Vaccines and Related Biological Products Advisory Committee June 14-15, 2022 Meeting Presentation

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mRNA-1273
PRIMARY SERIES 6 MONTHS TO 17 YEARS

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATES: JUNE 14–15, 2022

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List of Abbreviations

Acronym	Definition
Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Endpoint Adjudication Committee
CI	confidence interval
COVID-19	Coronavirus disease 2019
CoV	Coronavirus
DSMB	Data Safety Monitoring Board
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GM	geometric mean
GMC	geometric mean concentration
GMT	geometric mean titer
GMR	geometric mean ratio
LFT	liver function test
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MAAE	medically attended adverse events
MIS-C	Multisystem Inflammatory Syndrome in Children
mITT	modified Intent-to-Treat
mRNA	messenger ribonucleic acid
MSD	MesoScale Discovery
nAb	neutralizing antibody
PASS	Post-authorization safety study
PP	Per-Protocol
PsVNA	pseudovirus neutralizing antibody assay
PT	preferred term
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RTI	respiratory tract infection
SAE	serious adverse event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System organ class

Acronym	Definition
SRR	seroresponse rate
Study 203	Study mRNA-1273-P203, the pivotal Phase 2/3 safety and effectiveness study in adolescents 12–17 years of age
Study 204	Study mRNA-1273-P204, the pivotal Phase 2/3 safety and effectiveness study in children 6 months to 11 years of age
Study 301	Study mRNA-1273-P301, the pivotal Phase 3 safety, efficacy, and immunogenicity study in adults ≥ 18 years of age
TEAE	treatment-emergent adverse event
URI	Upper respiratory infection
US	United States
VE	vaccine efficacy

1 EXECUTIVE SUMMARY

1.1 Introduction

Following the outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ModernaTX, Inc. (Moderna) applied its messenger ribonucleic acid (mRNA) vaccine platform and coronavirus research experience to rapidly develop the mRNA-1273 vaccine against SARS-CoV-2. The safety and efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study mRNA-1273-P301 (Study 301), leading to Emergency Use Authorization (EUA) in the United States (US) on 18 Dec 2020 and licensure on 31 Jan 2022. As of 15 Apr 2022, more than 1 billion doses of mRNA-1273 have been distributed globally. Approximately 633 million doses of the mRNA-1273 (Moderna COVID-19 vaccine) have been administered to individuals in more than 100 countries, with over 220 million individuals fully vaccinated (Centers for Disease Control and Prevention 2022; Moderna 2022; New York Times 2022).

Based on robust pre-authorization data, which now includes > 10,800 children and adolescents aged 6 months to 17 years who received at least 1 dose of mRNA-1273, Moderna is seeking EUA for:

- a 100 µg dose level of mRNA-1273 for use in individuals 12 to 17 years of age as a two-dose primary series given 1 month apart
- a 50 µg dose level of mRNA-1273 for use in individuals 6 to 11 years of age as a two-dose primary series given 1 month apart
- a 25 µg dose level of mRNA-1273 for use in individuals 6 months to 5 years of age as a two-dose primary series given 1 month apart

The safety, immunogenicity, and efficacy data from the pediatric clinical development program presented here support the favorable benefit-risk profile of mRNA-1273 for individuals 6 months to 17 years of age and fulfill the recommendations outlined in the Food and Drug Administration (FDA) guidance for EUA for Vaccines to Prevent COVID-19 (Food and Drug Administration 2022).

1.2 Background and Unmet Need

As of 02 Jun 2022, confirmed COVID-19 mortality has surpassed 1 million deaths in the US with 1,086 deaths in children 0–17 years of age (Table 1). As of 17 May 2022 there have been more than 84 million COVID-19 cases in the US with 10.7 million cases reported in children 0 to 17 years (CDC).

While vaccinated adults continue to benefit from clinically meaningful levels of protection against COVID-19, children and adolescents continue to be disproportionately at risk (Figure 2 and Figure 3). Since March 2020, approximately 1 in 4 hospitalized children and adolescents (0 to 17 years old) with COVID-19 have required intensive care (Delahoy et al 2021). While rates of severe disease have not

increased since the start of the pandemic, the increase in absolute numbers of cases has added substantial burden, including the number of children requiring ICU admissions (Marks et al 2022a; Shen et al 2020).

Table 1: Number of COVID-19 Cases and Associated Deaths in the US in Infants, Children, and Adolescents

Age Group (Years)	# Cases	# Deaths
12 to 17	5.5 million	449
5 to 11	4.9 million	195
0 to 4	2.4 million	442
Total	10.7 million	1086

*# Cases as of 17 May 2022; # Deaths as of 02 Jun 2022
Source: https://covid.cdc.gov/covid-data-tracker/#demographicsovertime

An evaluation of COVID-19 incidence over time indicates marked increases in children ages 0 to 4 years old during the Delta and Omicron variant waves. Prior to the Delta wave, in June 2021, there were 14.1 incident cases of COVID-19 per 100,000 population among ages 0 to 4 years. Peak incidence among 0 to 4 years of age was 187.0 incident cases per 100,000 population in August 2021 during the Delta wave and increased to 894.6 cases per 100,000 population during the Omicron wave in January 2022 (Centers for Disease Control and Prevention).

After the onset of the Omicron wave, the demographics of hospitalized patients with COVID-19 shifted to younger age groups (Abdullah et al 2022; Goga et al 2021; United Kingdom Health Security Agency 2021). Furthermore, peak hospitalizations during Omicron were nearly four times that observed during the Delta variant wave (Delahoy et al 2021; Marks et al 2022a; Marks et al 2022b).

In addition to the increased incidence and hospitalizations observed, COVID-19 disease in children and adolescents can include a unique complication in conjunction with severe disease called Multisystem Inflammatory Syndrome in Children (MIS-C) (Vogel et al 2021). MIS-C shares some common features with Kawasaki disease, and is defined as fever, laboratory evidence of inflammation, and involvement of ≥ 2 organ systems in an individual < 21 years of age with no plausible alternative diagnosis and evidence of current or recent SARS-CoV-2 infection. MIS-C is also associated with cardiac complications. Through 31 May 2022, 8,525 cases of MIS-C have been reported in the US, with 69 MIS-C related deaths reported. The median age of patients with MIS-C was 9 years (range 5 to 13 years) (Centers for Disease Control and Prevention).

Myocarditis has been well described as a complication of pediatric COVID-19. Children under 16 years of age with COVID-19 are at an almost 37-fold higher risk of myocarditis than the uninfected age- and gender-matched control population (Boehmer et al 2021). Of note, the frequency of myocarditis due to COVID-19 is higher than that of vaccine-associated myocarditis. Additionally, the clinical syndrome of COVID-19 related

myocarditis is more severe and clinically meaningful than vaccine-associated myocarditis. Patients with vaccine-associated myocarditis generally have a milder clinical course than patients with classic myocarditis or MIS-C myocarditis, with a lower likelihood of cardiac dysfunction at presentation and more rapid recovery (Patel et al 2022).

Long COVID, a sequela of COVID-19, which affects up to 20% of persons infected with SARS-CoV-2, has been described in children as well, including in those with mild infection. This syndrome is manifested by symptoms that can include fatigue, muscle and joint pain, insomnia, concentration difficulties, respiratory problems, persistence anosmia and ageusia, and cardiac palpitations that may occur within 6 months after infection (Buonsenso et al 2022; Buonsenso et al 2021; Dembinski et al 2021).

Although the primary focus on COVID-19 in all age groups has been upon the physical consequences of SARS-CoV-2 infection, the pandemic also has had a detrimental impact on the mental health of children. Studies show that a combination of school disruptions, social isolation, and family loss/illness has led to a rise in depression, particularly among adolescents.

As the pandemic continues, vaccination coverage in pediatric populations has not reached the level in adults, leaving a group of individuals vulnerable to both COVID-19 as well as severe COVID-19 and downstream complications. Since May 2021, approximately 60% of the eligible adolescent population and approximately 30% of the 5 to 11 year old population has completed a primary vaccination series in the US.

There is no vaccine option currently available for children under 5 years of age, leaving this vulnerable population without access to the protection afforded by a safe and efficacious vaccine.

Immunization with safe and effective COVID-19 vaccines is a critical component of the strategy to reduce COVID-19-related illnesses, complications, hospitalizations, and deaths in all age groups, prevent interruptions in school and work attendance, and enable normal social interactions.

1.3 Clinical Development of mRNA-1273 in Adolescents, Children, Toddlers and Infants

1.3.1 Study Design

Data to support the EUA are derived from two studies:

- Study 203, a Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate mRNA-1273 in participants 12 to 17 years of age (study start: 09 Dec 2020; blinded efficacy data through 31 May 2021, and safety data through 31 Jan 2022).

- Study 204, a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate mRNA-1273 in participants 6 months to 11 years of age
    - 6 to 11 year old age group – study start: 15 Mar 2021; randomized, blinded portion start 09 Aug 2021, safety data through 21 Feb 2022
    - 2 to 5 year old age group – 21 Apr 2021; randomized, blinded portion start 18 Oct 2021, efficacy and safety data through 21 Feb 2022
    - 6 to 23 months old age group – study start: 20 May 2021; randomized, blinded portion start 18 Oct 2021, efficacy and safety data through 21 Feb 2022

In both studies, the primary safety objective was to evaluate the safety and reactogenicity of mRNA-1273 administered as 2 doses given 28 days apart. Vaccine effectiveness was successfully inferred by meeting the primary immunogenicity objectives, which were consistent with FDA recommendations as outlined at the 10 Jun 2021 VRBPAC meeting. In each age group, immune responses were compared to the immunogenicity subset of vaccine recipients 18–25 years of age from Study 301 where efficacy of mRNA-1273 against COVID-19 infection was demonstrated. The co-primary immunogenicity objectives included assessments of neutralizing antibody geometric mean titer (GMT) ratio and difference in seroresponse rates (SRR) after dose 2 (Day 57). In addition, while the study was not designed with vaccine efficacy (VE) as a primary objective, incidence of COVID-19 was included as a pre-specified secondary objective, based on two different case definitions requiring symptomatology of COVID-19 along with a positive reverse transcription polymerase chain reaction (RT-PCR) test.

Safety endpoints were consistent with those evaluated in Study 301, with some modifications in specific solicited systemic adverse reactions (ARs) and in grading scales for local and systemic solicited ARs for young children. Solicited ARs were collected within 7 days after any dose, all unsolicited adverse events (AEs) were collected within 28 days after any dose, and medically attended adverse events (MAAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and adverse events leading to discontinuation were collected for the duration of the study. Based on the post-authorization awareness of cases of myocarditis observed following receipt of an mRNA vaccine, an independent Cardiac Endpoint Adjudication Committee (CEAC), composed of external experts, was established and was responsible for adjudication of potential cases of myocarditis emerging in the studies.

See Section 3 for complete descriptions of study designs and enrolled participants.

1.3.2 Dose Selection

Table 2 describes the doses evaluated and selected for the various age groups in Studies 203 and 204. Dose selection for blinded, placebo-controlled evaluation of in

Study 204 was based on evaluation of the reactogenicity profile in combination with the observed immune response in the open-label, dose-escalation phase of the study. If a dose was eliminated in an older age group, it was not evaluated in the subsequent age groups.

Table 2: mRNA-1273 Dose Selection by Age Range

Study	Age Range	Doses Evaluated	Selected 2-Dose Primary Series
203	12–17 years	100 µg*	100 µg
204	6–11 years	50 µg and 100 µg	50 µg
	2–5 years	50 µg and 25 µg	25 µg
	6–23 months	25 µg	25 µg

*selected to match the dose used in adult population of Study 301

1.3.3 Exposure and Duration of Follow-up

Studies 203 and 204 enrolled more than 14,000 individuals who received either mRNA-1273 or placebo across the 4 age groups (Table 3). More than 10,800 participants have received at least one injection of mRNA-1273 at the dose selected for authorization in their respective age group. The median duration of follow-up in each study group exceeds the median 2-month recommendation as outlined in EUA guidance (Food and Drug Administration 2022). The median duration of follow-up for the different age groups ranges from 2.4 months to 11.1 months (Table 4).

Table 3: Number of Participants Receiving ≥ 1 Injection of mRNA-1273 (Safety Set)

Study	Age Range	Dose Selected	Participants Receiving ≥ 1 Injection		
			mRNA-1273	Placebo	Total
203	12–17 years	100 µg	2,486	1,240	3,726
204	6–11 years	50 µg	3,387	995	4,382
	2–5 years	25 µg	3,100	1,007	4,107
	6–23 months	25 µg	1,911*	589*	2,500
		Total	**10,884**	**3,831**	**14,715**

*Enrollment ongoing.

Table 4: Median Follow-Up in Each mRNA-1273 Age Group

Study	Age Range	Part	Dose	mRNA-1273 (N)	Median Follow-Up Post-Dose 2 (Months*)
203	12–17 years	Blinded, Randomized	100 µg	2,486	11.1
204	6–11 years	Dose-Ranging	50 µg	380	8.9
			100 µg	371	8.7
		Blinded, Randomized	50 µg	3,007	5.6
	2–5 years	Dose-Ranging	25 µg	75	7.4
			50 µg	149	8.5
		Blinded, Randomized	25 µg	3,031	2.5
	6–23 months	Dose-Ranging	25 µg	150	8.3
		Blinded, Randomized	25 µg	1,760	2.4

*1 month=28 days

1.4 Effectiveness and Efficacy of mRNA-1273 Primary Series in Participants 6 Months to 17 Years

The immune response to mRNA-1273, both in terms of GMT and SRR, is remarkably consistent across age groups from 6 months through 17 years of age. In all age groups, the pre-specified co-primary immunogenicity objectives were met (GMT Ratio: Lower 95% confidence interval [CI] ≥ 0.67 and Point Estimate ≥ 0.8; Difference in SRR: 95% CI > -10% and Point Estimate > -5%). Immune responses in terms of GMT ratio and SRR rates were non-inferior as compared to the young adults from Study 301, where efficacy was demonstrated (Table 5). Therefore, vaccine effectiveness was successfully inferred based on immunobridging.

Table 5: Studies 203 and 204 Summary of Serum Antibody Level and Seroresponse at Day 57 (PP Immunogenicity Subsets, 6 Months to 17 Years)

Study, Age Group	Day 57 Analysis, Part 2 PsVNA	
	Geometric Mean Ratio (vs Study 301 Young Adults) 95% CI	Seroresponse Difference (vs Study 301 Young Adults) 95% CI
Study 203, 12 – 17 Years (100 µg)	1.1 (0.9, 1.2)	0.2 (-1.8, 2.4)
Study 204, 6 – 11 Years (50 µg)	1.2 (1.1, 1.4)	0.1 (-1.9, 2.1)
Study 204, 2– 5 Years (25 µg)	1.0 (0.9, 1.2)	-0.4 (-2.7,1.5)
Study 204, 6 – 23 Months (25 µg)	1.3 (1.1, 1.5)	0.7 (-1.0, 2.5)

Abbreviations: CI=confidence interval; PP=per-protocol; PsVNA =pseudovirus neutralizing antibody assay
GMR & seroresponse difference based on comparison to young adults, 18–25 years of age in Study 301

Efficacy results per Centers for Disease Control (CDC) case definitions, pre-specified as secondary objectives in Studies 203 and 204, provide additional support for the EUA of

mRNA-1273 (Table 6). In all age groups, there was evidence of efficacy against COVID-19 conferred after completion of a primary series of mRNA-1273 administered as 2 doses given 28 days apart during the randomized blinded phase of each study. Assessment of VE in the 6 to 11 age group was limited due to a relatively short, blinded follow-up period (as another COVID-19 vaccine was authorized and participants were unblinded [to offer them access to the authorized vaccine] per protocol). The number of COVID-19 cases accrued 14 days post-dose 2 were too few to perform meaningful analysis, therefore a similar analysis of VE using cases accrued starting 14 days post-dose 1 was conducted (modified Intent-to-Treat 1 [mITT1] set).

VE in children 6 to 17 years of age (with 2-dose 50 µg primary series of mRNA-1273 for 6- to 11 years and 2-dose 100 µg primary series of mRNA-1273 for 12 to 17 years) was comparable to the efficacy observed in adults against the original strain in Study 301 (original strain) as well as real-world effectiveness demonstrated against Delta. Although the VE following 2-dose 25 µg primary series of mRNA-1273 in children 6 months to 5 years is lower than that observed in the pivotal adult or older pediatric studies, it is highly consistent with real-world vaccine effectiveness observed against Omicron in adults. Real-world effectiveness data continue to provide reassuring evidence that mRNA-1273 remains highly effective against hospitalizations and death in adults, even during the Omicron wave (Andrews et al 2022; Tseng et al 2022b).

Table 6: Studies 203 and 204 Summary of Efficacy in CDC Case Definition (6 Months to 17 Years)

Study, Age Group, Major Circulating Variants	Parameter	mRNA-1273	Placebo
Study 203, 12 – 17 Years (100 µg), Original, Alpha	Cases, n/N (%)	2/2139 (< 0.1)	7/1045 (0.7)
	VE (95% CI)	93.3% (47.9, 99.9)	
Study 204, 6 – 11 Years (50 µg), Delta	Cases, n/N (%)	7/2680 (0.3)	18/875 (2.1)
	VE (95% CI)	88.0% (70.0, 95.8)*	
Study 204, 2– 5 Years (25 µg), Omicron	Cases, n/N (%)	119/2594 (4.6)	61/858 (7.1)
	VE (95% CI)	36.8% (12.5, 54.0)	
Study 204, 6 – 23 Months (25 µg), Omicron	Cases, n/N (%)	51/1511 (3.4)	34/513 (6.6)
	VE (95% CI)	50.6% (21.4, 68.6)	

Abbreviations: VE=vaccine efficacy
CDC case definition: 1 systemic or respiratory symptom + PCR positive
*mITT1 population

1.5 Safety and Tolerability of mRNA-1273 Primary Series in Participants 6 Months to 17 Years of Age

Overall, mRNA-1273 was generally well tolerated in children 6 months to 17 years, and the safety profile is consistent with that seen in young adults. No new safety concerns have been identified.

In all age groups, the most common solicited local AR was pain. Local ARs were mostly Grade 1–2 in severity and lasted 2–3 days. Solicited systemic ARs were more common post-dose 2 than post-dose 1 in all age groups.

Among adolescents and children, the most common solicited systemic ARs were headache and fatigue; among young children fatigue was most common. ARs were mostly Grade 1–2 in severity with a median duration of 2–3 days. Among infants and toddlers, the most common solicited systemic ARs were irritability/crying; events were mostly Grades 1–2 in severity with a median duration of 2–3 days. Solicited systemic ARs in infants/toddlers 6 to 23 months were similar to placebo.

Fever was observed in 12% of adolescents and ~25% of infants, toddlers, and children (6 months to 11 years) who received vaccine. Most fevers occurred within 2 days of vaccination, with a median duration of 1 day. Fevers > 40°C were rare, occurring only in the 2 to 5 year (0.4%) and the 6 to 23 month (0.2%) age groups. Fever > 40°C also was of short duration, and the children often had symptoms of concurrent viral infections.

In the participants randomized to mRNA-1273, there were no deaths, cases of MIS-C, or myocarditis/pericarditis observed in any age group; within 28 days of vaccination, no related SAEs were observed in children or adolescents; 1 related SAE of fever/seizure was reported in the 6 to 23 month age group.

1.6 Ongoing Follow-up

The long-term safety and effectiveness of mRNA-1273 in Studies 203 and 204 will continue to be captured until study completion.

As the pandemic has continued to evolve, Study 203 was amended to offer a 50 µg booster dose to all study participants (~1,400 participants have been boosted). In addition, all Study 204 participants 6 to 11 years have been offered a booster dose with mRNA-1273 (~1700 participants have been boosted) and participants < 6 years will be offered a booster at least 4 months after their second dose (~100 participants 2 to 5 years of age and ~80 participants 6 to 23 months of age have been boosted as of 03 Jun 2022). The boosters for < 6 years will either be mRNA-1273 or mRNA-1273.214, an Omicron-containing vaccine. Follow-up will continue for all participants in these studies through 12 months after last dose.

Several post-authorization safety studies (PASS) in the US and EU are included in the Risk Management Plan addressing long-term safety information as well as characterization of important and potential identified risks included in the safety profile of mRNA-1273. The previously endorsed PASS assessing the risk of multiple AESI (US PASS protocol mRNA-1273-P903 and EU PASS mRNA-1273-P904) have been expanded to capture any use of mRNA-1273 observed, including subgroups of children and adolescents. Analyses in these studies will quantify the incidence of vaccine-associated myocarditis by age, sex, and dose of mRNA-1273, and will utilize both historical cohort and self-controlled risk interval methods to assess absolute and relative

risk. Further, new analyses currently in development will characterize the natural history, clinical course, short and long-term outcomes, and risk factors for myocarditis temporally associated with mRNA-1273.

