cases of myocarditis/pericarditis after mRNA-1273 retrieved the following events: chest pain, dyspnea, palpitations, syncope.

- No events met CDC criteria for probable or confirmed myocarditis or pericarditis through data cutoff of January 31, 2022 (median 312 days follow-up after Dose 2).

P203 Safety Analyses (12-17 Years)
Adverse Events of Clinical Interest—General

Lymphadenopathy-related events

- Within 28 days after each dose, lymphadenopathy-related events were reported by 5% of mRNA-1273 recipients compared to 0.5% of placebo recipients
- Plausibly related and consistent with solicited events of axillary swelling/tenderness

P203 Safety Analyses: Serious Adverse Events 12-17 Years

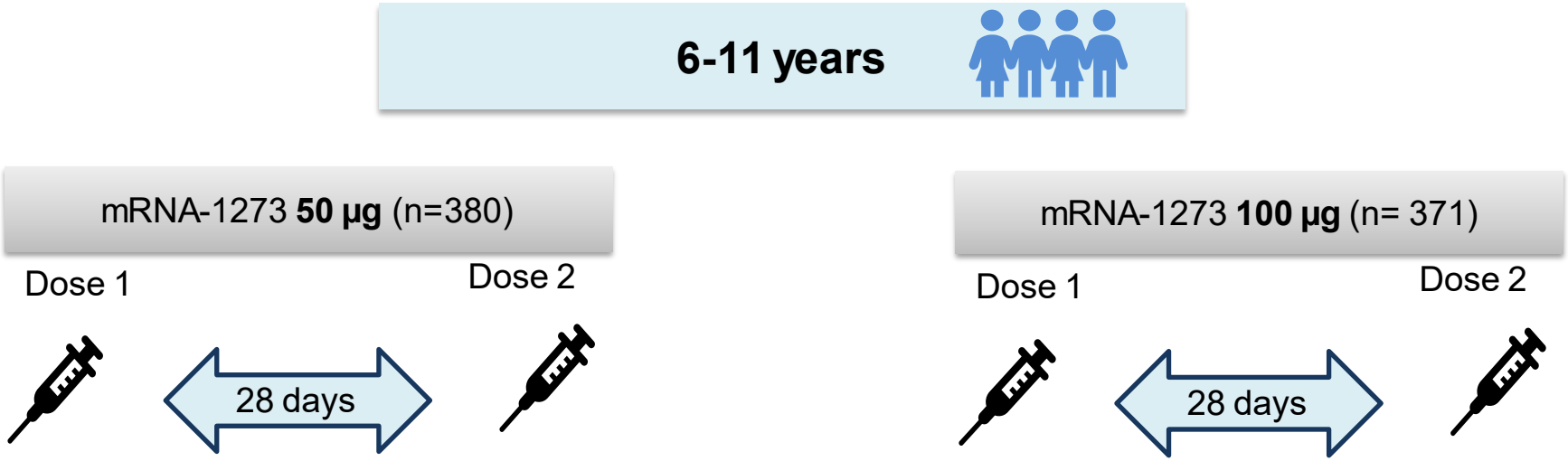
Serious adverse events (SAEs)

- From Dose 1 through data cutoff of May 8, 2021, SAEs were reported in 6 mRNA-1273 recipients (0.2%) and 2 placebo recipients (0.2%). No deaths were reported.
- Review of additional SAEs accrued during the open-label phase through data cutoff of January 31, 2022
- FDA agrees with the investigator's assessments that no SAEs were related to study vaccine.