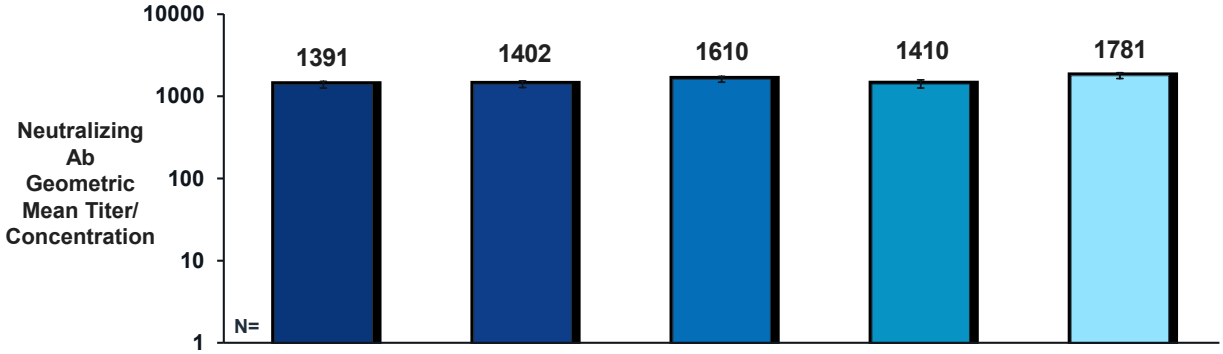
1.7 Benefit-Risk Conclusions

As the pandemic persists, and new, highly transmissible variants of concern, such as Omicron, emerge, real-world data continue to demonstrate that COVID-19 vaccines provide protection against severe disease and reduce COVID-19-associated hospitalizations in adults. However, there has also been a substantial increase in the number of COVID-19 infections and hospitalizations among infants, toddlers, children and adolescents. As hospitalizations have increased in this age group, so have severe complications of COVID-19, including admissions to ICUs, cases of MIS-C, and deaths in the pediatric population. As only 60% and 30%, respectively, of US populations of children 12 to 17 and 5 to 11 years of age have been vaccinated against COVID-19, and as there are currently no available vaccines in children between 6 months and 4 years of age, an unmet medical need for safe and effective vaccines to prevent SARS-CoV-2 remains.

The totality of safety, immunogenicity, and efficacy data from the clinical development program meet recommendations outlined by EUA guidance and support a favorable benefit-risk profile in all age groups evaluated. This data package supports the EUA of mRNA-1273 in children 6 months to 17 years of age:

- > 10,800 children and adolescents received at least 1 dose of mRNA-1273.
- Median duration of follow-up was > 2 months in each study group.
- mRNA-1273 was well tolerated in all age groups with a safety profile consistent with young adults. No new safety concerns have been identified.
- The doses selected met pre-specified co-primary immunogenicity objectives compared to young adults 18 to 25 years of age and is remarkably consistent across age strata (Figure 1). Therefore, vaccine effectiveness of mRNA-1273 is successfully inferred based on immunobridging.
- Protection from COVID-19 was conferred after completion of a primary series of mRNA-1273 administered as 2 doses given 28 days apart. The VE observed is consistent with efficacy/effectiveness in individuals ≥ 18 years of age. In all age groups, there was direct evidence of efficacy observed with mRNA-1273 during the circulation of the original strain (in ages 12 to 17), Delta (in ages 6 to 11), and Omicron variants (in ages 6 months to 5 years) after a two-dose primary series.
- Moderna has established plans for safety and effectiveness follow-up post-authorization.

Figure 1: Immunogenicity of mRNA-1273 1 Month after 2-Dose Primary Series Across Age Groups



Geometric Mean Ratio (vs Young Adults)	1.1	1.2	1.01	1.28

Abbreviation: Ab=antibody
Geometric mean titer displayed for 12 to 17 and 6 to 11 year age groups
Geometric mean concentration displayed for 18 to 25 year, 2 to 5 year, and 6 to 23 months age groups

2 COVID-19 BACKGROUND

Summary

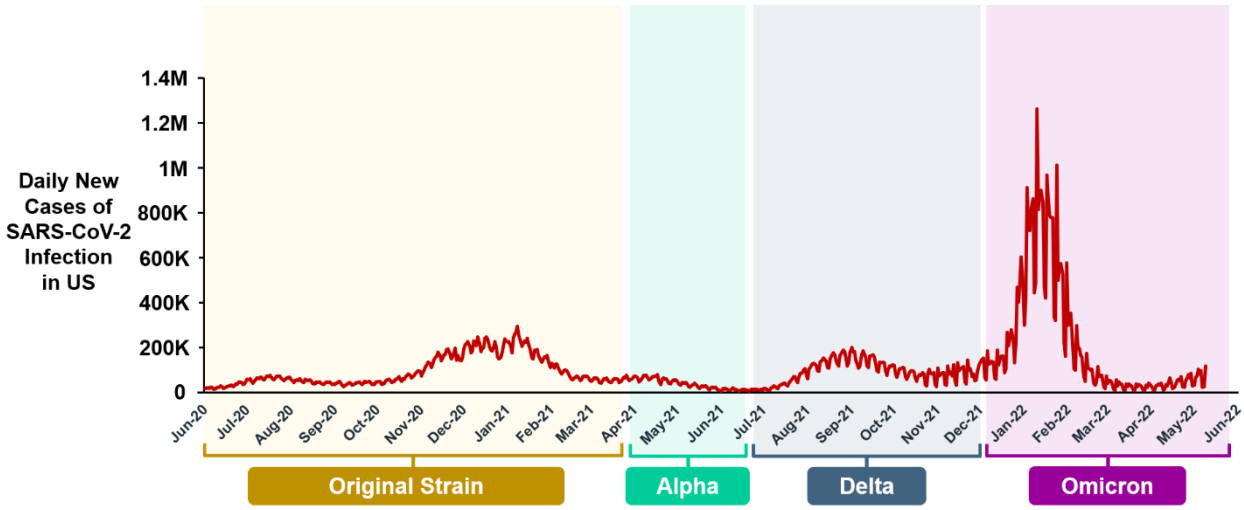
- COVID-19 has been a significant public health issue since early 2020.
- As of 02 Jun 2022 in the US, confirmed COVID-19 mortality has surpassed 1 million deaths, with more than 84 million cases of COVID-19.
  - 5.5 million cases of COVID-19 and 449 deaths reported among ages 12 to 17 years
  - 4.9 million cases of COVID-19 and 195 deaths reported among ages 5 to 11 years
  - 2.4 million cases of COVID-19 and 442 deaths reported among ages 0 to 4 years
- Hospitalization rates among children 0 to 4 years of age were approximately five times higher during the Omicron-predominant peak period than the Delta predominant period.
- Since March 2020, approximately 1 in 4 hospitalized infants, children and adolescents with COVID-19 have required intensive care.
- Through 31 May 2022, 8,525 cases of MIS-C have been reported in the US, including 69 MIS-C related deaths; the median age of patients with MIS-C was 9 years.
- There is no vaccine option currently available for children under 5 years of age, leaving this vulnerable population without access to the protection afforded by a safe and efficacious vaccine.
- Immunization with safe and effective COVID-19 vaccines is a critical component of the strategy to reduce COVID-19-related illnesses, complications, hospitalizations, and deaths in all age groups.

2.1 Clinical/Pathophysiology of Condition

Early in 2020, the World Health Organization declared COVID-19 to represent a Public Health Emergency of International Concern, denoting its highest level of public health emergency. Confirmed COVID-19 mortality has surpassed 6.3 million deaths worldwide and more than 1 million deaths in the US as of 02 Jun 2022, with COVID-19 cases numbered over 532 million worldwide and more than 84 million in the US (Centers for Disease Control and Prevention).

Figure 2 shows the daily new cases of SARS-CoV-2 infection in the US over time. Several highly transmissible variants of concern, including the Delta and Omicron variants, have resulted in continued viral transmission and an ongoing public health emergency.

Figure 2: Daily Cases of SARS-CoV-2 Infections and Predominant Circulating Variants Over Time



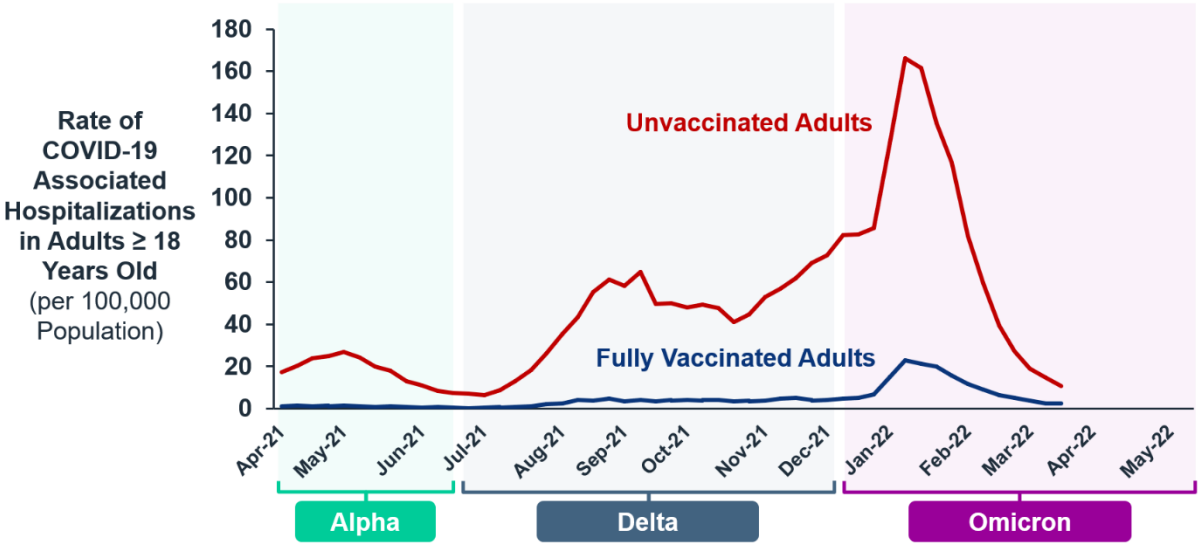
Abbreviations: SAR-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2; US=United StatesSource: Data as of 14 May 2022 –https://covid.cdc.gov/covid-data-tracker/#trends_dailycases

2.2 Currently Available COVID-19 Vaccines

It is widely acknowledged that the key to controlling this pandemic and mitigating its impact is primary prevention through vaccination. Currently available COVID-19 vaccines in the US for adults 18 years of age and older include mRNA-1273 (EUA: December 2020; Biologics License Application [BLA]: January 2022) and BNT162b2 (EUA: December 2020; BLA: August 2021) and Ad26.COV2.S (EUA: February 2021). BNT 162b2 is also available for children and adolescents, 5 to 17 years of age, in the US. Outside of the US, mRNA-1273 is indicated for use in adolescents 12 to 17 years of age and children 6 to 11 years of age in over 40 countries, as of 03 Jun 2022.

As the pandemic persists, and new, highly transmissible variants of concern, like Omicron, emerge – the data continue to demonstrate that COVID-19 vaccines provide protection against severe disease and reduce COVID-19-associated hospitalizations. Vaccinated adults have fewer COVID-19 associated hospitalizations as compared to unvaccinated adults (Figure 3).

Figure 3: Rate of Severe COVID-19 Hospitalizations in Vaccinated and Unvaccinated Adults (≥ 18 Years)



Fully Vaccinated=2-dose primary series
Data as of 14 May 2022
Source: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination

2.3 Unmet Medical Need

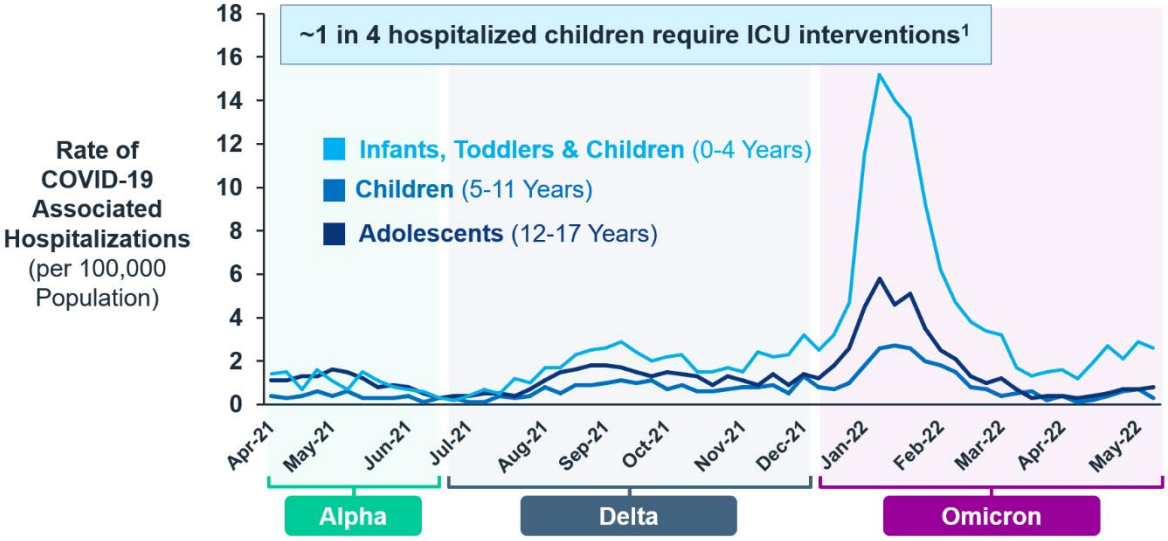
Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults (Ayoub et al 2020; Hay 2020); however, COVID-19 can also lead to severe outcomes in children and adolescents (Havers et al 2021; Kim et al 2020).

An evaluation of COVID-19 incidence over time indicates marked increases in the ages 0 to 4 years with the Delta and Omicron variant waves. Prior to the Delta wave, in June 2021, there were 14.1 incident cases of COVID-19 per 100,000 population among children ages 0 to 4 years. Peak incidence among children 0 to 4 years reached 187.0 incident cases per 100,000 population in August 2021 during the Delta wave and increased further to 894.6 cases per 100,000 population during the Omicron wave in January 2022 (Centers for Disease Control and Prevention).

Initial data suggest that the demographics of hospitalized patients with COVID-19 shifted to younger age groups after the onset of the Omicron wave (Abdullah et al 2022; Goga et al 2021; United Kingdom Health Security Agency 2021). The weekly hospitalization rates in the pre-Delta, Delta, and Omicron periods are shown in Figure 4. During the Omicron variant wave, peak COVID-19-related hospitalizations amongst older children were nearly four times that observed during the Delta variant wave and in children 0 to 4 years old were approximately five times higher than the rates observed during the Delta wave.

Since March 2020, approximately 1 in 4 hospitalized children, and adolescents (0 to 17 years) with COVID-19 have required intensive care (Delahoy et al 2021). While rates of severe disease in children have not increased since the start of the pandemic, the increase in absolute numbers of cases has added substantial burden overall, including the number of children requiring ICU admissions (Marks et al 2022a; Shen et al 2020). According to the Coronavirus Disease 2019 Associated Hospitalization Surveillance Network, a population-based surveillance system in the US that collects laboratory-confirmed COVID-19-associated hospitalizations among children and adults through a network of over 250 acute-care hospitals in 14 states, there were 3,606 hospitalized children between 0 to 4 years of age through 16 Apr 2022, with an estimated 24.1% of these children requiring ICU interventions, and with 21 related in-hospital deaths reported. Additionally, approximately 6% of children 0 to 17 years of age hospitalized due to COVID-19 required mechanical ventilation (COVID-NET 2022).

Figure 4: Weekly COVID-19–Associated Hospitalization Rates in the United States among Children and Adolescents by Age Group and Variant



COVID-19; Coronavirus disease 2019; ICU: Intensive Care Unit
Data as of 14 May 2022
Source: https://gis.cdc.gov/grasp/covidnet/covid19_3.html; 1. Delahoy, et al., Clin Infect Dis 20212; 73:336-340. Doi: 10.1093/cid/ciac388/6589788

MIS-C is amongst the most severe complications of COVID-19 in children and adolescents. While the long-lasting cardiovascular effects of MIS-C are still unknown, patients may suffer both acute and sub-acute complications from disease and cardiovascular manifestations range from mild to severe (Chin et al 2022). It has been reported that between 50 and 70% of patients with MIS-C have myocarditis. In a study evaluating hospitalized pediatric patients diagnosed with MIS-C (Son et al 2021), 47% required vasopressor support, 41% had depressed left ventricular systolic dysfunction,

12% developed coronary artery aneurysm, and 3% required extracorporeal membrane oxygenation. While short-term cardiac outcomes in these patients are reassuring, with almost all patients fully recovering at 2-week follow-up, there is some evidence that diastolic dysfunction may persist in a small subset of patients six months after acute illness (Capone et al 2021). Through 31 May 2022, there were a total of 8,525 cases of COVID-19 related MIS-C reported in the US, including 69 MIS-C related deaths. The median age of patients with MIS-C was 9 years (range 5 to 13 years).

COVID-19 is a strong and significant risk factor for myocarditis, with risk varying by age group. A large cohort study found that children under 16 years of age with COVID-19 are at 37 times higher risk of myocarditis than the uninfected age and gender-matched control population (Boehmer et al 2021). Manifestations of viral myocarditis can range from subclinical disease to sudden death, with new-onset atrial or ventricular arrhythmias, complete heart block, or an acute myocardial infarction–like syndrome. Cardiac symptoms are variable and may include fatigue, decreased exercise tolerance, palpitations, precordial chest pain, and syncope. Chest pain in acute myocarditis can result from an associated pericarditis or, occasionally, from coronary-artery spasm. The long-term sequalae of COVID-19 related myocarditis in children are not well understood, however, the major long-term sequela of general viral myocarditis is dilated cardiomyopathy with chronic heart failure (Cooper 2009). There is also evidence of chronic sequelae known as “long-COVID-19” in children even after mild infection; this includes fatigue, muscle and joint pain, insomnia, concentration difficulties, respiratory problems, persistence anosmia and ageusia, and cardiac palpitations that may persist 6 months or more after infection (Dembinski et al 2021). Immunization with a safe and effective COVID-19 vaccine is a critical component of the strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths in all age groups and to help restore societal functioning. Overall, the evidence suggests that the burden of COVID-19 has increased in younger age groups over time based on the number and proportion of cases. Vaccination is expected to prevent most of the morbidity and mortality consequences in children 6 months to 17 years of age.

Currently, there is only one authorized COVID-19 vaccine for the 5 to 11 and 12 to 17 year old age groups. Since May 2021, about 60% of eligible adolescent population and about 30% of eligible participants 5 to 11 years old have completed primary vaccination with this vaccine.

As the pandemic continues, it is evident that the vaccination coverage in pediatric and adolescent populations has not reached the level in adults, leaving a group of individuals vulnerable to both COVID-19 as well as severe COVID-19 and sequelae. For children and adolescents who remain unvaccinated, especially those less than 5 years of age for whom there is no authorized COVID-19 vaccine, there remains an urgent unmet need for a safe and effective vaccine that can reduce COVID-19-associated morbidity and mortality.

3 OVERVIEW OF CLINICAL DEVELOPMENT OF mRNA-1273 FOR ADOLESCENTS, CHILDREN, TODDLERS, AND INFANTS

Summary

- The pediatric development program consists of two clinical studies in > 10,800 children and adolescents, 6 months to 17 years of age.
- Studies progressed sequentially through age de-escalation: adolescents 12 to 17 years, older children 6 to 11 years, younger children 2 to 5 years, and, finally, infants/toddlers 6 to 23 months.
- Study 203 evaluated mRNA-1273 in adolescents 12 to 17 years of age in a randomized, placebo-controlled design.
- Study 204 evaluated mRNA-1273 in individuals 6 months to 11 years of age and included an open-label, Part 1 dose selection phase for each age group. Based on the review of Part 1 (i) safety and reactogenicity and (ii) available immunogenicity data, a dose was selected for randomized, placebo-controlled evaluation in Part 2.
- Effectiveness of mRNA-1273 was inferred by comparing the GMR for the antibody titer and SRR group difference from each age stratum (12 to 17 years, 6 to 11 years, 2 to 5 years and 6 to 23 months) to the pivotal adult study (Study 301), in which 93.2% VE against COVID-19 was demonstrated.

Moderna is requesting for EUA for a 2-dose primary series of mRNA-1273 for individuals 6 months to 17 years based on the following:

- Clinical trials enrolled > 14,000 individuals 6 months to 17 years of age
  - > 10,800 participants received ≥ 1 injection of mRNA-1273 (Table 3)
  - Median duration of follow-up ranges from 2.4 to 11 months in each study group (Table 4)
- Doses selected for each age group met pre-specified co-primary immunogenicity objectives compared to young adults 18 to 25 years of age
- Vaccine efficacy consistent with efficacy/effectiveness in individuals ≥ 18 years of age
- Established plans for safety and effectiveness follow-up post-authorization
- Favorable benefit-risk profile in each age stratum

3.1 Studies Supporting Pediatric Development of mRNA-1273

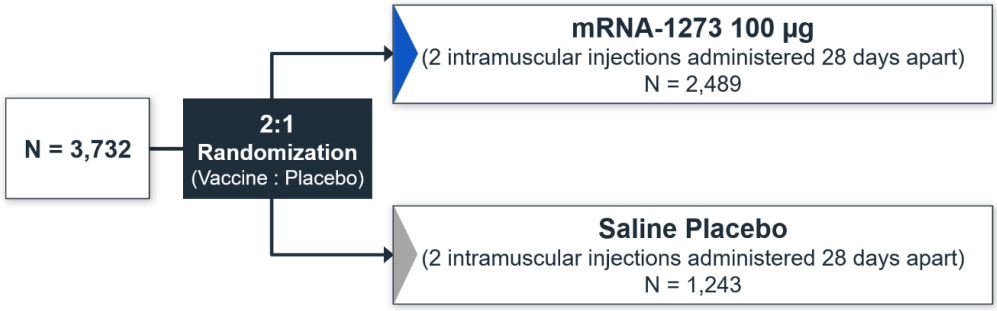
3.1.1 Study mRNA-1273-P203

Study 203 is an ongoing, 2-part (Part A and Part B), Phase 2/3, randomized, observer-blind, placebo-controlled study evaluating the safety, reactogenicity, and effectiveness

of the mRNA-1273 vaccine in healthy adolescents 12 to 17 years old. The goal of the study is to support an indication for use of mRNA-1273 (100 µg intramuscular, given as 2 doses, 28 days apart) in the 12 to 17 years age group.