P204 Study Design

P204: Study Design

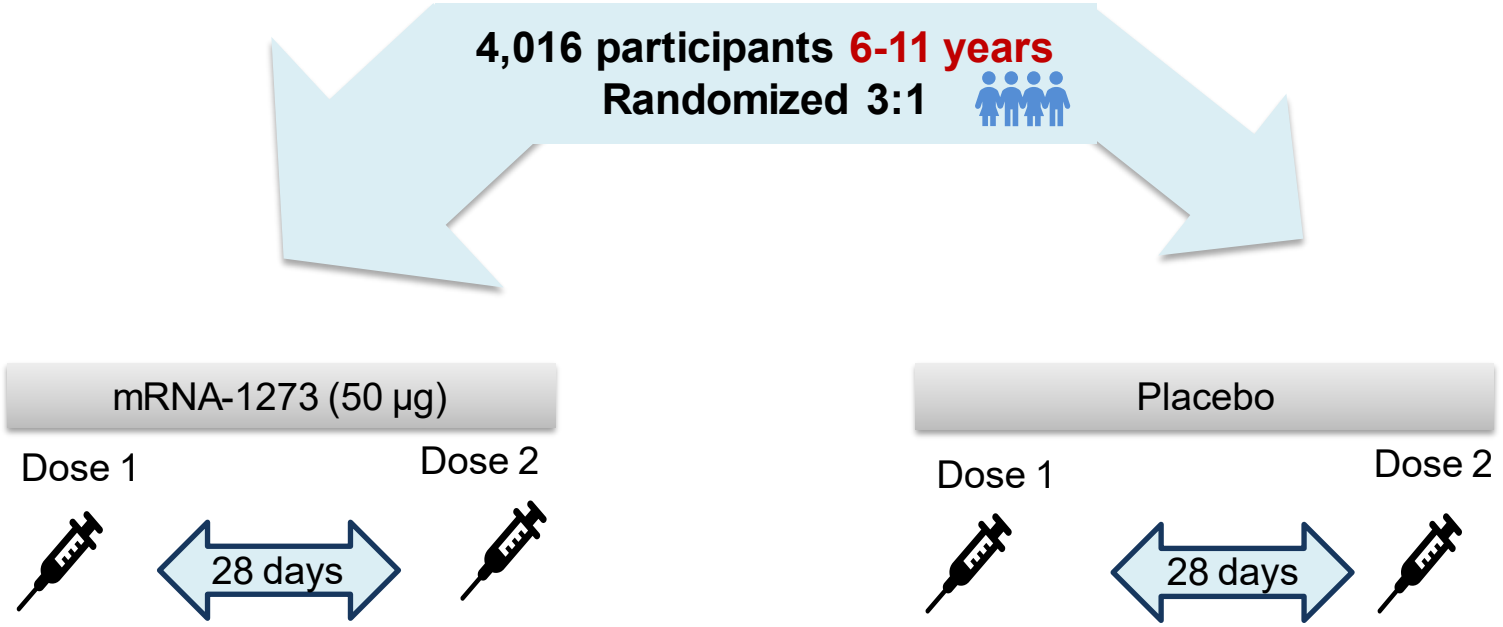
Part 1: Open-label, dose-escalation, age de-escalation phase



50 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: Follow-Up Time

Length of Follow-Up	mRNA-1273 50 µg N=3007	Placebo N=995	Total N=4002
Blinded follow-up (November 10, 2021 cutoff)			
Median follow-up post-Dose 2 (min, max)	52 days (0, 65)	49 days (0, 65)	51 days (0, 65)
≥1 month post-Dose 2, n (%)	2981 (99.1%)	996 (97.1%)	3947 (98.6%)
≥2 months post-Dose 2, n (%)	1066 (35.5%)	218 (21.9%)	1284 (32.1%)
Blinded + open-label follow-up (February 21, 2022 cutoff)			
Median follow-up post-Dose 2 (min, max)	158 days (0, 168)	--	--
≥2 months post-Dose 2, n (%)	2969 (98.7%)	--	--

P204 Demographics and Baseline Characteristics Safety Set 6-11 Years

Characteristic	mRNA-1273 50 µg N=3007	Placebo N=995
Sex	48% female	52% female
Median age	8 years	9 years
Race	65% White, 10% African American, 10% Asian, 11% Multiracial	67% White, 9% African American, 10% Asian, 10% Multiracial
Ethnicity	19% Hispanic	18% Hispanic
Country	US 99% Canada 1%	US 99% Canada 1%
Obesity	20%	20%
Positive baseline SARS-CoV-2 status	9%	9%