Study participants were randomly assigned to receive 2 injections (28 days apart) of either 100 µg of mRNA-1273 vaccine or saline placebo in a 2:1 randomization ratio (Part A, the blinded phase of Study 203; Figure 5).

Figure 5: Study 203 Study Design Schematic



- **Planned follow-up:** 12-months after last dose

Upon availability of another COVID-19 vaccine authorized for emergency use in adolescents, the study transitioned to Part B, the Open-label Observational Phase. In Part B, participants who were age-eligible for a COVID-19 vaccine authorized for emergency use could request unblinding. Placebo recipients were subsequently offered mRNA-1273. In Part C, all study participants were offered mRNA-1273 as a booster.

Follow-up will continue for all participants through 12 months after the last dose.

3.1.1.1 Study Objectives

The primary safety objective of Study 203 is to evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart. The primary immunogenicity objective of Study 203 is to infer effectiveness of mRNA-1273 (100 µg, 2 doses 28 days apart) 28 days after dose 2 of mRNA-1273 (Day 57) by comparison of immune responses in adolescents (12 to 17 years old) to the young adult (18 to 25 years old) group in Study 301, where efficacy was demonstrated. Secondary study endpoints are to assess the VE of mRNA-1273 on COVID-19.

Analysis methods are described in Section 3.2.

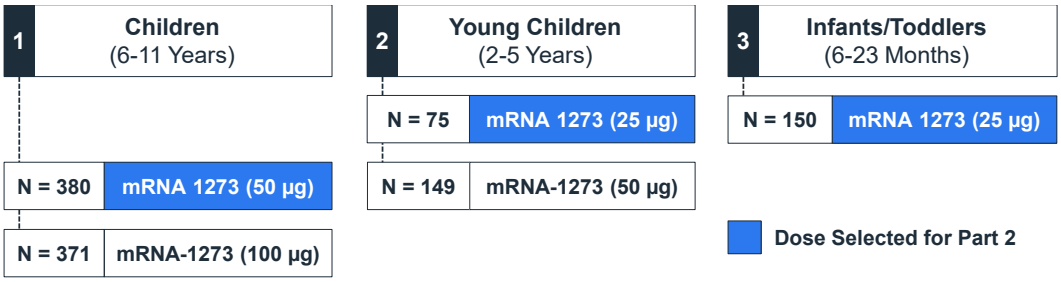
3.1.2 Study mRNA-1273-P204

Study 204 is an ongoing Phase 2/3, 2-part, open-label (Part 1), dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled (Part 2)

expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age.

Children were sequentially enrolled first in Part 1 for evaluation of escalating dose levels and then in Part 2 with the selected dose level for further evaluation. As the study followed a pattern of age de-escalation, children 6 to 11 years were enrolled to Part 1 to evaluate dose levels of 50 µg and 100 µg administered as a two-dose schedule one month apart prior to children 2 to 5 years and 6 to 23 months (Figure 6). In each age group, dose selection was based on a review of reactogenicity and immunogenicity data from the target age group. Dose escalation within Part 1 was also informed by observations of reactogenicity and immunogenicity in older age groups.

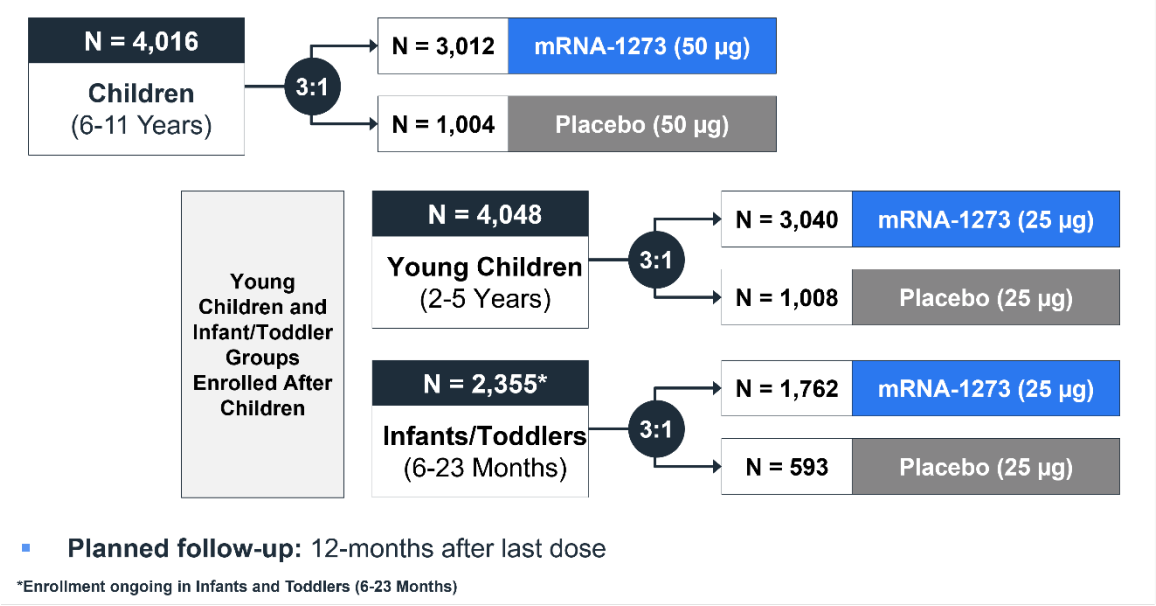
Figure 6: Study 204 Part 1 Design Schematic



Part 2 was designed to randomize children in a 3:1 ratio to receive either mRNA-1273 or saline placebo (Figure 7). Part 2 for children 6 to 11 years was conducted first, and Part 2 for the 2–5 year and the 6 to 23 month age groups was conducted concurrently thereafter.

In addition, all Study 204 participants 6 to 11 years have been offered a booster dose with mRNA-1273 (~1700 participants have been boosted) and participants < 6 years will be offered a booster at least 4 months after their second dose. The boosters for < 6 years will either be mRNA-1273 or mRNA-1273.214, an Omicron-containing vaccine. Follow-up will continue for all participants through 12 months after the last dose.

Figure 7: Study 204 Part 2 Design Schematic



3.1.2.1 Study Objectives

The primary safety objective of Study 204 is to evaluate the safety and reactogenicity of the selected dose of mRNA-1273. The co-primary effectiveness objective is to infer effectiveness based on immunobridging to adults enrolled in the pivotal clinical efficacy study (Study 301). Evaluation of the VE against COVID-19 was included as a secondary objective.

For these purposes, the focus of this Briefing Document is on the randomized, blinded, placebo-controlled portion of the study (Part 2).

Analysis methods are described in Section 3.2.

3.1.2.2 Dose Selection

In the open-label, dose selection part of Study 204, children 6 to 11 years of age were first enrolled into the mRNA-1273 50 µg group and then into the mRNA-1273 100 µg group. The 50 µg dosage was advanced for evaluation in children 6 to 11 years in the blinded, randomized part of Study 204 as fever rates among children receiving the 100 µg dose were higher than rates among children receiving the 50 µg dose.

Children 2 to 5 years old were enrolled at the planned initial mRNA-1273 50 µg dose group in the open-label, dose selection part of Study 204. Assessment of this 50 µg dose indicated a rate of fever similar to that after the 100 µg dose in the older age group (6 to 11 years), and a decision was made to assess a lower dose. Accordingly, a 25 µg dose was evaluated in a group of 2 to 5-year-old children in Part 1. The youngest

children (6 to 23 months) received 25 µg of mRNA-1273 in Part 1, and the tolerability profile was considered acceptable.

Part 1 immunogenicity assessments suggested that the 50 µg dose and the 25 µg dose could meet the stringent, pre-specified non-inferiority criteria to achieve immunobridging to the young adults from Study 301 for the respective age groups. Available data were also reviewed by the Data Safety Monitoring Board (DSMB) prior to the start of Part 2; the DSMB agreed with the selection of 50 µg for the 6 to 11 year age group and 25 µg for the 2 to 5 year and 6 to 23 month age groups.

3.1.3 Study mRNA-1273-P301: Immunogenicity Cohort Used as Control Group for Inference of Efficacy

The pivotal study of mRNA-1273 in adults, Study 301, is a Phase 3 efficacy, safety, and immunogenicity study that provides the primary clinical evidence of VE and safety in adults 18 years of age and older. The study was designed as a randomized, observer- and participant-blind, placebo-controlled study of the efficacy, safety, and immunogenicity of 2 doses of mRNA-1273 100 µg compared with placebo. More than 30,000 participants were randomized and > 96.7% of participants received dose 2 of mRNA-1273.

Vaccine efficacy was observed to be 94.1% with a median of 9 weeks of efficacy follow-up and remained high and durable with observed VE of 93.2% after 5.3 months of median efficacy follow-up. The safety profile was clinically acceptable (Baden et al 2021; El Sahly et al 2021).

Study 301 provided pivotal data for the support of the US EUA (18 Dec 2020) and Biologics License (31 Jan 2022), the Canadian Interim Order (23 Dec 2020), the European Medicines Agency Conditional Marketing Authorization (06 Jan 2021), and numerous other marketing authorizations worldwide, for use of mRNA-1273 to prevent COVID-19.

Based on regulatory recommendation, immunogenicity data from a subset of participants 18 to 25 year of age from Study 301 was used as the comparator for non-inferiority analyses in each pediatric age group.

3.2 Study Endpoints and Analysis Sets

3.2.1 Immunogenicity Endpoints

The primary objective to infer efficacy of mRNA-1273 in adolescents and children was evaluated by comparing the immune response to mRNA-1273 as measured by geometric mean (GM) values/titers of serum antibody (Ab) and SRR in Study 203 or 204 with those obtained from young adults (18 to 25 years old) in Study 301.

There were two pre-defined primary immunogenicity criteria; both had to be met in each age stratum to consider vaccine effectiveness successfully inferred:

- The GMR [pediatric age group over young adult group from Study 301] had to have a point estimate ≥ 0.8 and a lower limit (LL) of the 95% CI ≥ 0.67.
- The group difference [pediatric age group minus young adult group from Study 301] in seroresponse rates had to have a point estimate ≥-5% and a LL of the 95% CI >-10%.

In age groups where a dose below 100 µg was used, a GMR point estimate of ≥ 1.0 was requested by the FDA. The seroresponse rate was defined as the rate in participants achieving seroresponse based on at least a 4-fold rise from baseline for those with baseline titers greater than or equal to the lower limit of quantitation for the assay (≥ LLOQ) or achieving a titer at least equal to the LLOQ where baseline titers were < LLOQ at baseline are set to LLOQ for the analysis. The difference in seroresponse rate is defined as seroresponse rate in Studies 203 or 204 participants in the mRNA-1273 group minus that in Study 301 young adults in the mRNA-1273 group.

3.2.1.1 Bioassays for the Assessment of Immunogenicity Endpoints

The primary effectiveness endpoint was evaluated through use of a validated pseudovirus neutralization assay (PsVN). The strategy to support mRNA-1273 clinical development includes an extensive panel of assays to assess SARS-CoV-2 infection and characterize the immune response induced by mRNA-1273 (Table 7).

Table 7: Overview of Bioassays for the Assessment of Clinical Endpoints

Virus Strain	Method	Study Number(s)
Prototype (D614G)	PsV neutralization	203, 204, and 301
Prototype, Beta, Delta, Omicron	Multiplex ECL	204, and 301
Delta	PsV neutralization	204 and 301
Omicron	PsV neutralization	203, 204, and 301

Abbreviations: ECL=electrochemiluminescent; PsV=pseudotyped virus

3.2.2 Efficacy Endpoints

VE was assessed against COVID-19 using the same methods as those employed for adults 18 years of age and older in Study 301. Cases of symptomatic SARS-COV-2 infection were defined as follows:

- Primary case definition (“CDC definition”): At least one respiratory or one systemic symptom (fever [≥ 38°C/≥ 100.4°F], chills, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, cough, shortness of breath or difficulty breathing congestion or runny nose, nausea, vomiting or diarrhea, [and for Study 204 only: poor appetite/feeding]) AND confirmed SARS-CoV-2 infection by RT-PCR.
- Secondary Case definition (“Study 301 definition”): Either TWO systemic symptoms (Fever [≥ 38°C/≥ 100.4°F], chills, myalgia, headache, sore throat, new olfactory and taste disorder[s]) OR ONE respiratory sign or symptom (cough, shortness of breath or difficulty breathing, clinical or radiographical evidence of pneumonia) AND confirmed SARS-CoV-2 infection by RT-PCR.

3.2.3 Safety Endpoints

Safety assessment included monitoring:

- Solicited local and systemic ARs that were reported during the 7 days following each injection, recorded daily using an eDiary
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days)
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation
- AESIs, including acute myocarditis or pericarditis and MIS-C (see the Appendix: Specified Adverse Events of Special Interest in Section 11 for additional details)
- SAEs and MAAEs from first dose on Day 1 through the entire study period
- Symptoms suggestive of potential myocarditis or pericarditis were sought from participants during safety calls from 28 Jul 2021 onward

Descriptive statistics were provided for each safety endpoint.

3.2.4 Analysis Sets

The key analysis sets presented for Studies 203 and 204 are summarized in Table 8.

Table 8: Key Analysis Sets for Studies 203 and 204

Analysis Set	Study 203 (12 – 17 years) Description	Study 204 (6 month – 11 years) Description
PP Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset 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 who were seropositive at baseline were excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset was used for analyses of immunogenicity unless specified otherwise.	A subset of participants in the FAS who met all the following criteria: • baseline (Day 1) SARS-CoV-2 status available • baseline and ≥ 1 post-injection Ab assessment for the analysis endpoint • received planned doses of IP per schedule • complied with the immunogenicity window based on the 2nd dose injection timing • had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline • not receiving HAART (for participants who have a diagnosis of HIV) • baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint • had no major protocol deviations that impact critical or key study data
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.	All participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline
mITT1 Set	All participants in the mITT Set excluding those who received the wrong treatment.	Participants in the Solicited Safety Set who received the first study injection and contributed any solicited AR data from the time of 1st study injection through the following 6 days
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.	All enrolled participants (Part 1) All randomized participants who received any study injection (Part 2)

Abbreviations: Ab=antibody; AR=adverse reaction; bAb=binding antibodies; FAS=full analysis set; HAART=highly active antiretroviral therapy; IP=investigational product; mITT=modified Intent-to-Treat; PP=per-protocol; RT-PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2.

3.3 Evaluation of Myocarditis and Pericarditis in Clinical Trials of Infants, Toddlers, Children, and Adolescents

The first cases of myocarditis in association with vaccination were reported during vaccination campaigns in the US and Israel while Studies 203 and 204 were ongoing. Based on these reports, along with additional supporting information reviewed at Advisory Committee on Immunization Practices meetings, Moderna updated the mRNA-1273 fact sheets, Investigator brochures, and informed consent forms to increase awareness of symptoms of these conditions amongst clinical investigators, study participants, and their parents. As part of this effort, Investigators were advised of the CDC working case definitions for myocarditis and pericarditis (Gargano et al 2021). The safety call script –used 7 days after dose 1 and after dose 2 and in subsequent safety calls - was revised to specifically solicit symptoms potentially related to myocarditis and pericarditis. Medical evaluation based on the Investigator medical judgment were undertaken for positive reports.

In addition to this enhanced approach to collecting AE, the full safety database was interrogated for events or symptoms that might indicate potential events of clinical interest. Two overlapping approaches were used to interrogate all AEs using:

(i) narrow, and narrow and broad, cardiomyopathy standard Medical Dictionary for Regulatory Activities (MedDRA) Standardized Medical Dictionary for Regulatory Activities Query (SMQs),

(ii) an algorithm generated using MedDRA terms v.23.0 included in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al 2021).

Any potential events were adjudicated by an independent CEAC comprised of pediatric and adult cardiologists.

In addition to these measures in the clinical trials, the ongoing PASS also captured myocarditis and pericarditis as AESIs.

3.4 Enrolled Participants

3.4.1 Study 203 Study Populations (12 to 17 Years)

3.4.1.1 Disposition

A total of 3,732 participants 12 to 17 years of age were randomly assigned to receive a two-dose primary series of either 100 µg of mRNA-1273 vaccine or placebo in a 2:1 randomization ratio. Table 9 shows the participant disposition in Study 203. More than 99% of participants received both doses of their treatment regimen. One participant in the mRNA-1273 discontinued the study due to an AE.

Table 9: Study 203 Participant Disposition (Randomization Set, 12 to 17 Years)

	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Randomized	N=2489	N=1243	N=3732
Completed 1 dose	2486 (99.9)	1240 (99.8)	3726 (99.8)
Completed 2 doses	2480 (99.6)	1222 (98.3)	3702 (99.2)
Discontinued study vaccine	5 (0.2)	16 (1.3)	21 (0.6)
Reason for discontinuation of study vaccine			
Adverse event	1 (< 0.1)	0	1 (< 0.1)
Lost to Follow-Up	2 (< 0.1)	6 (0.5)	8 (0.2)
Physician decision	1 (< 0.1)	0	1 (< 0.1)
Withdrawal of consent	1 (< 0.1)	9 (0.7)	10 (0.3)
Other	0	1 (< 0.1)	1 (< 0.1)
Discontinued from study	57 (2.3)	188 (15.1)	245 (6.6)
Reason for discontinuation			
Adverse event	1 (< 0.1)	0	1 (< 0.1)
Withdrawal by participant	27 (1.1)	102 (8.2)	129 (3.5)
Lost to follow up	3 (0.1)	6 (0.5)	9 (0.2)
Protocol deviation	8 (0.3)	14 (1.1)	22 (0.6)
Physician decision	1 (< 0.1)	0	1 (< 0.1)
Other	17 (0.7)	66 (5.3)	83 (2.2)

Datacut: 08 May 2021
Source: Study 203 EUA Amendment Table 1 (Table 14.1.1.1.1, Table 14.1.2.1.1.1.)

3.4.1.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of participants in the Study 203 Safety Set were representative of the target population and generally balanced between the mRNA-1273 and placebo groups (Table 10).

The Per-Protocol (PP) Immunogenicity Subset included 340 mRNA-1273 recipients in Study 203; the demographics were consistent with the Safety Set.

Table 10: Study 203 Participant Demographics and Baseline Characteristics (Safety Set, 12 to 17 Years)

Characteristic	mRNA-1273 (N=2,486)	Placebo (N=1,240)	Total (N=3,726)
Age			
Mean (SD)	14.3 (1.6)	14.2 (1.6)	14.3 (1.6)
Median	14.0	14.0	14.0
Min, max	12, 17	12, 17	12, 17
16 to < 18 years	648 (26.1)	311 (25.1)	959 (25.7)
12 to < 16 years	1,838 (73.9)	929 (74.9)	2,767 (74.3)
Sex, n (%)			
Female	1,203 (48.4)	608 (49.0)	1,811 (48.6)
Male	1,283 (51.6)	632 (51.0)	1,915 (51.4)
Race, n (%)			
American Indian or Alaska Native	12 (0.5)	7 (0.6)	19 (0.5)
Asian	142 (5.7)	79 (6.4)	221 (5.9)
Black or African American	83 (3.3)	42 (3.4)	125 (3.4)
Native Hawaiian or Other Pacific Islander	2 (< 0.1)	0	2 (< 0.1)
White	2,085 (83.9)	1,041 (84.0)	3,126 (83.9)
Other	27 (1.1)	9 (0.9)	36 (1.0)
Multiracial	118 (4.7)	50 (4.0)	168 (4.5)
Not reported	11 (0.4)	11 (0.9)	22 (0.6)
Unknown	6 (0.2)	1 (< 0.1)	7 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	280 (11.3)	152 (12.3)	432 (11.6)
Not Hispanic or Latino	2,188 (88.0)	1,076 (86.8)	3,264 (87.6)
Not reported	17 (0.7)	10 (0.8)	27 (0.7)
Unknown	1 (< 0.1)	2 (0.2)	3 (< 0.1)
Body mass index			
< 30 kg/m^2	2,316 (93.2)	1,146 (92.4)	3,462 (92.9)
≥ 30 kg/m^2	170 (6.8)	94 (7.6)	264 (7.1)
Baseline SARS-CoV-2 status[a], n (%)			
Positive	147 (5.9)	69 (5.6)	216 (5.8)
Negative	2,167 (87.2)	1,075 (86.7)	3,242 (87.0)
Missing	172 (6.9)	96 (7.7)	268 (7.2)

Abbreviations: COVID-19=coronavirus disease 2019; RT-PCR=reverse transcriptase polymerase chain-reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SD=standard deviation.

[a] Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.

Datacut: 08 May 2021

Source: Adolescent EUA Table 3, Study 203 Table 1.3

3.4.2 Study 204 Study Populations (6 to 11 Years)

3.4.2.1 Disposition

In the randomized, blinded phase of Study 204 for children 6 to 11 years of age, 4,016 participants were randomly assigned to receive a two-dose primary series of 50 µg of mRNA-1273 or placebo in a 3:1 randomization ratio. Table 11 shows the participant disposition for this age group in Study 204. More than 96% of participants completed their assigned treatment regimen. Of note, 2 participants randomized to placebo actually received 2 doses of mRNA-1273 due to a dosing error. One participant in the mRNA-1273 and two participants in the placebo group discontinued the study due to an AE.

Table 11: Study 204 Participant Disposition (Randomization Set, 6 to 11 Years)

	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Randomized	N=3012	N=1004	N=4016
Completed 1 dose	3005 (99.8)	997 (99.3)	4002 (99.7)
Completed 2 doses	2988 (99.2)	973 (96.9)	3961 (98.6)
Discontinued study vaccine	13 (0.4)	14 (1.4)	27 (0.7)
Reason for discontinuation of study vaccine			
Adverse event	1 (< 0.1)	2 (0.2)	3 (< 0.1)
COVID-19	0	2 (0.2)	2 (< 0.1)
Other	1 (< 0.1)	0	1 (< 0.1)
Participant receiving EUA vaccine outside of protocol	0	2 (0.2)	2 (< 0.1)
Physician decision	2 (< 0.1)	2 (< 0.2)	4 (< 0.1)
Withdrawal of consent	6 (0.2)	4 (0.4)	10 (0.2)
Participant entered open-label or cross-over phase	3 (< 0.1)	3 (0.3)	6 (0.1)
Other	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Discontinued from study	39 (1.3)	139 (13.8)	178 (4.4)
Reason for discontinuation			
Adverse event	1 (< 0.1)	0	1 (< 0.1)
Lost to follow up	4 (0.1)	1 (< 0.1)	5 (0.1)
Participant receiving EUA vaccine outside of protocol	0	67 (6.7)	67 (1.7)
Protocol deviation	0	1 (< 0.1)	1 (< 0.1)
Physician decision	3 (< 0.1)	2 (0.2)	5 (0.1)
Withdrawal of consent	28 (0.9)	65 (6.5)	93 (2.3)
Other	1 (< 0.1)	3 (0.3)	4 (< 0.1)
Missing	2 (<0.1)	0	2 (<0.1)

Two participants who were randomized to the placebo group received mRNA-1273 50 µg due to a dosing error.
Datacut: 10 Nov 2021
Source: Study 204 EUA Table 14.1.1.1.2

3.4.2.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of participants 6 to 11 years old in the Study 204 Safety Set were representative of the intended target population and were generally balanced between the mRNA-1273 group and placebo group (Table 12).

The PP Immunogenicity Subset included 320 mRNA-1273 recipients in this group of Study 204; the demographics were consistent with the Safety Set.

Table 12: Study 204 Participant Demographics and Baseline Characteristics (Safety Set, 6 to 11 Years)

	mRNA-1273 50 µg N=3007	Placebo N=995	Total N=4002
Age, years			
Mean (SD)	8.5 (1.65)	8.5 (1.64)	8.5 (1.65)
Median	8.0	9.0	9.0
Min, Max	6, 11	6, 11	6, 11
6–8 years	1514 (50.3)	484 (48.6)	1998 (49.9)
9–11 years	1493 (49.7)	511 (51.4)	2004 (50.1)
Sex, n (%)			
Male	1554 (51.7)	481 (48.3)	2035 (50.8)
Female	1453 (48.3)	514 (51.7)	1967 (49.2)
Race, n (%)			
White	1957 (65.1)	668 (67.1)	2625 (65.6)
Black	309 (10.3)	93 (9.3)	402 (10.0)
Asian	298 (9.9)	100 (10.1)	398 (9.9)
American Indian or Alaska Native	14 (0.5)	3 (0.3)	17 (0.4)
Native Hawaiian or Other Pacific Islander	4 (0.1)	0	4 (< 0.1)
Multiracial	327 (10.9)	97 (9.7)	424 (10.6)
Other	62 (2.1)	22 (2.2)	84 (2.1)
Not Reported	23 (0.8)	10 (1.0)	33 (0.8)
Unknown	9 (0.3)	1 (0.1)	10 (0.2)
Missing	4 (0.1)	1 (0.1)	5 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	561 (18.7)	181 (18.2)	742 (18.5)
Not Hispanic or Latino	2417 (80.4)	805 (80.9)	3222 (80.5)
Not Reported	22 (0.7)	5 (0.5)	27 (0.7)
Unknown	7 (0.2)	4 (0.4)	11 (0.3)
Weight, kg			
Mean (SD)	33.33 (11.273)	33.52 (11.434)	33.38 (11.312)
Median	30.60	30.91	30.73
Min, Max	15.4, 112.0	14.2, 99.8	14.2, 112.0
Baseline SARS-CoV-2 Status[a], n (%)			
Negative	2703 (89.9)	880 (88.4)	3583 (89.5)
Positive	257 (8.5)	87 (8.7)	344 (8.6)
Missing	47 (1.6)	28 (2.8)	75 (1.9)

Abbreviations: COVID-19=coronavirus disease 2019; max=maximum; min=minimum; RT-PCR=reverse transcription polymerase chain ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SD=stable disease.
[a.] Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
Datacut: 10 Nov 2021
Source: Module 2.5 (6–11 yrs), Table 13, Table 14.1.3.2 (data cut 10 Nov 2021) for 6–11y

3.4.3 Study 204 Study Populations (2 to 5 Years)

3.4.3.1 Disposition

In the randomized, blinded phase of Study 204 for children 2 to 5 years of age, 4,048 participants were randomly assigned to receive a two-dose primary series of 25 µg of mRNA-1273 or placebo in a 3:1 randomization ratio. Table 13 shows the participant disposition for this age group in Study 204. More than 97% in both groups completed their assigned treatment regimen. One participant in the mRNA-1273 discontinued the study due to an AE.

Table 13: Study 204 Participant Disposition (Randomization Set, 2 to 5 Years)

	mRNA-1273 25 µg n (%)	Placebo n (%)	Total n (%)
Randomization Set	3040 (100)	1008 (100)	4048 (100)
Completed 1 dose	3031 (99.7)	1007 (> 99.9)	4038 (99.8)
Completed 2 doses	2960 (97.4)	970 (96.2)	3930 (97.1)
Discontinued study vaccine	20 (0.7)	21 (2.1)	41 (1.0)
Reason for discontinuation of study vaccine			
AE	1 (< 0.1)	0	1 (< 0.1)
Lost to follow-up	1 (< 0.1)	0	1 (< 0.1)
Participant receiving EUA vaccine outside protocol	0	5 (0.5)	5 (0.5)
Withdrawal of consent	11 (0.4)	1 (< 0.1)	12 (0.3)
Participant entered open-label or crossover phase	5 (0.2)	15 (1.5)	20 (0.5)
Other	1 (< 0.1)	0	1 (< 0.1)
Missing	1 (< 0.1)	0	1 (< 0.1)
Discontinued from study	57 (1.9)	31 (3.1)	88 (2.2)
Reason for discontinuation			
Adverse event	1 (< 0.1)	0	1 (< 0.1)
Lost to Follow-up	7 (0.2)	0	7 (0.2)
Patient Receiving EUA Vaccine Outside of Protocol	0	8 (0.8)	8 (0.2)
Physician decision	2 (< 0.1)	0	2 (< 0.1)
Protocol deviation	0	2 (0.2)	2 (< 0.1)
Withdrawal of consent	40 (1.3)	17 (1.7)	57 (1.4)
Other	4 (0.1)	3 (0.3)	7 (0.2)
Missing	3 (< 0.1)	1 (< 0.1)	4 (< 0.1)

Abbreviation: EUA=Emergency Use Authorization
Datacut: 21 Feb 2022
Source: EUA (2.5) Table 14.1.1.1.2

3.4.3.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of participants 2 to 5 years of age in the Study 204 Safety Set were representative of the intended target population and were generally balanced between the mRNA-1273 group and placebo group (Table 14).

The PP Immunogenicity Subset included 264 mRNA-1273 recipients in this group of Study 204; the demographics were consistent with the Safety Set.

Table 14: Study 204 Participant Demographics and Baseline Characteristics (Safety Set, 2 to 5 Years)

	mRNA-1273 25 µg N=3031	Placebo N=1007	Total N=4038
Age, years			
Mean (SD)	3.0 (0.88)	3.0 (0.89)	3.0 (0.88)
Median	3.0	3.0	3.0
Min, max	1, 5	1, 5	1, 5
Sex, n (%)			
Male	1543 (50.9)	510 (50.6)	2053 (50.8)
Female	1488 (49.1)	497 (49.4)	1985 (49.2)
Race, n (%)			
White	2297 (75.8)	792 (78.6)	3089 (76.5)
Black	142 (4.7)	38 (3.8)	180 (4.5)
Asian	191 (6.3)	51 (5.1)	242 (6.0)
American Indian or Alaska Native	12 (0.4)	3 (0.3)	15 (0.4)
Native Hawaiian or other Pacific Islander	7 (0.2)	4 (0.4)	11 (0.3)
Multiracial	322 (10.6)	99 (9.8)	421 (10.4)
Other	43 (1.4)	16 (1.6)	59 (1.5)
Not reported	13 (0.4)	4 (0.4)	17 (0.4)
Unknown	4 (0.1)	0	4 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	433 (14.3)	142 (14.1)	575 (14.2)
Not Hispanic or Latino	2579 (85.1)	856 (85.0)	3435 (85.1)
Not reported	14 (0.5)	8 (0.8)	22 (0.5)
Unknown	5 (0.2)	1 (0.1)	6 (0.1)
Weight, kg			
Mean (SD)	16.13 (3.201)	16.02 (2.974)	16.10 (3.146)
Median	15.73	15.64	15.70
Min, max	7.0, 56.9	9.6, 44.4	7.0, 56.9
Baseline SARS-CoV-2 Status[a], n (%)			
Negative	2695 (88.9)	898 (89.2)	3593 (89.0)
Positive	266 (8.8)	82 (8.1)	348 (8.6)
Missing	70 (2.3)	27 (2.7)	97 (2.4)

Abbreviations: COVID-19=coronavirus disease 2019; IRT=interactive response technology; max=maximum; min=minimum; RT-PCR=reverse transcription-polymerase chain ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SD=standard deviation.

Percentages are based on the number of participants in the Part 2 Safety Set.

a Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 13

3.4.4 Study 204 Study Populations (6 to 23 Months)

3.4.4.1 Disposition

In the randomized, blinded phase of Study 204 for children 6 to 23 months of age, 2,355 participants were randomly assigned to receive a two-dose primary series of 25 µg of mRNA-1273 or placebo in a 3:1 randomization ratio. Table 15 shows the participant disposition of this age group in Study 204. Approximately 90% of participants in both groups completed their assigned treatment regimen.

Table 15: Study 204 Participant Disposition (Randomization Set; 6 to 23 Months)

	mRNA-1273 25 µg n (%)	Placebo n (%)	Total n (%)
Randomization Set[a]	1762	593	2355
Completed 1 dose	1760 (99.9)	590 (99.5)	2350 (99.8)
Completed 2 doses	1600 (90.8)	529 (89.2)	2129 (90.4)
Discontinued study vaccine	4 (0.2)	5 (0.8)	9 (0.4)
Reason for discontinuation of study vaccine			
AE	0	1 (0.2)	1 (< 0.1)
COVID-19	0	1 (0.2)	1 (< 0.1)
Withdrawal of consent	1 (< 0.1)	3 (0.5)	4 (0.2)
Participant entered open-label or cross-over phase	1 (< 0.1)	0	1 (< 0.1)
Other	1 (< 0.1)	0	1 (< 0.1)
Missing	1 (< 0.1)	1 (0.2)	2 (< 0.1)
Discontinued from study	19 (1.1)	15 (2.5)	34 (1.4)
Reason for discontinuation			
Adverse event	1 (< 0.1)	1 (0.2)	2 (< 0.1)
Lost to follow-up	5 (0.3)	1 (0.2)	6 (0.3)
Physician decision	1 (< 0.1)	0	1 (< 0.1)
Withdrawal of consent	8 (0.5)	10 (1.7)	18 (0.8)
Other	2 (0.1)	2 (0.3)	4 (0.2)
Missing	2 (0.1)	1 (0.2)	3 (0.1)

Datacut: 21 Feb 2022
Source: EUA (6 mos-23 mos) Table 14.1.1.1.2

3.4.4.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of participants 6 to 23 months of age in the Study 204 Safety Set were representative of the target population and generally balanced between the mRNA-1273 group and placebo group (Table 16).

The PP Immunogenicity Subset included 230 mRNA-1273 recipients in this group of Study 204; the demographics were consistent with the Safety Set.

Table 16: Study 204 Participant Demographics and Baseline Characteristics (Safety Set, 6 to 23 Months)

	mRNA-1273 25 µg N=1761	Placebo N=589	Total N=2350
Age, months			
Mean (SD)	15.8 (5.01)	15.9 (4.86)	15.9 (4.97)
Median	16.0	17.0	16.0
Sex, n (%)			
Male	910 (51.7)	290 (49.2)	1200 (51.1)
Female	851 (48.3)	299 (50.8)	1150 (48.9)
Race, n (%)			
White	1390 (78.9)	466 (79.1)	1856 (79.0)
Black	57 (3.2)	16 (2.7)	73 (3.1)
Asian	79 (4.5)	35 (5.9)	114 (4.9)
American Indian or Alaska Native	4 (0.2)	0	4 (0.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	186 (10.6)	64 (10.9)	250 (10.6)
Other	31 (1.8)	5 (0.8)	36 (1.5)
Not reported	9 (0.5)	2 (0.3)	11 (0.5)
Unknown	5 (0.3)	1 (0.2)	6 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	227 (12.9)	84 (14.3)	311 (13.2)
Not Hispanic or Latino	1517 (86.1)	498 (84.6)	2015 (85.7)
Not reported	15 (0.9)	6 (1.0)	21 (0.9)
Unknown	2 (0.1)	1 (0.2)	3 (0.1)
Weight, kg			
Mean (SD)	10.88 (2.053)	10.88 (2.089)	10.88 (2.062)
Median	10.80	10.80	10.80
Min, max	5.0, 29.3	1.1, 27.4	1.1, 29.3
Baseline SARS-CoV-2 status[a], n (%)			
Negative	1575 (89.4)	530 (90.0)	2105 (89.6)
Positive	106 (6.0)	38 (6.5)	144 (6.1)
Missing	80 (4.5)	21 (3.6)	101 (4.3)

Abbreviations: COVID-19=coronavirus disease 2019; IRT=interactive response technology; max=maximum; min=minimum; RT-PCR=reverse transcription-polymerase chain ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SD=standard deviation.

Percentages are based on the number of participants in the Part 2 Safety Set.

[a] Baseline SARS-CoV-2 status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 27

4 OVERVIEW OF IMMUNOGENICITY AND EFFICACY

Summary

- Immunogenicity was a primary objective of the pediatric studies, with effectiveness to be inferred in infants, children, and adolescents by immunobridging to young adults in Study 301, where efficacy was demonstrated.
- Immunobridging was successfully demonstrated (by meeting the pre-specified co-primary non-inferiority criteria for GMR and seroresponse rate) for a 2-dose primary series of mRNA-1273 administered over 1 month in all age groups:
  - 12 to 17 years – GMR: 1.1 (95% CI: 0.9, 1.2); SRR difference: 0.2% (95% CI: -1.8, 2.4)
  - 6 to 11 years – GMR: 1.2 (95% CI: 1.1, 1.4), SRR difference: 0.1% (95% CI: -1.9, 2.1)
  - 2 to 5 years – GMR: 1.0 (95% CI: 0.9, 1.2), SRR difference: -0.4% (95% CI: -2.7, 1.5)
  - 6 to 23 months – GMR: 1.3 (95% CI: 1.1, 1.5), SRR difference: 0.7% (95% CI: -1.0, 2.5)
- Efficacy was a secondary objective of the pediatric studies. VE assessment was dependent on the circulation of SARS-CoV-2 and the amount of time available for follow-up blinded follow-up.
- Efficacy was demonstrated in all age groups, regardless of the SARS-CoV-2 variant circulating.
  - 12 to 17 years, VE 93.3 (95% CI: 47.9, 99.9), Original and Alpha
  - 6 to 11 years, VE (measured starting 14 days post-dose 1) 88.0% (95% CI: 70.0, 95.8), Delta
  - 2 to 5 years, VE 36.8% (95% CI: 12.5, 54.0), Omicron
  - 6 to 23 months, VE 50.6% (95% CI: 21.4, 68.6), Omicron
- Efficacy in pediatric groups also was consistent with efficacy (original strain)/effectiveness (Delta and Omicron) in adults against those variants in clinical trials and observational studies.
- Immune responses against multiple variants also were demonstrated using both binding and neutralizing antibodies.

4.1 Immunogenicity in Participants 6 Months to 17 Years of Age

Vaccine effectiveness was inferred by demonstrating non-inferiority of both serum nAb GMRs and SRRs from adolescents and children in Studies 203 and 204 compared with

those from young adults enrolled in Study 301 (18 to 25 years) for each respective age group.

4.1.1 Immunogenicity (12 to 17 Years)

The GMT ratio of the serum nAb in participants 12 to 17 years of age was 1.1 (95% CI: 0.9, 1.2), meeting the pre-specified non-inferiority criterion (Table 17). The SRR difference was 0.2% (95% CI: -1.8, 2.4), meeting the pre-specified non-inferiority criteria as well. Immunobridging in 12 to 17 year age group was therefore successfully demonstrated.

Table 17: Study 203 Analysis of Serum Antibody Level and Seroresponse at Day 57 (PP Immunogenicity Subset, 12 to 17 Years)

Day 57 Analysis PsVNA	Study 203 Adolescents (12–17 Years) mRNA-1273 (100 µg) N=340	Study 301 Young Adults (18–25 Years) mRNA-1273 (100 µg) N=296
GMT (Geometric Mean Titer) 95% CI	**1401.7** **(1276.3, 1539.4)**	**1301.3** **(1177.0, 1438.8)**
GMT Ratio (Study 203 vs 301)[a] 95% CI	**1.1** (0.9, 1.2)	
Seroresponse[b]**, n/N (%)** 95% CI	**336 (98.8%)** (97.0, 99.7)	**292 (98.6%)** (96.6, 99.6)
Difference (Study 203 vs 301) 95% CI	**0.2%** (-1.8, 2.4)	

Abbreviations: CI=confidence interval; PsVNA=pseudovirus neutralization antibody assay
[a]The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b]Seroresponse at a subject level is defined as at least 4-fold rise from baseline if baseline is equal to or above LLOQ, or at least 4-fold rise from LLOQ if baseline is below LLOQ.
Datacut: 08 May 2021
Source: Fact sheet table 7 EUA Adolescents Table 20, Sources: Study P203, Table 2.1.1.3.1 and Table 2.1.2.3.1.

4.1.2 Immunogenicity (6 to 11 Years)

The GMR of the serum nAb in participants 6 to 11 year of age was 1.2 (95% CI: 1.1, 1.4), meeting the pre-specified non-inferiority criterion (Table 18). The SRR difference was 0.1% (95% CI: -1.9, 2.1), meeting the pre-specified non-inferiority criteria as well. Immunobridging in the 6 to 11 year age group was therefore successfully demonstrated.

Table 18: Study 204 Co-primary Immunobridging Comparison to Study 301 (PP Immunogenicity Subset, 6 to 11 Years)

Day 57 Analysis, Part 2 PsVNA	**Study 204** **Children (6–11 Years)** **mRNA-1273 (50 µg)** **N=320**	**Study 301** **Young Adults (18–25 Years)** **mRNA-1273 (100 µg)** **N=295**
Baseline GMT	9.250	9.285
GMT (Geometric Mean Titer) 95% CI	**1610** (1457, 1780)	**1300** (1171, 1443)
GMT Ratio (Study 204 vs 301)[a] 95% CI	**1.2** (1.1, 1.4)	
Seroresponse[b]**, n/N (%)** 95% CI	**313/316 (99.1%)** (97.3, 99.8)	**292/295 (99.0%)** (97.1, 99.8)
Difference (Study 204 vs 301) 95% CI	**0.1%** (-1.9, 2.1)	

Abbreviations: CI=confidence interval; PsVNA=pseudovirus neutralizing antibody assay
[a] The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b] 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.
Datacut: 10 Nov 2021
Source: Module 2.5 (6–11 yrs), Table 17

4.1.3 Immunogenicity (2 to 5 Years)

The GMR of the serum nAb in participants 2 to 5 years of age was 1.0 (95% CI: 0.9, 1.2), meeting the pre-specified non-inferiority criterion (Table 19). The SRR difference was -0.4% (95% CI: -2.7, 1.5), meeting the pre-specified non-inferiority criteria as well. Immunobridging in 2 to 5 year age group was therefore successfully demonstrated.