P204 Immunogenicity Data

P204 Immunobridging Based on GMT Ratio 6-11 Years

Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57 Per-Protocol Immunogenicity Subsets

6-11 Years P204 mRNA-1273 50 µg GMT (95% CI) N=319	**18-25 Years P301 mRNA-1273 100 µg GMT (95% CI) N=295**	**GMT Ratio (6-11 Years/18-25 Years) (95% CI)**
1610.2 (1456.6, 1780.0)	1299.9 (1171.2, 1442.7)	**1.2 (1.1, 1.4)**

Success criteria met

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

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

P204 Immunobridging Based on Seroresponse 6-11 Years

Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57, Per-Protocol Immunogenicity Subsets

6-11 Years P204 mRNA-1273 50 µg Seroresponse n (%) (95% CI) N1=316	18-25 Years P301 mRNA-1273 100 µg Seroresponse n (%) (95% CI) N1=295	Difference in Seroresponse Rate % (6-11 Years−18-25 Years) (95% CI)
313 (99.1%) (97.3, 99.8)	292 (99.0%) (97.1, 99.8)	**0.1% (-1.9, 2.1)**

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)

Subgroup Analyses of GMT by Baseline SARS-CoV-2 Status

Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID_{50})* at Day 57 by Baseline SARS-CoV-2 Status, Immunogenicity Subsets

Baseline SARS-CoV-2 Status	6-11 Years Study P203 GMT (n)	18-25 Years of Age Study P301 GMT (n)
Positive	4081.4 (38)	1260.7 (15)
Negative	1616.5 (321)	1264.3 (300)

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

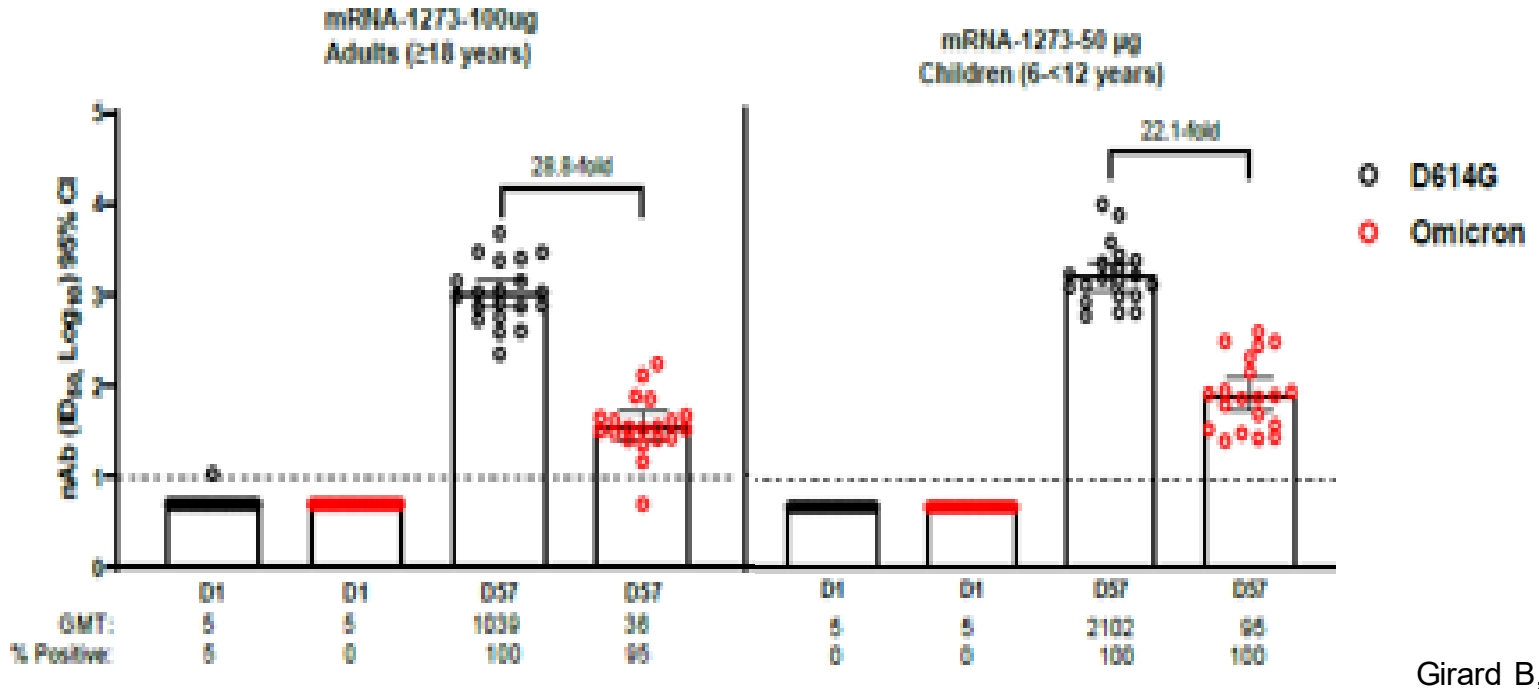
Exploratory Immunogenicity Analyses Delta Variant