Table 19: Study 204 Co-primary Immunobridging Comparison to Study 301 (PP Immunogenicity Subset, 2 to 5 Years)

Day 57 Analysis PsVNA	**Study 204** **Young Children (2–5 Years)** **mRNA-1273 (25 µg)** **N=264**	**Study 301** **Young Adults (18–25 Years)** **mRNA-1273 (100 µg)** **N=295**
Baseline GMC	7.7	11.1
GMC (Geometric Mean Concentration) 95% CI	**1410** (1274, 1561)	**1391** (1262, 1532)
GMC Ratio (Study 204 vs 301)[a] 95% CI	**1.0** (0.9, 1.2)	
Seroresponse[b]**, n/N (%)** 95% CI	**261/264 (98.9%)** 96.7, 99.8	**289/291 (99.3%)** 97.5, 99.9
Difference (Study 204 vs 301) 95% CI	**-0.4%** (-2.7, 1.5)	

Abbreviations: CI=confidence interval; GMC: geometric mean concentration ; PsNVA=pseudovirus neutralization antibody assay;

[a]The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b]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.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 17

4.1.4 Immunogenicity (6 to 23 Months)

The GMR of the serum nAb in participants 6 to 23 month of age was 1.3 (95% CI: 1.1, 1.5), meeting the pre-specified non-inferiority criterion (Table 20). The SRR difference was 0.7% (95% CI: -1.0, 2.5), meeting the pre-specified non-inferiority criteria as well. Immunobridging in the 6 to 23 month age group was therefore successfully demonstrated.

Table 20: Study 204 Co-primary Immunobridging Comparison to Study 301 (PP Immunogenicity Subset, 6 to 23 Months)

Day 57 Analysis PsVNA	**Study 204** **Infants/Toddlers** **(6–23 Months)** **mRNA-1273 (25 µg)** **N=230**	**Study 301** **Young Adults** **(18–25 Years)** **mRNA-1273 (100 µg)** **N=295**
Baseline GMC	7.9	11.1
GMC (Geometric Mean Concentration) 95% CI	**1781** (1606, 1974)	**1391** (1262, 1524)
GMC Ratio (Study 204 vs 301)[a] 95% CI	**1.28** (1.12, 1.47)	
Seroresponse[b]**, n/N (%)** 95% CI	**230/230 (100)** (98.4, 100.0)	**289/291 (99.3)** (97.5, 99.9)
Difference (Study 204 vs 301) 95% CI	**0.7** (-1.0, 2.5)	

Abbreviations: CI=confidence interval; LLOQ=lower limit of quantification; LS=least squares; PP=per protocol; PsNVA=pseudovirus neutralization antibody assay;

[a]The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] 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.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 31

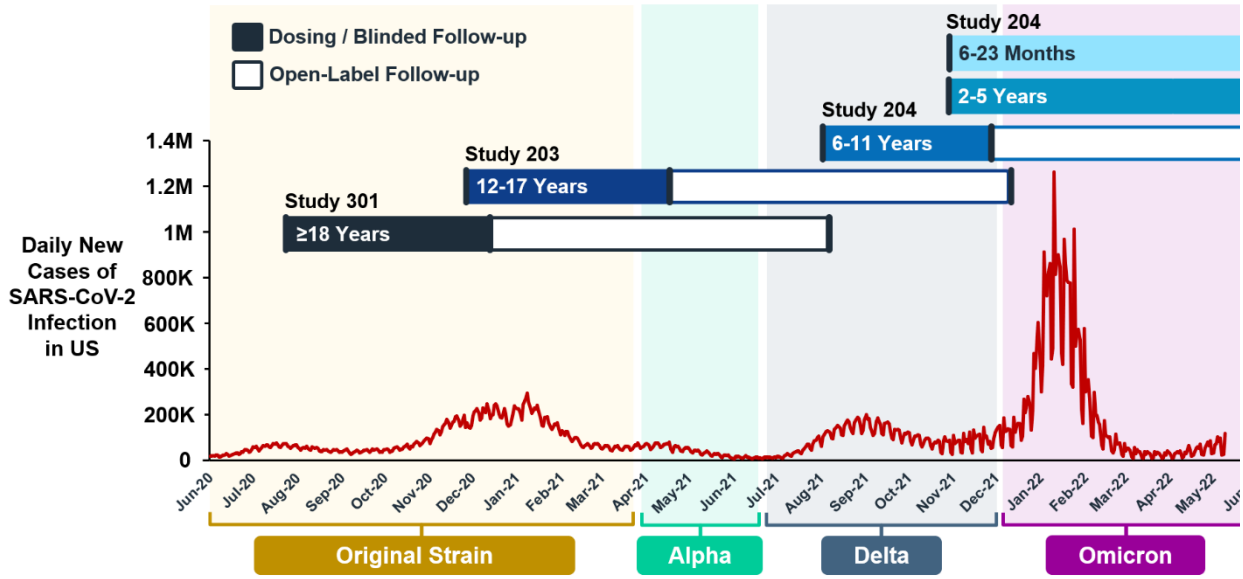
4.2 Efficacy in Participants 6 Months to 17 Years of Age

4.2.1 SARS-CoV-2 Landscape During mRNA-1273 Trials

Although the studies were not specifically designed or powered to evaluate VE, given the widespread transmission of SARS-CoV-2 during the time of study conduct, evaluation of VE to prevent COVID-19 according to the CDC and Study 301 case definitions was pre-specified as a secondary endpoint in both studies. As these pediatric studies were conducted and efficacy follow-up was performed, the predominant SARS-CoV-2 strain circulating in the US changed over time, and the efficacy results must be interpreted in this context (Figure 8). During Study 301, the original strain was almost exclusively circulating, and the efficacy follow-up for adolescents (12 to 17 years) was conducted when the original strain was still the dominant strain. In contrast, the 6 to 11 years of age group was followed when the Delta variant was dominant, and the two youngest groups were followed during the recent Omicron wave.

The impact of the Omicron daily incidence is apparent from the large increase in the incidence curve observed in Figure 8 from December 2021 through March 2022. The daily US incidence of SARS-CoV-2 infections rose from fewer than 200,000 cases per day to a peak of 1.4 million cases per day, indicating that the epidemiology of SARS-CoV-2 changed significantly during the time the youngest groups (6 months to 11 years) were followed.

Figure 8: Clinical Studies Conducted During Different Periods of COVID-19 Pandemic



Abbreviations: COVID-19=Coronavirus disease 2019; SARS-CoV-2 =Severe Acute Respiratory Syndrome Coronavirus-2

4.2.2 Efficacy (12 to 17 Years)

4.2.2.1 Blinded Efficacy

Study 203 results demonstrated direct clinical benefit of mRNA-1273 in the reduction in COVID-19 cases in adolescents 12 to 17 years of age (Table 21).

Applying the same case definitions and interval (starting 14 days after dose 2) as that used in the adult efficacy study, VE through 08 May 2021 was 93.3% using the CDC case definition (case split: 7 cases in the placebo group vs 1 cases in the mRNA-1273 group) and 100% using the 301 case definition (case split: 4 cases in placebo group vs 0 cases in the mRNA-1273 group).

Importantly, these results are consistent with results obtained in Study 301, the pivotal adult efficacy study (93.2% after 5 months) (El Sahly et al 2021).

Table 21: Study 203 Blinded Efficacy Analysis (PP Set for Efficacy, 12 to 17 Years)

COVID-19 Cases Starting 14 Days After Dose 2	**mRNA-1273 (100 µg)** N=2139	**Placebo** N=1042
CDC case definition of COVID-19		
Cases, n/N (%)	1/2139 (< 0.1)	7/1042 (0.7)
Incidence rate per 1000 person-years (95% CI)[a,b]	1.9 (0.0, 10.8)	29.0 (11.7, 59.7)
VE (%) based on incidence rate (95% CI)[c]	**93.3% (47.9, 99.9)**	
301 case definition of COVID-19		
Cases, n/N (%)	0/2139 (0)	4/1042 (0.4)
Incidence rate per 1000 person-years (95% CI)[a,b]	0 (NE, 7.1)	16.5 (4.5. 42.3)
VE (%) based on incidence rate (95% CI)[c]	**100% (28.9, NE)**	

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID-19=Coronavirus disease 2019; VE=vaccine efficacy

[a] Person-years is defined as the total years from the randomization date to the date of event (CDC case definition of COVID-19, or 301 case definition of COVID-19, depending upon endpoint), last date of study participation, or efficacy data snapshot date, whichever is the earliest.

[b] Incidence rate is defined as 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. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[c] VE is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Datacut: 08 May 2021

Source: Table 2.8.1.1, Table 2.7.1.1

4.2.2.2 Open-Label COVID-19 Incidence Rates

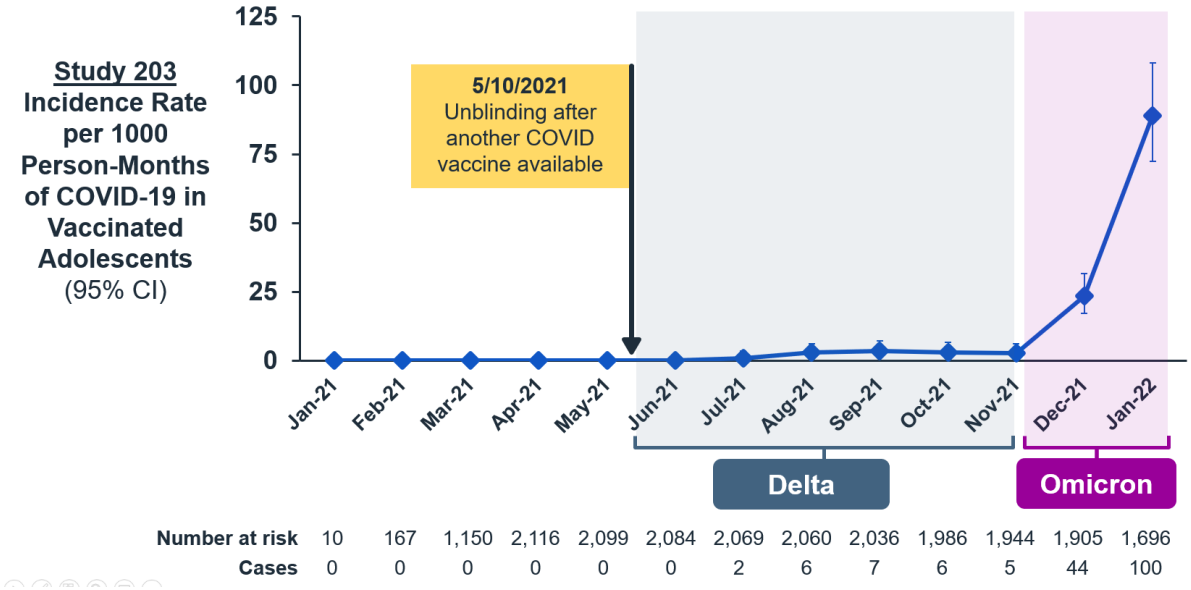
The Study 203 protocol was amended to transition from the original blinded, placebo-controlled phase to an open-label phase, to permit unblinding of study participants upon emergency authorization of a non-study COVID-19 vaccine on 10 May 2022. Immediately following emergency authorization of a non-study COVID-19 vaccine, many participants originally randomized to placebo withdrew from the study and received the authorized non-study COVID-19 vaccine. Crossover of participants randomized to placebo to receive an mRNA-1273 primary series began in October 2021.

Participants in the original mRNA-1273 group continued to be followed for COVID-19. Monthly COVID-19 case numbers and incidence rates per 1000 person-months were calculated for the combined blinded and open-label phases in the mRNA-1273 group using COVID-19 cases based on the protocol-specified definition of symptoms plus RT-PCR data.

Long-term assessment of monthly incidence rates, using the protocol-specified COVID-19 case definition (RT-PCR-confirmed), among all participants who received mRNA-1273 as randomized and remained on study until 31 Jan 2022 (combined blinded and unblinded) shows low monthly incidence rates of COVID-19 until November 2021, using to the Study 301 case definition (Figure 9). An increase in COVID-19 incidence rates was observed in December 2021 and January 2022, when the Omicron variant prevailed. These findings are consistent with increases in COVID-19 incidence

documented from real-world evidence collected during the US Omicron wave (Wang et al 2022).

Figure 9: Long-term Analysis of Incidence Rate of COVID-19 (Study 301 Case Definition) Starting 14 Days After Second Injection by Calendar Month, mRNA-1273 Group (Combined Blinded and Open-Label Phases) – Based on RT-PCR only



Abbreviations: CI=confidence interval; RT-PCR=reverse transcription polymerase chain reaction; COVID-19=Coronavirus disease 2019;
This is the number of cases per the number at risk (ie, participants who were not a COVID-19 case prior and remained in the study at the beginning of the time interval); percentages are based on the number at risk.
Person-months for each calendar month is defined as the total months from the earlier date of the start of each month or 14 days after second injection to the earliest date of the first occurrence of COVID-19, the end of each month, study discontinuation, non-study COVID-19 vaccination, booster dose, or data cutoff.
Incidence rate for each time period is defined as the number of participants with an event during the month divided by the number of participants at risk at the beginning of each month and adjusted by person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months.
Datacut: 31 Jan 2022
Source: Table 14.2.7.6.3.1.1.2

4.2.3 Efficacy (6 to 11 Years)

As described in Section 4.2.1, efficacy in participants 6 to 11 years of age was assessed during the Delta period. Assessment of secondary efficacy endpoints in Study 204 was limited due to a relatively short, blinded follow-up period (as another COVID-19 vaccine was authorized and participants were unblinded per protocol; the median blinded follow-up time from dose 2 was 1.8 months [51 days]). Therefore, an analysis of VE using cases accrued starting 14 days post-dose 1 was conducted (mITT1 population). The overwhelming majority of study participants went on to receive the 2nd

dose, but case counting post-dose 1 allowed for the accrual of a greater number of cases.

Based on the mITT1 population, VE through 10 Nov 2021 was 88% using the CDC cases definition (case split: 18 cases in the placebo group vs 7 in the mRNA-1273 group) and 91.8% using the 301 case definition (case split 15 cases in the placebo vs 4 in the mRNA-1273 group; Table 22). These results show consistently high protection after vaccination with mRNA-1273 similar to the VE observed in the Study 301.

There were few COVID-19 cases accrued 14 days post-dose 2 (CDC case definition: mRNA-1273 3/2644 [0.1%] and placebo 4/853 [0.5%]). The point estimates of VE were consistent but the 95% CIs were wide.

Table 22: Study 204 Secondary Efficacy Endpoint Analysis Results Starting 14 Days after Dose 1 (mITT1 Population, 6 to 11 Years)

Endpoint	Part 2	
	mRNA-1273 50 µg N=2687	Placebo N=880
CDC case definition of COVID-19		
Cases, n/N1 (%)	7/2680 (0.3)	18/875 (2.1)
Incidence rate per 1000 person-years (95% CI)[a,b]	14.0 (5.6, 28.8)	117.1 (69.4, 185.1)
VE based on incidence rate (95% CI)[c]	**88.0%** (70.0, 95.8)	
Study 301 case definition of COVID-19		
Cases, n/N1 (%)	4/2681 (0.1)	15/877 (1.7)
Incidence rate per 1000 person-years (95% CI)[a,b]	8.0 (2.2, 20.5)	97.1 (54.4, 160.2)
VE based on incidence rate (95% CI)[c]	**91.8%** (74.2, 98.0)	

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID 19=coronavirus disease 2019; mITT=modified Intent-to-Treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; VE=vaccine efficacy.
N1=number of participants at risk at 14 days after dose 1 for specific efficacy endpoint
[a]. Person-years is defined as the total years from the first day of the analysis to the date of event (CDC case definition of COVID-19, or P301 case definition of COVID-19, depending upon endpoint), last date of study participation, or efficacy data cutoff date, whichever is the earliest.
[b]. Incidence rate is defined as 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. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
[c]. VE, defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
Datacut: 10 Nov 2021
Source: Module 2.5 (6–11 yrs), Table 24

4.2.4 Efficacy (2 to 5 Years)

As described in Section 4.2.1, efficacy in participants 2 to 5 years of age was assessed during the Omicron period, and the results must be interpreted in this context.

VE through 21 Feb 2022 was 36.8% using the CDC definition (case split: 61 cases in the placebo group vs 119 cases in the mRNA-1273 group) and 46.4% using the 301 case definition (case split: 43 cases in the placebo group vs 71 cases in the mRNA-1273 group; Table 23).

VE in this age group is highly consistent with real-world vaccine effectiveness in adults during the time period when Omicron was the dominant circulating variant (Tseng et al 2022a; Tseng et al 2022b).

Table 23: Study 204 Efficacy Endpoint Analysis Results Starting 14 Days After Dose 2 (PP Set for Efficacy, 2 to 5 Years)

Endpoint	Part 2	
	mRNA-1273 25 µg N=2594	Placebo N=858
CDC case definition of COVID-19		
Cases, n/N (%)	119/2594 (4.6)	61/858 (7.1)
Incidence rate per 1000 person-years (95% CI)[a,b]	175.0 (145.0, 209.4)	277.0 (211.9, 355.8)
VE (%) based on incidence rate (95% CI)[c]	**36.8% (12.5, 54.0)**	
301 case definition of COVID-19		
Cases, n/N (%)	71/2594 (2.7)	43/858 (5.0)
Incidence rate per 1000 person-years (95% CI)[a,b]	103.8 (81.0, 130.9)	193.5 (140.1, 260.7)
VE (%) based on incidence rate (95% CI)[c]	**46.4% (19.8, 63.8)**	

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID-19=coronavirus disease 2019; PP=per protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; VE=vaccine efficacy.

[a] Person-years is defined as the total years from the randomization date for Part 2 to the date of event (CDC case definition of COVID-19, or 301 case definition of COVID-19, depending upon endpoint), last date of study participation, or efficacy data snapshot date, whichever is the earliest.

[b] Incidence rate is defined as 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. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[c] VE is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 18

4.2.5 Efficacy (6 to 23 Months)

As described in Section 4.2.1, efficacy in participants 6 to 23 month of age was assessed during the Omicron period, and the results must be interpreted in this context.

VE through 21 Feb 2022 was 50.6% using the CDC case definition (case split 34 cases in the placebo group vs 51 cases in the mRNA-1273 group) and 31.5% using 301 case definition (18 cases in the placebo group vs 37 cases in the mRNA-1273 group; Table 24).

VE in this age group is highly consistent with real-world vaccine effectiveness in adults during the time period when Omicron was the dominant circulating variant (Tseng et al 2022a; Tseng et al 2022b).

Table 24: Study 204 Efficacy Endpoint Analysis Results Starting 14 Days After Dose 2 (PP Set for Efficacy, 6 to 23 Months)

Endpoint	Part 2	
	mRNA-1273 (25 µg) N=1511	Placebo N=513
CDC case definition of COVID-19		
Cases, n/N (%)	51/1511 (3.4)	34/513 (6.6)
Incidence rate per 1000 person-years (95% CI)[a,b]	138.2 (102.9, 181.8)	279.8 (193.8, 391.0)
VE based on incidence rate (95% CI)[c]	**50.6% (21.4, 68.6)**	
301 case definition of COVID-19		
Cases, n/N (%)	37/1511 (2.4)	18/513 (3.5)
Incidence rate per 1000 person-years (95% CI)[a,b]	100 (70.4, 137.8)	146.0 (86.6, 230.8)
VE based on incidence rate (95% CI)[c]	**31.5% (-27.7, 62.0)**	

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID-19=coronavirus disease 2019; PP=per protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; VE=vaccine efficacy.

[a] Person-years is defined as the total years from the randomization date for Part 2 to the date of event (CDC case definition of COVID-19, or 301 case definition of COVID-19, depending upon endpoint), last date of study participation, or efficacy data snapshot date, whichever is the earliest.

[b] Incidence rate is defined as 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. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[c] VE is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Datacut: 21 Feb 2022

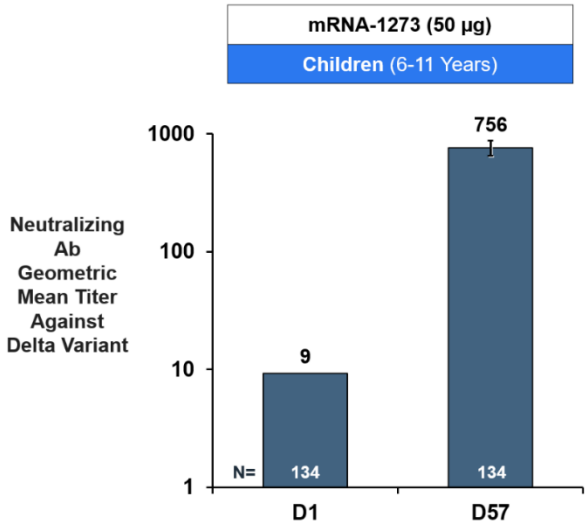
Source: Module 2.5 (< 6 yrs), Table 32

4.3 Immunogenicity Against Variants of Concern

As described above, direct efficacy was demonstrated against multiple circulating variants across the pediatric groups in Study 203 and 204. Immune responses against variants also were investigated using both nAbs and binding antibodies (bAbs). For the Delta-specific neutralization, a cohort from the Study 204 6 to 11 year old age group (n=134) was tested for nAb responses. Pre-vaccination and post-vaccination nAb titers are shown in Figure 10. Participants were initially seronegative for antibody titers against the Delta variant. At Day 57, one month post-dose 2, the GMT was 756.36. Furthermore, 99.3% of children met the definition of seroresponse against the Delta

variant. Interestingly, the absolute nAb GMTs against the Delta variant in this group were similar to that observed in adults following a booster dose (Chu et al 2022).

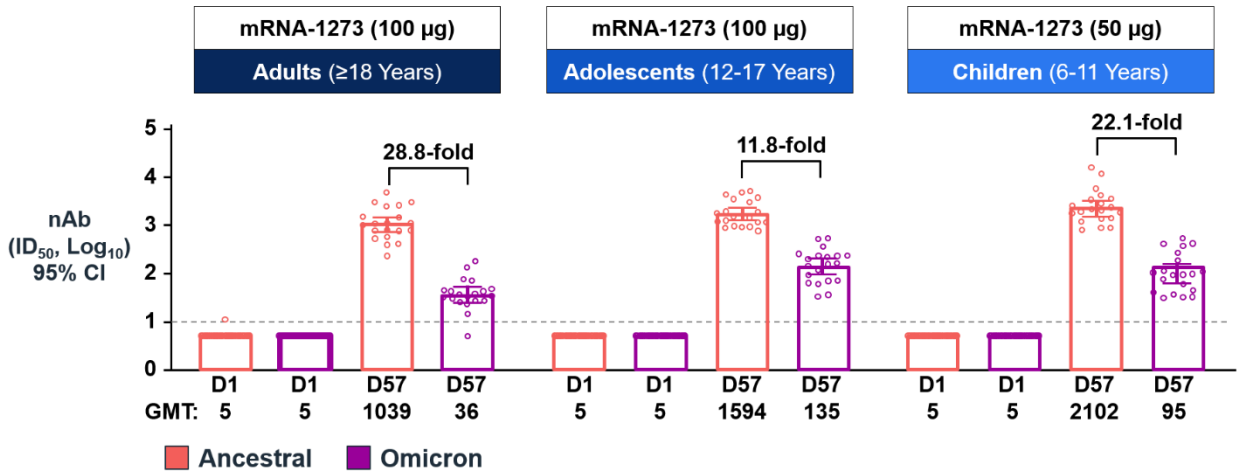
Figure 10: Study 204 nAb Against Delta Variant (6 to 11 Years)



Abbreviation: Ab=antibody

With the rise of the Omicron variant, small groups (N=20) were randomly selected from adults (Study 301), adolescents (Study 203) and 6 to 11 year old children (Study 204) to investigate Omicron-specific neutralization. Figure 11 shows pre-vaccination and post-vaccination nAb responses against Omicron. Responses against the Omicron variant were reduced compared to those against the ancestral strain, consistent with the observation in adults (Pajon et al 2022). Neutralizing titers for Omicron were 2.5-fold higher in children than in adults (Figure 11) (Girard et al 2022). At 4 weeks after dose 2, Omicron neutralization was observed in 100% of participants tested and nAb GMT was 135 and 95 in the adolescent 12 to 17 year old and children 6 to 11 year old groups, respectively.

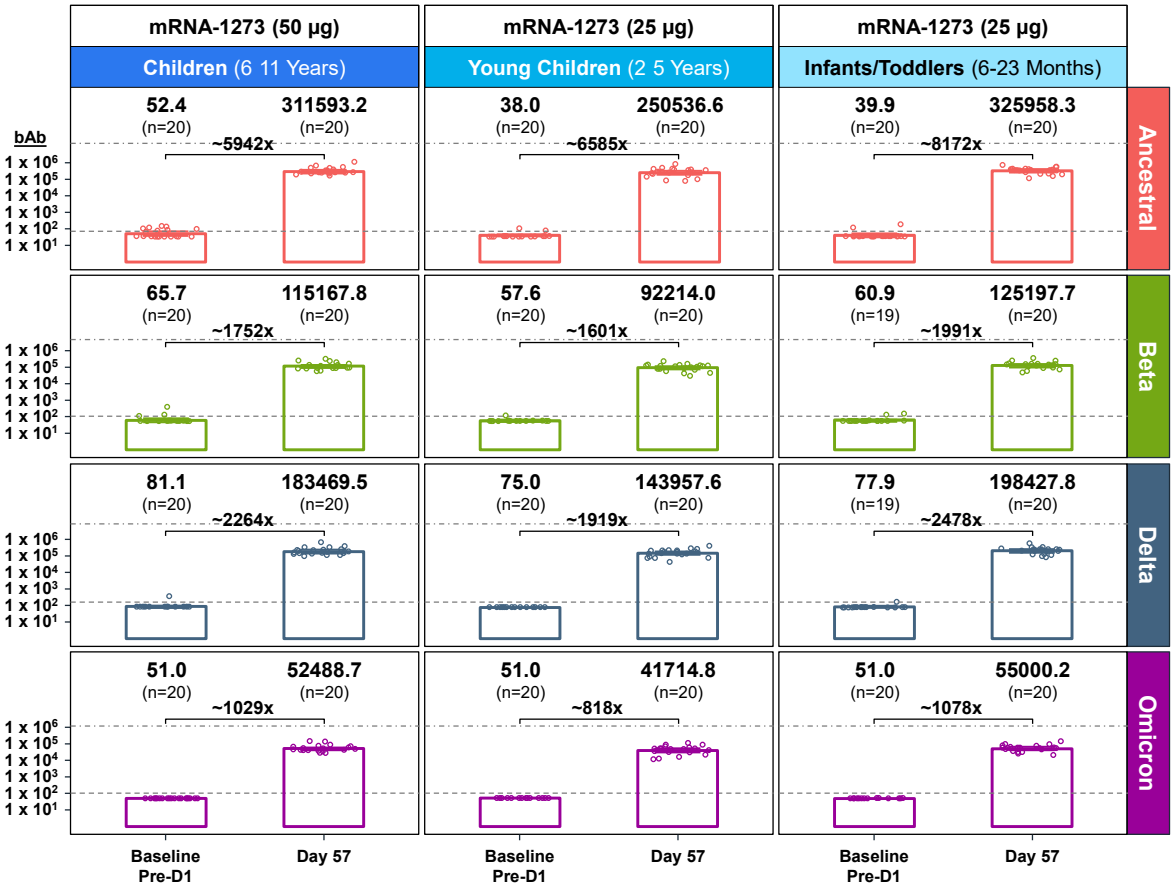
Figure 11: Neutralization of Original Viral Strain (D614G) and Omicron SARS-CoV-2 Pseudoviruses by Sera from mRNA-1273 Primary Vaccination Recipients



Abbreviations: CI=confidence interval; GMT=geometric mean titer; nAb=neutralizing antibody; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2.
Datacut: 10 Nov 2021
Source: Module 2.5 (6–11 yrs), Figure 4

Figure 12 presents the Study 204 MesoScale Discovery (MSD) multiplex (VAC123) data for randomly selected (N=20) participants from each of the 3 age groups in Study 204 (6 to 23 months, 2 to 5 years, and 6 to 11 years). The figures present bAb responses to 4 strains: ancestral (Original strain), Beta, Delta, and Omicron at Day 1 and Day 57 of the primary series for the 3 age groups. Across all age groups, the 2-dose primary series of mRNA-1273 leads to robust bAb responses across closely related (Original and Delta) as well as divergent (Beta and Omicron) variants. Although the original and Beta strains are no longer circulating, these data are evidence of the ability of mRNA-1273 to induce immunity against a broad range of variants.

Figure 12: MesoScale Discovery Results for Original, Beta, Delta, and Omicron Variants at Day 1 and Day 57 of the Primary Series



Source: P204 Figure Adhoc_VAC123_2Visit_DataTransfer-May31th.22_Plots_Annotation_N20-RandomlySelected (07Jun2022_To FDA_FollowupOmicronDataP204)

4.4 Immunogenicity and Efficacy Conclusions

In each of the age groups, across two studies, all pre-specified primary immunogenicity success criteria were met after a two-dose primary series of mRNA-1273, enabling the inference of vaccine effectiveness at the selected dose levels across age strata (Figure 1).

The 100 µg dose was used for adolescents, and the GMR of adolescents compared to young adults of 1.1 confirmed the selection of the dose. In Study 204, the doses of 50 µg (for children 6 to 11 years) and 25 µg (for children 2 to 5 years as well as 6 to 23 months) were selected, and the consistent GMRs observed (1.2, 1.0, and 1.3, respectively) in the study confirmed the dose selection. The immunogenicity of mRNA-1273 was remarkably consistent across all age groups from 6 months to adults.

VE was also evaluated as a secondary endpoint in Studies 203 and 204. VE estimates in all pediatric age groups were consistent with VE and effectiveness estimates in adults during the matched time of the various SARS-CoV-2 variant waves (Table 25).

Table 25: Efficacy of mRNA-1273 in Pediatric Age Groups is Consistent with that Observed in Adults During Each SARS-CoV-2 Variant Wave

Circulating Variant	Study 301 Efficacy / RWE	Study 203 12 to 17 years	Study 204 6 to 11 years	Study 204 2 to 5 years	Study 204 6 to 23 months
Original Strain	93.2%[1]	93.3%[3]			
Delta	80.2%[2]		88%[4]		
Omicron	44%[2]			36.8%[5]	50.6%[6]

Abbreviations: RWE=Real-World Effectiveness; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2
1 301 Case Definition (El Sahly et al 2021), blinded median follow-up 5.3 months (data cutoff 26 Mar 2021)
2 (Tseng et al 2022b) real world data for 2-dose vaccine effectiveness 14–90 days after dose 2 (Kaiser Permanente)
3 CDC Case Definition; blinded post-dose 2 median follow-up 1.9 months (53 days, data cutoff 08 May 2021)
4 CDC Case Definition; post-dose 1; too few cases to reliably assess post-dose 2; blinded post-dose 2 median follow-up 1.8 months (51 days, data cutoff 10 Nov 2021)
5 CDC Case Definition; blinded post-dose 2 median follow-up 2.5 months (71 days, data cutoff 21 Feb 2022)
6 CDC Case Definition; blinded post-dose 2 median follow-up 2.4 months (68 days, data cutoff 21 Feb 2022)

The consistency in observed rates of protection against Omicron and Delta variants among infants, toddlers, and school-age children compared to adults suggests that such rates of protection are dictated by the variant and not age or dosage. Based on the successful immunobridging to adults and the alignment between VE and vaccine effectiveness against the circulating variants, it is expected that the 2-dose series of mRNA-1273 (100 µg for adolescents 12 to 17 years, 50 µg for children 6 to 11 years, and 25 µg for infants/toddlers, and children 6 months to 5 years) would induce similar levels of protection to that observed in adults.

Effectiveness data among adults additionally show that mRNA-1273 continues to protect adults against Omicron-related severe outcomes such as hospitalization and death (Shi et al 2022; Tseng et al 2022b), and based on the successful immunobridging data, this same level of protection is expected to be consistent among children.

5 OVERVIEW OF SAFETY

Summary

- mRNA-1273 was generally well tolerated in infants, toddlers, children and adolescents with a safety profile consistent with that of young adults. No new safety concerns were identified.
- In all age groups, the most common solicited local AR was pain. Local ARs were mostly Grade 1–2 in severity and lasted 2–3 days.
- Solicited systemic ARs were more common post-dose 2 than post-dose 1 in all age groups.
    - Among adolescents and children, the most common solicited systemic ARs were headache and fatigue; among young children fatigue was most common. ARs were mostly Grade 1–2 in severity with a median duration of 2–3 days.
    - Among infants and toddlers, the most common solicited systemic ARs were irritability/crying; events were mostly Grades 1–2 in severity with a median duration of 2–3 days.
    - Solicited systemic ARs in infants/toddlers 6 to 23 months were similar to placebo.
- Fever was observed in 12% of adolescents and ~25% of infants, toddlers, and children (6 months to 11 years) who received vaccine. Most fevers occurred within 2 days of vaccination, with a median duration of 1 day.
- Fevers > 40°C were rare, occurring only in the 2 to 5 year (0.4%) and the 6 to 23 month (0.2%) age groups. Fever > 40°C also was of short duration, and the children often had symptoms of concurrent viral infections.
- In the participants randomized to mRNA-1273, there were no deaths, cases of MIS-C, or myocarditis/pericarditis observed in any age group; within 28 days of vaccination, no related SAEs were observed in children or adolescents; 1 related SAE of fever/seizure was reported in the 6 to 23 month age group.

5.1 Safety Data Presentation from Study 203

Study 203 was initiated in November 2020 as a blinded, randomized, placebo-controlled study. The study was amended to an open-label study to permit unblinding of study participants upon EUA of a non-study COVID-19 vaccine in May 2021. Placebo recipients who remained in Study 203 after unblinding were offered cross-over vaccination with mRNA-1273.

Data were obtained from: (i) the randomized, blinded phase – allowing comparison of mRNA-1273 and placebo groups and (ii) long-term follow-up of participants originally randomized to mRNA-1273. Occurrence of AR and AE should be interpreted in the context of the asymmetric 2:1 randomization ratio (mRNA-1273: placebo).

SAEs within 28 days of any injection are presented for Part 2. Beyond 28 days, SAEs are presented for events considered related to vaccination. AESIs are presented if considered related to vaccination. In addition, SAEs and AESIs that were reported outside of Part 2 (eg, in Part 1 or placebo-crossover participants) that were considered related or otherwise meaningful are presented.

5.2 Overview of Safety in Study 203 Participants 12 to 17 Years of Age

5.2.1 Duration of Follow-Up and Data Cutoff Dates for Analyses

Safety data for participants 12 to 17 years of age in Study 203 include:

- *Randomized, blinded phase:* median duration 1.8 months (53 days) post-dose 2 (N=2486; 08 May 2021 data extraction); includes solicited ARs and all unsolicited AEs within 28 days
- *Long-term (including open-label) follow-up:* median duration of 11.1 months (312 days) post-dose 2 for participants randomized to mRNA-1273 (N=2486; 31 Jan 2022 data extraction); includes MAAEs, SAEs, AESIs, and AEs leading to discontinuation

5.2.2 Solicited Adverse Reactions (12 to 17 Years)

5.2.2.1 Solicited Local Adverse Reactions (12 to 17 Years)

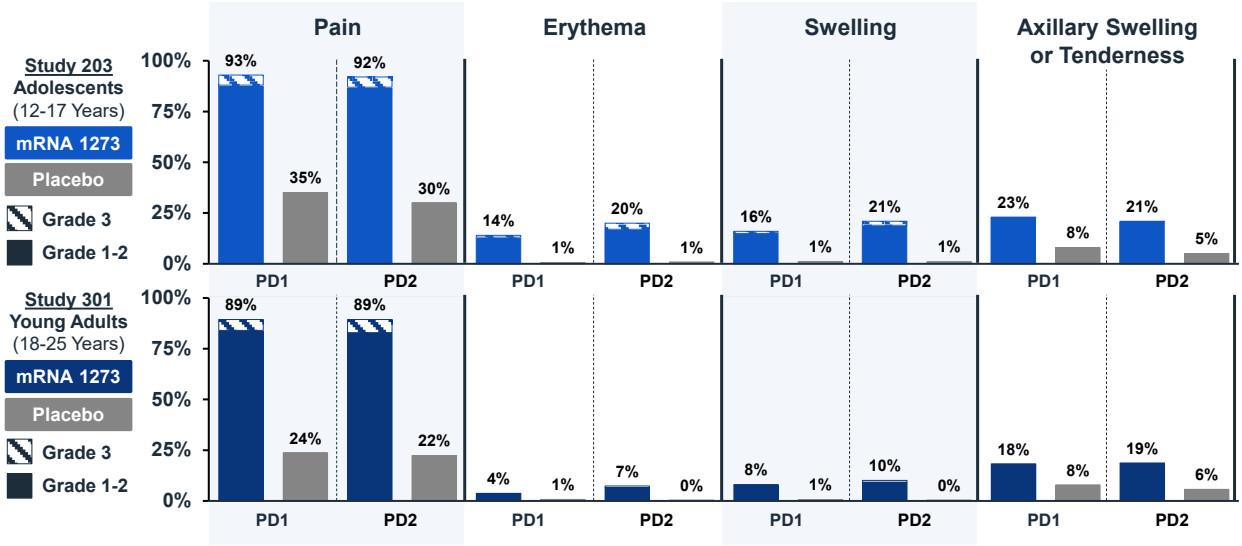
Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness.

Solicited local AEs were more common in the mRNA-1273 group than in the placebo group (Figure 13); pain was the most commonly reported solicited AE in the mRNA-1273 recipients. Solicited ARs were mostly Grade 1 or Grade 2. No Grade 4 solicited local ARs were reported.

Most solicited local ARs in the mRNA-1273 group were reported within the first 2 days after any dose. The median duration was 3 days.

Numerically higher rates of localized swelling and erythema were reported in adolescents (Study 203) compared to young adults (Study 301; Figure 13).

Figure 13: Solicited Local Adverse Reactions in Study 203 Participants 12 to 17 Years and Study 301 Participants 18 to 25 Years (Solicited Safety Set)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
No Grade 4 solicited local adverse reactions were reported
Datacut: Study 203: 08 May 2021, Study 301: 26 Mar 2021Source: P203 Tables 3.1.1.1 and 3.1.1.2; Response to Clinical Clarifax #2 (Adolescent extension)

5.2.2.2 Solicited Systemic Adverse Reactions (12 to 17 Years)

Solicited systemic ARs assessed included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting.

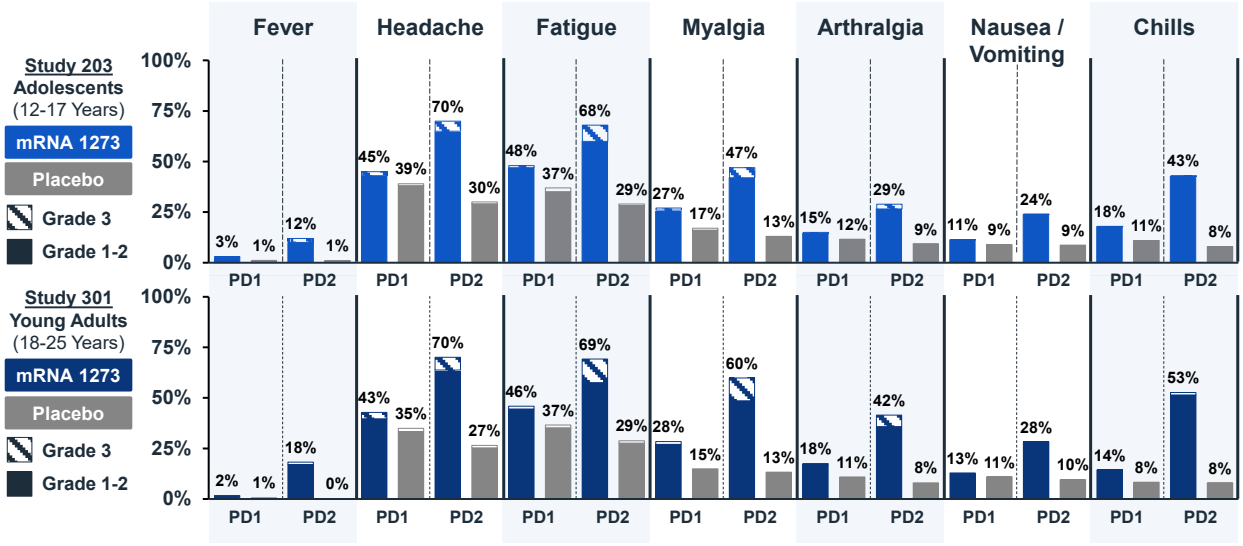
Solicited systemic ARs were more frequent in the mRNA-1273 group than in the placebo group and also more frequent after dose 2 than after dose 1 for the mRNA-1273 group. The most commonly reported solicited ARs were headache and fatigue, followed by myalgia and chills (Figure 14).

Among mRNA-1273 recipients, most solicited systemic ARs were Grade 1 or 2. A total of 4 solicited systemic Grade 4 ARs were reported: fever in 2 participants (1 placebo and 1 mRNA-1273 recipient), headache in 1 participant (mRNA-1273 recipient) and nausea/vomiting (mRNA-1273 recipient).

Most solicited systemic ARs in participants in the mRNA-1273 group were reported within the within 1 to 2 days after either dose and lasted a median of 2 days.

While rates of solicited systemic ARs of mRNA-1273 in adolescents were higher than those in Study 203 placebo participants, they were similar or lower than rates in young adult in Study 301.