Pseudovirus nAb Level Against the Ancestral Strain and Delta Strain
Participants 6 Through 11 Years of Age (P204 Part 1)
Expansion Per-Protocol Immunogenicity Set

Measurement	Ancestral Strain mRNA-1273 50 µg N=134	Delta (B.1.617.2) mRNA-1273 50 µg N=134
Baseline GMT	9.4	9.3
GMT observed at Day 57	1964.6	756.4
GMFR (95% CI) at Day 57 from baseline	209.5 (182.9, 239.8)	81.8 (70.4, 95.0)
Seroresponse, n (%) at Day 57 (95% CI)	133 (99.3%) (95.9, 100.0)	133 (99.3%) (95.9, 100.0)

Exploratory Immunogenicity Analyses Omicron Variant

Immunogenicity against the B.1.1.529 (Omicron) variant was assessed by neutralizing antibody geometric mean ID50 titers (GMT) using a non-validated pseudovirus neutralization assay at Day 1 and Day 57 following Dose 2 of mRNA-1273 in a subgroup of adults ≥18 years from P301 (n= 20) and children 6-11 years from P204 (n= 20)



*Not verified from datasets (published report)

Girard B, Tomassini JE, Deng W, et al. mRNA-1273 Vaccine-elicited Neutralization of SARS-CoV-2 Omicron in Adolescents and Children. medRxiv 2022.01.24.22269666. https://www.medrxiv.org/content/10.1101/2022.01.24.22269666v1

P204 Descriptive Efficacy Data

P204 Descriptive Efficacy Analysis 6-11 Years

Vaccine Efficacy, First Occurrence COVID-19 Starting 14 Days After Dose 2
Participants 6 Through 11 Years of Age, Study P204 (Part 2), Per-Protocol Set for Efficacy
Data accrued through November 10, 2021 **(Delta variant predominant period)**

Endpoint	mRNA-1273 50 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=2644	Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI) N=853	Vaccine Efficacy (95% CI)
P301 definition	3 (0.1%) 5.0 (1.0, 14.7)	3 (0.4%) 16.3 (3.4, 47.5)	69.0% (−131.4, 95.8)
CDC definition	3 (0.1%) 5.0 (1.0, 14.7)	4 (0.5%) 21.7 (5.9, 55.6)	76.8% (−37.3, 96.6)

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).