Figure 14: Solicited Systemic Adverse Reactions in Study 203 Participants 12 to 17 Years and Study 301 Participants 18 to 25 Years (Solicited Safety Set)



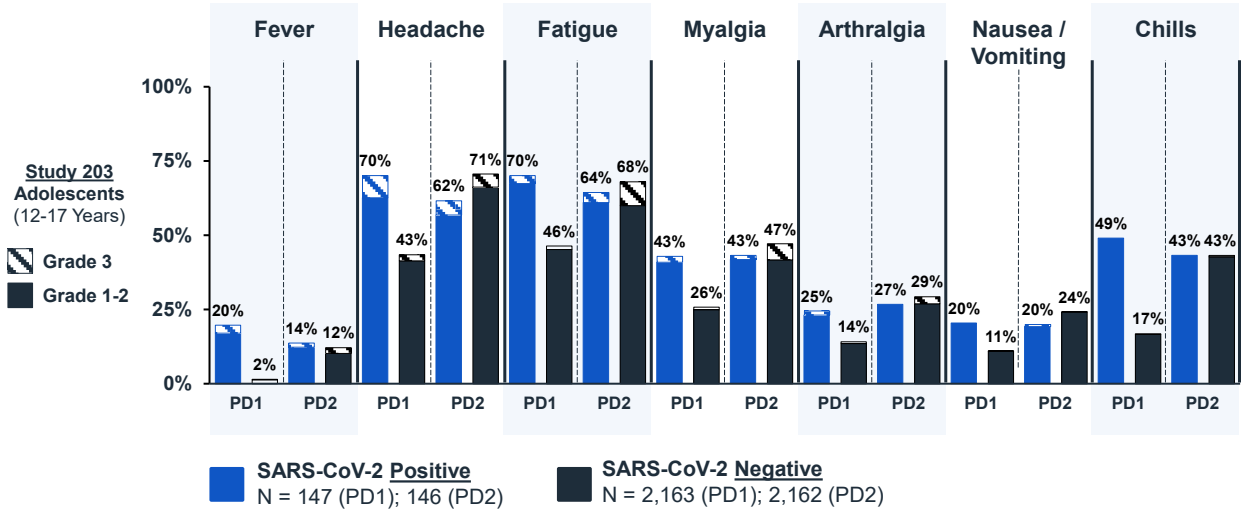
Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Note: Grade 4 systemic adverse reactions reported PD2: fever, headache, and nausea/vomiting in 3 vaccine recipients & fever in 1 placebo recipient
Datacut: Study 203: 08 May 2021; Study 301: 26 Mar 2021
Study P203 Table 3.1.1.1, Table 3.1.1.2, Table 1.7.1, Table 1.7.2; Response to Clinical Clarifax #2 (Adolescent extension)

5.2.2.2.1 Solicited Systemic Adverse Reactions by Baseline Serostatus

An assessment of reactogenicity among participants with evidence of prior SARS-CoV-2 infection (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]) compared to those with no evidence of infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1) was conducted. In ages 12 through 17 years, 5.8% of participants had evidence of prior SARS-CoV-2 infection at baseline.

Figure 15 presents the percentage of the solicited systemic ARs in mRNA-1273 participants starting within 7 days after each dose by SARS-CoV-2 status. Some solicited systemic ARs were higher after the first dose in baseline seropositive recipients of mRNA-1273 compared to baseline seronegative recipients of the vaccine. The difference was no longer evident after the second dose. Axillary swelling and tenderness was the only local AR that had a higher rate post-dose 1 in baseline SARS-CoV-2 positive participants. Similar to the systemic reactions, the difference was not observed post-dose 2.

Figure 15: Study 203 Solicited Systemic Adverse Reactions by Baseline Serostatus (12 to 17 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2; SARS-COV-2=Severe Acute Respiratory Syndrome Coronavirus-2 Datacut: 08 May 2021
Source: Study P203 Table 3.1.1.7, Table 3.1.1.8

5.2.3 Unsolicited Adverse Events Within 28 Days (12 to 17 Years)

Unsolicited AEs were collected within 28 days after each dose. Reported rates of any unsolicited AEs within 28 days after any dose were more common in the mRNA-1273 (20.5%) than in the placebo group (15.9%; Table 26). Differences in unsolicited AE between groups are in part related to occurrence of injection site reactions and lymphadenopathy in the mRNA-1273 group.

Unsolicited AEs within 28 days after any dose assessed by the Investigator as related to study treatment were more frequent in the mRNA-1273 group than in the placebo group (12.6% vs 5.8% respectively). Similarly, this difference was also primarily attributable to events related to injection site reactions and lymphadenopathy.

The frequency of MAAEs within 28 days of any dose was similar between the mRNA-1273 and placebo groups (6.3% vs 6.5%, respectively). The incidence of unsolicited severe AEs and SAEs within 28 days after any dose was low and generally similar in the mRNA-1273 and placebo groups. SAEs are further described in Section 5.2.4.1.

Of note, at the time of the 08 May 2021 data extraction, the only specified AESI was MIS-C. Subsequently, a priority list of AESIs potentially related to COVID-19 was introduced by the Brighton Collaboration; Study 203 was then amended (27 Jul 2021 protocol amendment) to include these AESIs. The Sponsor reviewed Study 203 AE data retrospectively (at the 31 Jan 2022 data extraction) to identify events that would meet the revised AESI designation. Two AESIs were retrospectively identified at the

31 Jan 2022 data cut: appendicitis (n=1, described in the SAE section) and injection site hypersensitivity (n=1, described in the AESI section). No events of MIS-C were reported in Study 203.

Table 26: Study 203 Proportion of Participants with Unsolicited AEs within 28 Days after Any Dose (Safety Set, 12 to 17 Years)

	mRNA-1273 N=2486		Placebo N=1240	
Category, n (%)	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	510 (20.5)	312 (12.6)	197 (15.9)	72 (5.8)
SAE	2 (< 0.1)	0	1 (< 0.1)	0
Fatal	0	0	0	0
Medically Attended AEs	156 (6.3)	19 (0.8)	81 (6.5)	5 (0.4)
Leading to Discontinuation - Vaccine	0	0	0	0
Leading to Discontinuation - Study	1 (< 0.1)	0	0	0
Severe	4 (0.2)	0	1 (< 0.1)	0
AESI of MIS-C	0	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event
Datacut: 08 May 2021
Source: Study P203, Table 3.2.1.1

5.2.4 Unsolicited Adverse Events in the Entire Study Period (12 to 17 Years)

As noted above, long-term (cumulative as of study start) safety data are available for adolescents randomized to mRNA-1273 (31 Jan 2022 data extraction; median follow-up of 11.1 months post-dose 2). Review of these data did not identify any new safety concerns (Table 27). SAEs, MAAEs, AESIs, and AEs leading to discontinuation are summarized in the following sections based on the latest data cut to provide the most comprehensive accounting. Since the study was ongoing and events may have been added or removed by Investigators, the counts of the events may be different from unsolicited AEs within 28 days, which is based on an earlier data extraction.

Table 27: Study 203 Proportion of Participants Reporting Unsolicited AEs in the Entire Study after Any Dose (Safety Set, 12 to 17 Years)

Category, n (%)	mRNA-1273 N=2,486	
	Any AE	Related to Vaccination
Any AE	1386 (55.8)	372 (15.0)
SAE	21 (0.8)	0
Fatal	0	0
Medically Attended AEs	980 (39.4)	25 (1.0)
Leading to Discontinuation - Vaccine	3 (0.1)	1 (< 0.01)
Leading to Discontinuation - Study	0	0
AESI – Any	13 (0.5)	1 (< 0.01)
AESI of MIS-C	0	0
AESI of Other	13 (0.5)	1 (< 0.01)

Abbreviations: AE=adverse event; AESI=adverse event of special interest; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event
Datacut: 31 Jan 2022
Source: Study P203 Table 14.3.1.7.4.1

5.2.4.1 SAEs in the Entire Study Period (12 to 17 Years)

SAE are summarized first for the period within 28 days of any dose and subsequently for the entire study period (cumulatively).

SAEs reported within 28 days:

A total of 5 SAEs were reported within 28 days after any injection in 4 participants: 1 (< 0.1%) in the placebo group and 3 (< 0.1%) in the mRNA-1273 group (Table 28). None of the SAEs were considered related to vaccination by the Investigator.

Table 28: Serious Adverse Events within 28 Days of Any Injection (Safety Set, 12 to 17 Years)

Treatment group	Age (years)	Sex	Preferred Term	Post Dose #	Time to Onset (days)	Causality per Investigator	Additional Information
mRNA-1273 100 µg	15	M	Appendicitis	1	4	Not Related	No sign of perforation; discharged in 2 days.
			Diarrhoea, Vomiting, Post procedural fever	1	7	Not Related	Post-appendicitis above, readmitted; no apparent etiology; resolved in 1 day.
mRNA-1273 100 µg	16	F	Drug-induced liver injury	1	14	Not Related	Developed rash, fever, fatigue, myalgia and elevated liver function tests after a course of Trimethoprim/Sulfamethoxazole. Resolved within 2 weeks; attributed to antibiotic
mRNA-1273 100 µg	14	F	Major depression & Suicidal ideation	2	14	Not Related	Pre-existing anxiety and depression
Placebo	13	F	Obstructive nephropathy	1	5	Not Related	Due to kidney stone resolved with lithotripsy

Abbreviations: F=female; M=male
Datacut: 31 Jan 2022
Source: EUA Submission, Module 2.5 Long-term Safety Follow-up

SAE reported in the entire study period:

A total of 29 SAEs were reported in 21 participants (including those described above within the 28 day follow-up period) among all participants randomized to mRNA-1273 (with a median of 11.1 months of follow-up post-dose 2). No SAEs were assessed by Investigators as related to study vaccine

In this long-term follow-up, the most common SAEs by system organ class (SOC) were psychiatric disorders (depression and suicidal ideation) occurring in 11 of the 21 participants reporting SAEs. No temporal pattern was observed (time to onset 14 to 311 days post last dose). Nine of the 11 participants had prior psychiatric diagnoses and reported precipitating events (eg, bullying, school or home challenges); 2 had a new diagnosis of depression. The occurrence of these events is consistent with reports of significant increases in pediatric and adolescent depression since the pandemic began (Racine et al 2021).

Apart from psychiatric disorders, the only other event reported by more than one participant was appendicitis (also classified as an AESI), reported by 2 of the 21 participants reporting SAE: (i) a 15 year old male 4 days post-dose 1 (mRNA-1273) and (ii) a 17 year old male 182 days post-dose 2 (mRNA-1273). Neither event was considered related, and both resolved without complication (Section 5.2.4.4).

5.2.4.2 Deaths in the Entire Study Period (12 to 17 Years)

No participant deaths were reported in Study 203.

5.2.4.3 MAAEs in the Entire Study Period (12 to 17 Years)

Cumulatively, among participants randomized to mRNA-1273 (median follow-up of 11.1 months post-dose 2), a total of 39.4% of participants reported at least one MAAE. The proportion of MAAEs should be considered in the context of the duration of follow-up, as well as the study criteria for MAAEs (the study required illness visits for upper respiratory infections [URIs] to allow for testing for COVID-19; these visits were then classified as MAAEs). The most common MAAEs by SOC were infection and infestations (n=712, 27.6%), and COVID-19 was the most common preferred term (PT) within that SOC, consistent with the Omicron wave (December 2021 and January 2022). Few participants (26, 1.0%) had MAAEs considered related to mRNA-1273. Overall, no new safety concerns were identified in the review of the MAAEs.

5.2.4.4 AESI in the Entire Study Period (12 to 17 Years)

One AESI (hypersensitivity), which occurred 11 days post-dose 1, was initially considered related to study vaccination by the Investigator. This event was subsequently updated to a delayed cutaneous reaction at injection site and was clarified as not an AESI.

No events of myocarditis or pericarditis have been reported in Study 203.

Enhanced surveillance was implemented in Study 203 to solicit symptoms included in the CDC working definition of myocarditis and pericarditis during phone contacts. If any symptoms were reported, the Investigator evaluated the participants. Additionally, to identify potential cases, the safety database was evaluated by (i) aggregate analysis of the Cardiomyopathy SMQs and by (ii) analysis of PTs included in the CDC definition.

One participant with chest pain was evaluated as a potential case of myocarditis. This participant, a 14 year old male with previous history of gastroesophageal reflux, was randomized to placebo and received mRNA-1273 as a cross-over vaccination following study unblinding. Two days post-dose 2, the participant reported nausea, vomiting, chest pain, and tachycardia. Clinical evaluation yielded a normal physical exam. Serum troponin and imaging studies were not obtained. A bedside electrocardiogram (EKG) was interpreted by the physician as ST-elevation with right axis deviation; heart rate was 79. The Investigator suspected either mild myocarditis or costochondritis. The participant was not hospitalized and reported improvement 6 days later with supportive care (rest, hydration, ibuprofen). The case was submitted to the CEAC and underwent adjudication. The final adjudication was that the case did not meet the CDC definition of acute myocarditis, acute pericarditis, or myopericarditis. The participant was recommended for cardiology follow-up, and the CEAC requested to see the cardiology follow-up report once available. The participant was seen by a pediatric cardiologist approximately 5 months after the event. According to the report, the participant was asymptomatic and physical examination was unremarkable. Echocardiogram and 12 lead EKG were both normal. Given that the clinical work-up was reassuring, no further follow-up was requested.

No cases meeting the CDC definition of myocarditis or pericarditis were identified from the surveillance activity in Study 203.

5.2.4.5 Discontinuation from Investigational Product or Study (12 to 17 Years)

Three participants (0.1%) in the mRNA-1273 group discontinued study vaccine because of an AE. No pattern in these events was identified, with diverse AEs leading to discontinuation: COVID-19 (n=1); drug-induced liver injury assessed as not related (n=1; likely related to use of sulfamethoxazole-trimethoprim) and throat tightness assessed as related (n=1; reported occurring within 1 minute of dose 1 and resolving within 10 minutes with no other associated symptoms).

5.3 Safety Data Presentation from Study 204

Safety was monitored identically in Part 1 (open-label dose-finding phase) and Part 2 (randomized, blinded, placebo-controlled) of Study 204. Safety data were also collected in a similar fashion for placebo recipients who crossed over to receive mRNA-1273 after unblinding, which occurred for children 6 to 11 years for whom an authorized COVID-19 vaccine became available.

For solicited ARs and unsolicited AEs through 28 days, data from Part 2 are presented because this represents the largest group of study participants and allows comparison to a placebo control group. Occurrence of ARs and AEs should be interpreted in the context of the asymmetric 3:1 randomization ratio (mRNA-1273:placebo).

SAEs within 28 days of any injection are presented for Part 2 in each age group. For the 6 to 11 year age group, SAEs are presented for events considered related to vaccination beyond 28 days. In the 2 to 5 years and 6 to 23 months age groups, SAEs for the entire study period are presented comprehensively for Part 2, as the blinded follow-up was ongoing at the time of the data cut. AESIs are presented if considered related to vaccination across each age group. In addition, SAEs and AESIs that occurred outside of the specified groups (eg, in Part 1 or placebo-crossover participants) above that were considered related or otherwise meaningful are presented.

5.4 Overview of Safety in Study 204 Participants 6 to 11 Years of Age

5.4.1 Duration of Follow-Up and Data Cutoff Dates

Safety data for participants 6 to 11 years of age in Study 204 include:

- *Blinded phase follow-up*: median duration 1.8 months (49 days) post-dose 2 (N=4,002 including placebo, 10 Nov 2021 data extraction); includes solicited ARs and all unsolicited AEs within 28 days
- *Long-term (including open-label) follow-up:* median duration of 5.6 months (158 days) post-dose 2 for participants randomized to mRNA-1273 (N=3007, 21 Feb 2022 data extraction); includes MAAEs, SAEs, AESIs, and AEs leading to discontinuation

5.4.2 Solicited Adverse Reactions (6 to 11 Years)

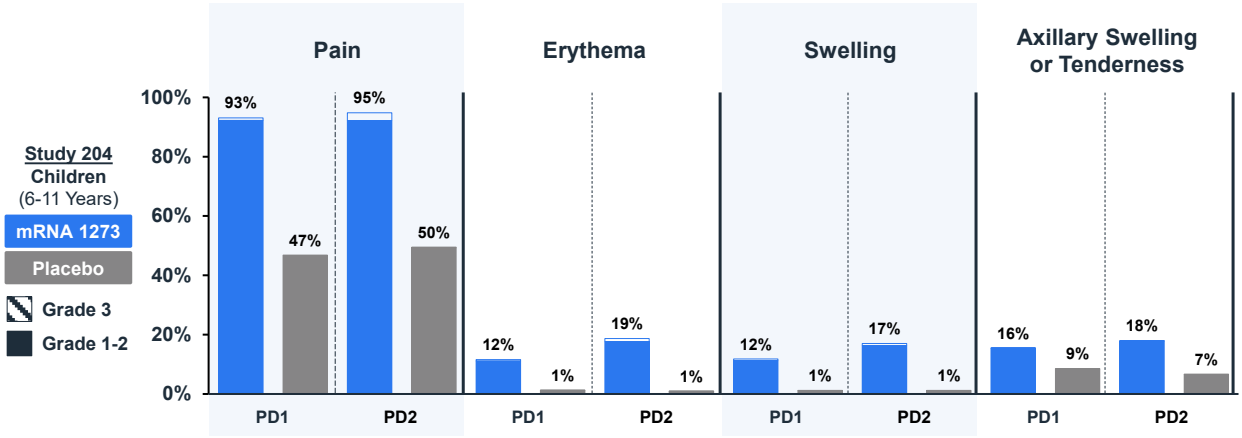
5.4.2.1 Solicited Local Adverse Reactions (6 to 11 Years)

Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness.

Solicited local ARs were more common in the mRNA-1273 than in the placebo group (Figure 16); pain was the most commonly reported solicited AR in the mRNA-1273 recipients. Solicited local ARs were mostly Grade 1 or 2. No Grade 4 solicited local ARs were reported.

Most solicited local ARs in the mRNA-1273 group occurred within the first 2 days after any dose and the median duration was 3 days.

Figure 16: Study 204 Solicited Local Adverse Reactions (Solicited Safety Set, 6 to 11 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
No Grade 4 solicited local adverse reactions were reported.
Datacut: 10 Nov 2021
Source: Study P204 Table 14.3.1.1.2.2.1, Table 14.3.1.1.1.2.1

5.4.2.2 Solicited Systemic Adverse Reactions (6 to 11 Years)

Children 6 to 11 years of age were assessed for systemic ARs of fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills.

Solicited systemic ARs were more frequent in the mRNA-1273 group than in the placebo group and more frequent after dose 2 than after dose 1 for the mRNA-1273 group (Figure 17). The most common solicited systemic ARs were headache and fatigue.

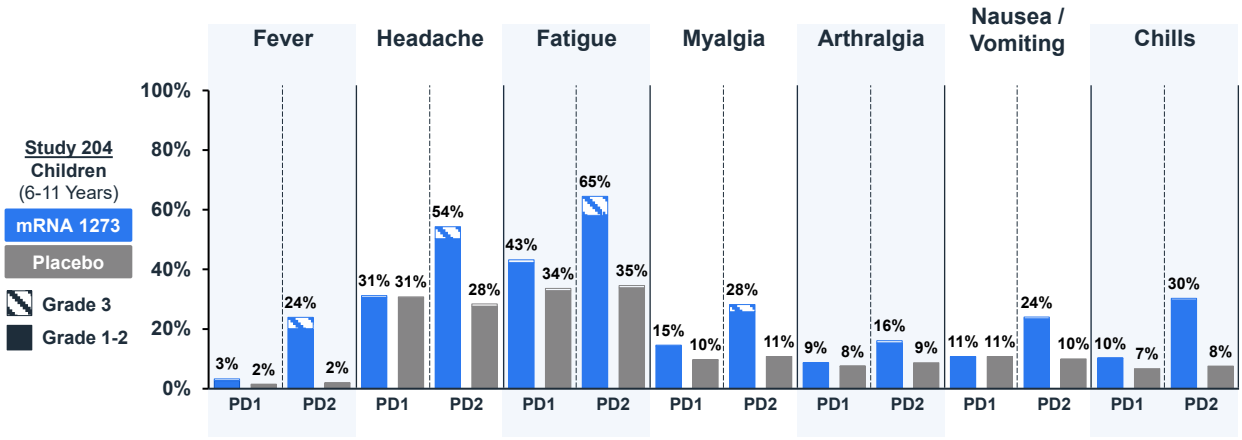
Among mRNA-1273 recipients, most solicited systemic ARs were Grade 1 or 2. No Grade 4 solicited systemic ARs were reported (one Grade 4 event of fever in a placebo participant was reported due to an error in eDiary data entry).

Most solicited systemic ARs in participants in the mRNA-1273 group occurred within the first 2 days after each dose, and the median duration was 2 days.

Fever was reported more frequently after both dose 1 and dose 2 in the mRNA-1273 group than in placebo group. Grade 3 fever (39°C–40.0°C) after dose 2 was also more common in the mRNA-1273 group than in the placebo group. No Grade 4 fevers (> 40.0°C) were reported in the mRNA-1273 group.

The median onset of fever in the mRNA-1273 group after any dose was 2 days with a median duration of 1 day.