P204 Descriptive Efficacy Analysis 6-11 Years

Incidence of COVID-19 (CDC Case Definition) by Time Period Participants 6-11 Years of Age (P204 Part 2), mITT1 Set

Endpoint	mRNA-1273 50 µg Cases/N1 (%) Incidence Rate per 1,000 Person-Years (95% CI)	Placebo Cases/N1 (%) Incidence Rate per 1,000 Person-Years (95% CI)	Vaccine Efficacy (95% CI)
Any time after Dose 1	14/2687 (0.5%) 23.2 (12.7, 39.0)	22/880 (2.5%) 117.4 (73.6, 177.8)	80.2% (59.6, 90.6)
Any time after Dose 1 to before Dose 2	9/2687 (0.3%) 40.9 (18.7, 77.6)	15/880 (1.7%) 71.4 (117.5, 346.3)	80.5% (52.5, 92.5)
Any time after Dose 2	5/2668 (0.2) 13.1 (4.3, 30.6)	7/855 (0.8) 60.7 (24.4, 125.1)	78.4% (21.1, 94.6)

mITT1: All participants in the full analysis set who had no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of study vaccine (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline, excluding those who received the wrong treatment.

N1=number of participants at risk. Percentages are based on N1

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).

P204 Safety Data

P204 Safety Analyses: Local Reactions 6-11 Years

Frequency of Solicited Local Reactions Within 7 Days After Each Dose
P204 6-11 Years, Solicited Safety Set

Event	mRNA-1273 50 µg Dose 1 N=3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2988	Placebo Dose 2 N=969
Any local adverse reaction (%)				
Any	93.7	48.3	95.3	50.6
Grade 3	1.8	0.3	4.1	0.5
Pain at injection site (%)				
Any	93.1	46.8	94.8	49.5
Grade 3	0.9	0	2.7	0.2
Erythema (redness) (%)				
Any	11.6	1.3	18.7	1.0
Grade 3	0.5	0.1	1.1	0.1
Swelling (hardness) (%)				
Any	11.8	1.2	17.0	1.2
Grade 3	0.6	0.1	0.7	0
Axillary swelling or tenderness (%)				
Any	15.5	8.5	18.0	6.7
Grade 3	<0.1	0.1	0.1	0.2

Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 2=51-100 mm; Grade 3=>100 mm.
Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity.

P204 Safety Analyses: Systemic Reactions 6-11 Years

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose
P204 6-11 Years, Solicited Safety Set

Event	mRNA-1273 50 µg Dose 1 N=3002-3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2986-2988	Placebo Dose 2 N=969
Any systemic adverse reaction (%)	57.9	52.2	78.1	50.1
Grade 3	1.8	1.2	12.2	1.4
Fever ≥38.0° C	3.3	1.5	23.9	2.0
39° C to 40.0° C	0.6	0.2	3.8	0.2
Any Headache (%)	31.2	30.8	54.3	28.4
Grade 3	0.6	0.4	4.0	0.8
Any Fatigue (%)	43.2	33.6	64.5	34.6
Grade 3	1.0	0.8	6.4	0.8
Any Myalgia (%)	14.6	9.7	28.2	10.8
Grade 3	0.4	0.1	2.4	0.1
Any Arthralgia (%)	8.7	7.6	16.1	8.7
Grade 3	<0.1	0.1	0.8	0
Any Nausea/vomiting (%)	10.8	10.8	24.0	10.0
Grade 3	0.2	0	0.6	0
Any Chills (%)	10.3	6.7	30.3	7.6
Grade 3	<0.1	0	0.6	0
Any use of antipyretic or pain medication (%)	24.3	9.6	47.6	9.6

Toxicity grade for headache, fatigue, myalgia, arthralgia is defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Toxicity grade for nausea/vomiting is defined as Grade 1=no interference with activity or 1-2 episodes/24 hours; Grade 2=some interference with activity or >2 episodes/24 hours; Grade 3=prevents daily activity; Toxicity grade for chills is defined as Grade 1=no interference with activity; Grade 2=some interference with activity not requiring medical intervention; Grade 3=prevents daily activity and requires medical intervention;

P204 Safety Analyses Solicited ARs by Baseline SARS-CoV-2 Status, 6-11 years

Frequency of Solicited Adverse Reactions Within 7 Days After Dose 1 by Baseline SARS-CoV-2 Status, P204 6-11 Years, Solicited Safety Set (mRNA-1273 Recipients)

Event	Baseline SARS-CoV-2 Negative N=2703 Dose 1 %	Baseline SARS-CoV-2 Positive N=257 Dose 1 %
Any Fever	2.0	16.3
≥39.0°C	0.4	1.9
Any Headache	29.5	49.4
Grade 3	0.4	3.1
Any Chills	9.3	19.8
Grade 3	<0.1	0.4
Any Myalgia	13.6	24.5
Grade 3	0.3	0.8
Any Axillary swelling or tenderness	14.6	24.5
Grade 3	<0.1	0.4

- Rates of solicited ARs comparable between the two groups after Dose 2

Myalgia, headache, axillary swelling or tenderness: Grade 3 significant, prevents daily activity;
Chills: Grade 3 prevents daily activity and requires medical intervention;

P204 Safety Analyses: Unsolicited Adverse Events 6-11 Years

Unsolicited adverse events	mRNA-1273 50 µg N= 3007 n (%)	Placebo N= 995 n (%)
Unsolicited TEAE within 28 days after any injection	891 (29.6)	250 (25.1)
Non-serious unsolicited TEAE	889 (29.6)	249 (25.0)
Related non-serious unsolicited TEAE	319 (10.6)	50 (5.0)
Severe non-serious unsolicited TEAE	11 (0.4)	1 (0.1)
Related severe non-serious unsolicited TEAE	9 (0.3)	1 (0.1)
Medically attended adverse event (MAAE) throughout study	523 (17.4)	180 (18.1)
Related MAAE	36 (1.2)	4 (0.4)

TEAE= Treatment emergent adverse event

P204 Safety Analyses
Adverse Events of Clinical Interest—Cardiac
6-11 Years

Cardiac events

- Symptoms of myocarditis and pericarditis were specifically 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, angina pectoris, and cardiac flutter.

- No events met CDC criteria for probable or confirmed myocarditis or pericarditis through data cutoff of February 21, 2022 (median 158 days follow-up after Dose 2) .

P204 Safety Analyses
Adverse Events of Clinical Interest—General
6-11 Years

Events*	mRNA-1273 N=3007	Placebo N= 995	Comments
Lymphadenopathy-related events	1.9%	0.6%	Plausibly related and consistent with solicited events of axillary swelling/tenderness.
Abdominal pain	1.1%	0.6%	All mild to moderate in severity. Related events all within 7 days of vaccination. Likely manifestation of systemic reactogenicity

*November 10, 2021 data cutoff (median 51 days blinded follow-up after Dose 2)

P204 Safety Analyses: Serious Adverse Events 6-11 Years

SAEs

- From Dose 1 through the data cutoff of November 10, 2021, SAEs were reported in 6 mRNA-1273 recipients (0.2%) and 2 placebo recipients (0.2%). No deaths were reported.

- No SAEs were assessed as related to the vaccine by the investigator or FDA

- Review of additional SAEs accrued during open-label phase through data cutoff of February 21, 2022: no SAEs were assessed as related, except for SAE of ileus in a participant with complex medical history; FDA considers this possibly related.

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 in children and adults; Cases of COVID-19 that result in hospitalization or death. Additionally, the sponsor submits 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 6-17 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-P203 substudy	To prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 years through <18 years of age.
mRNA-1273-P204 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

- Review of AESI
- Data Abstraction

Coordination
Data Sharing

FDA

- 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 through 17 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 -17 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 Questions for VRBPAC

1. Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine when administered as a 2-dose series (100 mcg each dose) outweigh its risks for use in adolescents 12-17 years of age?

2. Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine when administered as a 2-dose series (50 mcg each dose) outweigh its risks for use in children 6-11 years of age?

END