Figure 17: Study 204 Solicited Systemic Adverse Reactions (Solicited Safety Set, 6 to 11 Years)

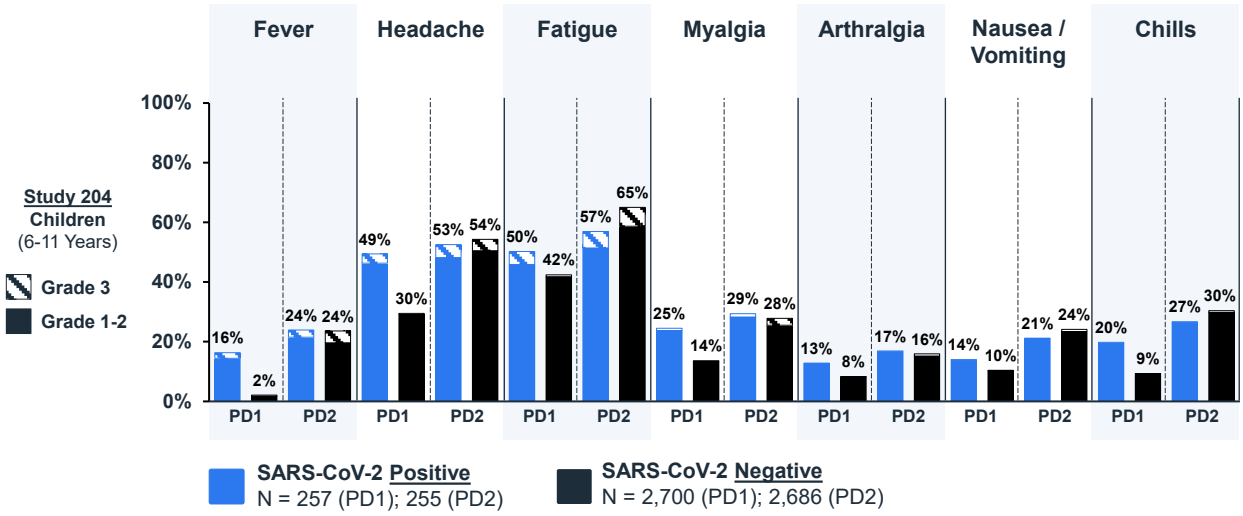


Abbreviations: PD1=post-dose 1; PD2=post-dose 2
No Grade 4 systemic reactions reported
Datacut: 10 Nov 2021
Source: Study P204 Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1

5.4.2.2.1 Solicited Systemic Adverse Reactions by Baseline Serostatus

An assessment of reactogenicity among participants with evidence of prior SARS-CoV-2 infection (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]) compared to those with no evidence of infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1) was conducted. In the 6 to 11 year age group, 8.6% of participants had evidence of prior SARS-CoV-2 infection at baseline. Figure 18 presents the solicited systemic ARs in mRNA-1273 participants starting within 7 days after each dose by SARS-CoV-2 status. Similar to what was observed in the 12 to 17 year age group, some solicited systemic ARs were higher after the first dose in baseline seropositive recipients of mRNA-1273 compared to baseline seronegative recipients of the vaccine. The difference was no longer evident after the second dose. Axillary swelling and tenderness was the only local AR that had a higher rate post-dose 1 in baseline SARS-CoV-2 positive participants. Similar to the systemic reactions, the difference was not observed post-dose 2.

Figure 18: Study 204 Solicited Systemic Adverse Reactions by Baseline Serostatus (Solicited Safety Set, 6 to 11 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2Source: Study P204 Table 14.3.1.1.5.1 and Table 14.3.1.1.5.2

5.4.3 Unsolicited Adverse Events within 28 Days (6 to 11 Years)

Unsolicited AEs were collected during the 28 days after each injection and occurred at generally balanced rates in the mRNA-1273 (30%) and placebo (25%) groups (Table 29). Differences in overall rates are attributable to higher rates of injection site reactions reported in the mRNA-1273 compared to the placebo group.

The majority of unsolicited AEs in both groups reflect common childhood illnesses such as URIs. Abdominal pain (including PTs of abdominal pain, abdominal pain upper and abdominal pain lower) was observed in 1.1% of mRNA-1273 recipients and 0.6% of placebo recipients. Most events were non-specific, and no clear patterns in time to onset or etiology have been identified.

Unsolicited AE within 28 days after any dose assessed by the Investigator as related to study treatment were more common in the mRNA-1273 (11%) group than the placebo (5%) group, primarily attributable to injection site reactions.

Within 28 days after any dose, rates of SAEs were similar between mRNA-1273 (3 participants [< 0.1%]) and placebo (2 participants [0.2%]) groups. None of these SAEs were considered vaccine-related by the Investigator. A comprehensive description of all SAEs occurring within 28 days is provided below (Section 5.4.4.1).

Within 28 days after any dose, rates of MAAE were similar between mRNA-1273 (13%) and placebo (14%) groups. Differences in related MAAE between groups in this period (1% in mRNA-1273; 0.4% in placebo) were primarily attributed to events occurring in

the SOC General administration and injection site conditions and Skin and subcutaneous tissue disorders.

Two participants in the mRNA-1273 group were discontinued from study vaccine due to an AE, and one mRNA-1273 participant discontinued from the study for an AE. Comprehensive description of discontinuations among mRNA-1273 recipients is provided in Section 5.2.4.5.

Table 29: Study 204 Participants Reporting ≥ 1 Unsolicited Adverse Event within 28 Days after Any Dose (Safety Set, 6 to 11 Years)

Category, n (%)	mRNA-1273 N=3,007		Placebo N=995	
	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	891 (29.6)	319 (10.6)	250 (25.1)	50 (5.0)
SAE	3 (< 0.1)	0	2 (0.2)	0
Fatal	0	0	0	0
Medically Attended AEs	404 (13.4)	34 (1.1)	141 (14)	4 (0.4)
Leading to Discontinuation – Vaccine	2 (< 0.1)	0	0	0
Leading to Discontinuation – Study	1 (< 0.1)	0	0	0
Severe	12 (0.4)	9 (0.3)	2 (0.2)	1 (0.1)
AESI – Any	3 (< 0.1)	0	2 (0.2)	0
AESI of MIS-C	0	0	0	0
AESI of Myocarditis/Pericarditis	0	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity Grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Datacut: 10 Nov 2021
Source: Study P204 Table 14.3.1.7.1.2

5.4.4 Unsolicited Adverse Events in the Entire Study Period (6 to 11 Years)

Review of long-term safety data (cumulative, as of study start) in children 6 to 11 years of age randomized to mRNA-1273 (21 Feb 2022 data extraction; median follow-up of 5.6 months post-dose 2) did not identify any new safety concerns (Table 30). The placebo recipients are not included as they crossed over to receive mRNA-1273. Cumulative SAEs, MAAEs, and AESIs (including those noted within the 28 day period) are summarized in the following sections based on the latest data cut to provide the most comprehensive accounting. As events may have been added or removed by Investigators, the counts of events may be different from unsolicited AEs within 28 days, which is based on an earlier data extraction.

Table 30: Study 204 mRNA-1273 Recipients Reporting Unsolicited AEs in the Entire Study after Any Dose (Safety Set, 6 to 11 Years)

Category, n (%)	mRNA-1273 N=3,007	
	Any AE	Related to Vaccination
All	1517 (50.4)	364 (12.1)
SAE	15 (0.5)	0
Fatal	0	0
Medically Attended AEs	1028 (34.2)	38 (1.3)
Leading to Discontinuation – Vaccine	3 (< 0.1)	1 (< 0.1)
Leading to Discontinuation – Study	1 (< 0.1)	0
Severe	23 (0.8)	11 (0.4)
AESI – Any	12 (0.4)	1 (< 0.1)
AESI of MIS-C	0	0
AESI of Myocarditis/Pericarditis	0	0

Abbreviations: AE=adverse events; AESI: adverse events of special interest; MAAEs=medically attended adverse events; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event
Datacut: 21 Feb 2022
Source: Study P204 Table 14.31.7.1.6.1

5.4.4.1 SAEs in the Entire Study Period (6 to 11 Years)

SAE are summarized first for the period within 28 days and subsequently for the entire study period (cumulatively).

SAEs reported within 28 days:

In the randomized, blinded phase of the study within 28 days, Table 31, a total of 5 participants reported an SAE – 3 in the mRNA-1273 group (< 0.1%) and 2 in the placebo group (0.2%). One additional SAE in an mRNA-1273 recipient was identified in the most recent data extraction (21 Feb 2022), an event of upper abdominal pain in a participant that subsequently was diagnosed with cholecystitis. All SAEs occurring within 28 days are described below (Table 31). None of these SAEs were considered related by the Investigator.

Beyond the randomized, blinded study period, an SAE of ileus was reported in a participant randomized to placebo and subsequently crossed over to receive mRNA-1273; the event was considered related by the Investigator. The event was reported 1 day after dose 2 mRNA-1273 in a child with a complex medical history, including prior surgical repair of a congenital gastrointestinal malformation, and requiring regular enemas. The event of ileus resolved within 3 days and the participant did not require hospital admission.

Of note, one participant in the placebo group (a 10 year old male) reported an SAE of 'long COVID' requiring hospitalization. Six weeks earlier an event of mild COVID (approximately 3 weeks post-dose 1 placebo) was reported in the participant. The

diagnosis of long COVID was based on new severe neurological symptoms (bilateral paresthesias) for which he was hospitalized. He had a neurological workup to exclude other causes for symptoms which was negative and was discharged with diagnosis of "long COVID-19 Effects."

Table 31: Study 204 SAEs within 28 Days of Any Injection (Safety Set, 6 to 11 Years)

Treatment group	Age (years)	Sex	Preferred Term	Post Dose #	TTO in days	Causality per Investigator	Additional Information
mRNA-1273 50 µg	8	M	Cellulitis orbital	2	2	Not Related	CT of the orbits with IV contrast showed right maxillary and ethmoid sinusitis with right medial orbital wall subperiosteal abscess. Responded well to IV antibiotics
mRNA-1273 50 µg	9	M	Cellulitis	2	16	Not Related	Cellulitis in left elbow area
mRNA-1273 50 µg	8	M	Abdominal pain upper	1	21	Not Related	Subsequently reported SAE of cholecystitis (65 days post-dose 2)
mRNA-1273 50 µg	7	F	Appendicitis	1	26	Not Related	Appendectomy without complications. Admitted for 2 days
mRNA-1273 50 µg (Cross-over participant)	6	F	Ileus	1	1	Related	Complex medical history including repair of imperforate anus and caecostomy, requiring regular enemas. Admitted; diagnosed with diffuse ileus, given oral challenge and discharged home.
Placebo	7	M	Affective disorder	2	4	Not Related	History of depression and impulse control issues
Placebo	10	M	COVID-19	2	25	Not Related	Hospitalized with neurological symptoms, diagnosis of "long COVID"

Abbreviations: SAE=serious adverse event; TTO=time-to-onset
Source: Study P204 Listing 16.2.7.5.2 (Datacut: 10 Nov 2021) and Listing 16.2.7.5.3 (Datacut: 21 Feb 2022)

SAE reported in the entire study period:

Cumulatively, among participants randomized to mRNA-1273 (median follow-up of 5.6 months post-dose 2), a total of 16 SAEs were reported in 15 participants (0.5%; including those reported within 28 days). No additional SAEs were considered related to vaccine by the Investigator. No trends or patterns were identified among reported SAEs.

One SAE was also reported as an AESI - appendicitis was reported in a 10 year old male 49 days post-dose 2. Beyond the data extraction of 21 Feb 2022, an SAE of Kawasaki Disease (also an AESI) was reported in a 7 year old male 190 days post-dose 2; the Investigator considered this event not related to study vaccine.

5.4.4.2 Deaths in the Entire Study Period (6 to 11 Years)

No deaths were reported in Study 204.

5.4.4.3 MAAEs in the Entire Study Period (6 to 11 Years)

Cumulatively, among participants randomized to mRNA-1273 (median follow-up of 5.6 months post-dose 2), a total of 34.2% of participants reported at least one MAAE. The proportion of MAAEs should be considered in the context of the duration of follow-up as well as the study criteria for MAAEs (the study required "illness visits" for URIs in order to allow for testing for COVID-19; these visits were then classified as MAAEs). Accordingly, the most frequent SOC for MAAEs was Infections and Infestations, with the articipants (38, 1.3%) had MAAEs considered related to mRNA-1273 (Table 30).

5.4.4.4 AESIs in the Entire Study Period (6 to 11 Years)

In the blinded phase of the study (median follow-up 1.8 months post-dose 2), a total of 5 participants reported AESIs, balanced between placebo (2 [0.2%] participants) and mRNA-1273 (3 [< 0.1%] participants) groups. In the mRNA-1273 group, the 3 participants reported AESIs of appendicitis (n=1), ageusia (n=1), and ageusia and anosmia (n=1).I In the placebo group, the 2 participants reported ageusia (n=1) and ageusia and anosmia (n=1). No AESI were considered related by the Investigator.

Cumulatively, among recipients randomized to mRNA-1273 (median follow-up of 5.6 months post-dose 2), a total of 12 (0.4%) participants reported 16 AESIs. One participant reported an AESI considered related by the Investigator. The participant was a 7-year-old male who reported a mild AE of intermittent chest pain and dyspnea 3 days post dose 2 of mRNA-1273, for which he was evaluated in the emergency department. Physical examination, electrocardiogram, and echocardiogram were all considered 1320ormal. The participant tested negative for SARS-CoV-2 and received supportive care. 1he dyspnea resolved within 1 day, chest pain within 4 days. The participant was continuing in the study at the time of the 21 Feb 2022 data extraction. While these events of chest pain and dyspnea were not protocol-specified AESI, they are nonetheless included in the summary table as they were entered into the case report form as AESIs by the Investigator.

In the open-label dose-finding phase (Part 1), one participant reported an AESI that was considered related by the Investigator. The participant was an 11 year old male who reported non-cardiac chest pain (as noted above, not considered to be an AESI per protocol) 72 days post-dose 2. The child was well-appearing with normal vital signs on physical examination. The participant's mother reported that the chest pain had resolved within a few hours of the clinic visit and she considered it similar to indigestion he had reported previously.

No events of myocarditis or pericarditis have been reported in Study 204 in the 6 to 11 year old age group.

Enhanced surveillance (regular telephone safety calls) was implemented in Study 204 to solicit symptoms included in the CDC working definition of myocarditis and pericarditis. If any symptoms were reported, the Investigators evaluated the children.

Additionally, to identify potential cases, this safety database was then evaluated by (i) aggregate analysis of the Cardiomyopathy SMQs and by (ii) analysis of PT included in the CDC definition. No cases meeting the CDC definition of myocarditis or pericarditis were identified from this surveillance activity.

5.4.4.5 Discontinuation from Investigational Product or Study (6 to 11 Years)

A total of 5 participants in the randomized, blinded phase reported AE leading to discontinuation of study vaccine: 3 in the mRNA-1273 group and 2 in the placebo group. None were considered related; for one event of urticaria reported 24 days post-dose 1 of mRNA-1273, the Investigator did not provide a causality assessment. No trends or safety concerns have been identified from review of AEs leading to discontinuation from study vaccine or participation.

5.5 Overview of Safety in Study 204 Participants 2 to 5 Years of Age

5.5.1 Duration of follow-Up and Data Cutoff Dates

Safety data for participants 2 to 5 years of age in Study 204 derive from the blinded phase with a median follow-up of 2.5 months (71 days) post-dose 2 (21 Feb 2022 data extraction).

5.5.2 Solicited Adverse Reactions (2 to 5 Years)

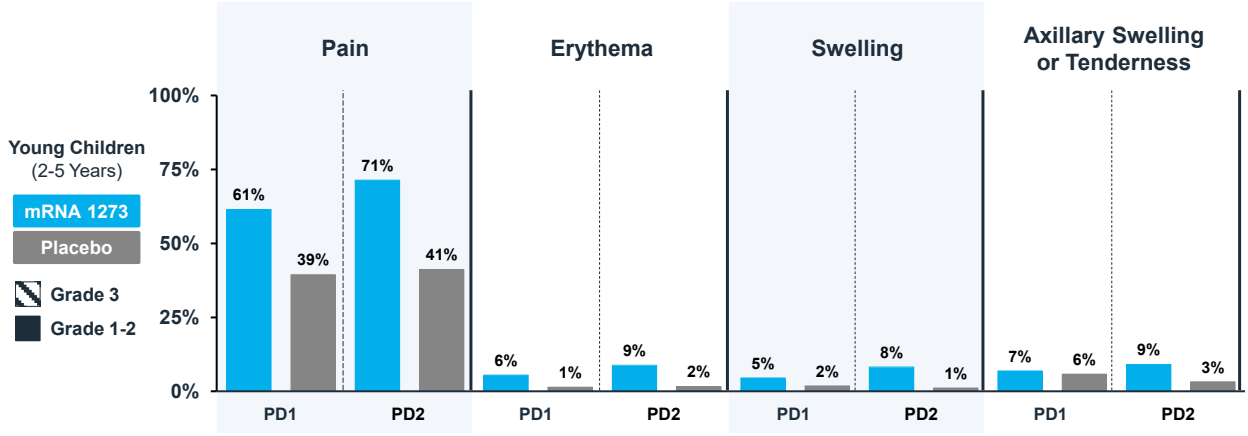
5.5.2.1 Solicited Local Adverse Reactions (2 to 5 Years)

Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness.

Solicited local ARs were more common in the mRNA-1273 than in the placebo group after either dose (Figure 19). Pain was the most commonly reported solicited local AR. Most solicited local ARs were Grade 1 or 2 in mRNA-1273 recipients; no Grade 4 local AR were reported. After any dose, the most common solicited local AR was pain.

Most solicited local ARs in the mRNA-1273 group occurred within 1 day. Local ARs had a median duration of 2 days in the mRNA-1273 group.

Figure 19: Study 204 Solicited Local Adverse Reactions (Solicited Safety Set, 2 to 5 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
No Grade 4 events reported
Datacut: 21 Feb 2022
Source: Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1

5.5.2.2 Solicited Systemic Adverse Reactions (2 to 5 Years)

Different systemic ARs were solicited in this age group as follows: (i) children 37 months to 5 years were assessed for reactions of fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills (Figure 20), and (ii) children 24 to 36 months were assessed for fever, irritability/crying, sleepiness and loss of appetite (Figure 21).

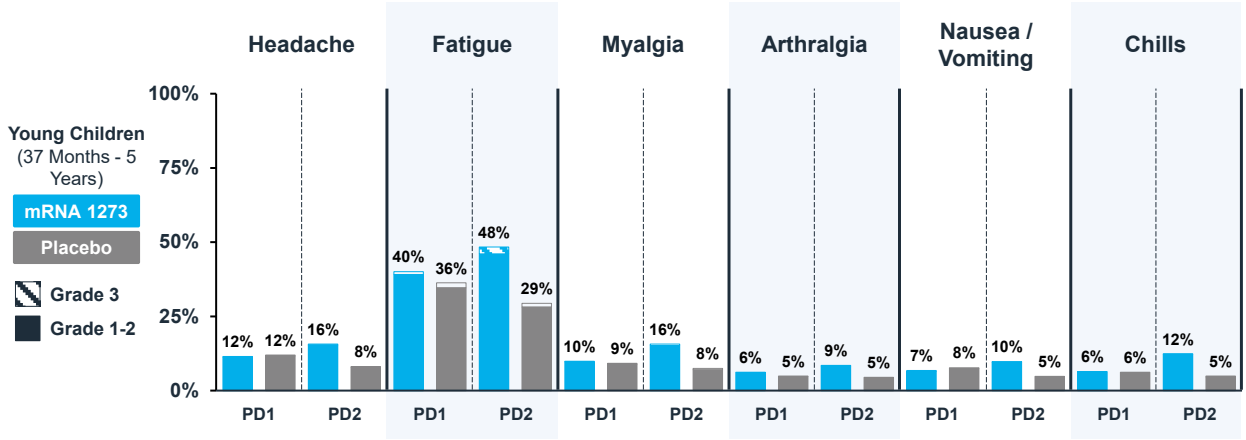
Solicited systemic ARs were more frequent in the mRNA-1273 group than in the placebo group after both doses and more common after dose 2 than after dose 1 for the mRNA-1273 group. Among mRNA-1273 recipients, solicited systemic ARs were Grade 1 or 2. The median duration of solicited systemic ARs was 2 days.

In the older age group (37 months to 5 years, N=1,975), after any dose, the most common solicited systemic AR in the mRNA-1273 group, was fatigue (Figure 20). ARs were generally Grade 1 or Grade 2.

Fever was reported in 23% of participants receiving mRNA-1273. Fever was the only Grade 4 solicited systemic AR reported in the 2 to 5 year age group. An analysis of fever in this age group is found in Section 5.5.2.2.1.

Most solicited systemic ARs in the mRNA-1273 group occurred within the first 2 days after either dose.

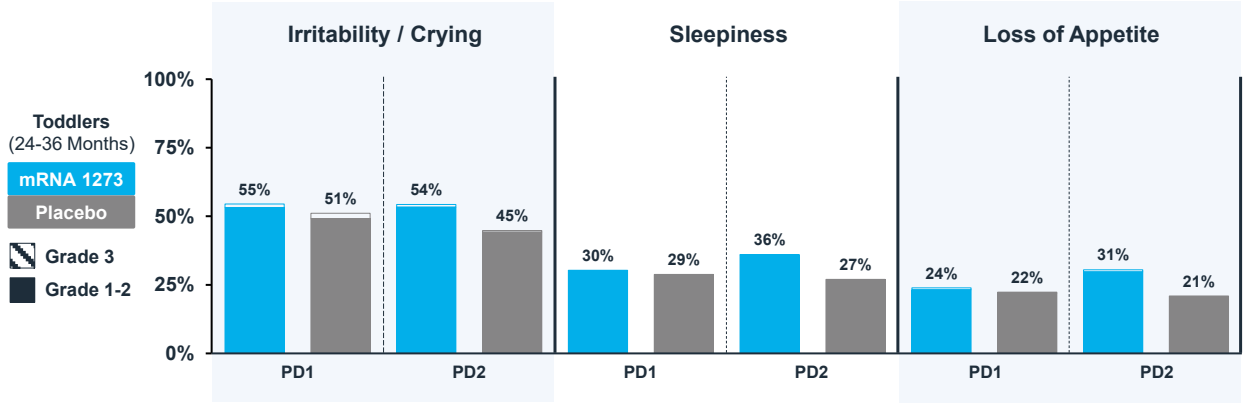
Figure 20: Study 204 Solicited Systemic Adverse Reactions Other than Fever (Solicited Safety Set, 37 months to 5 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
No Grade 4 events reported except fever, described in Section 5.5.2.2.1
Datacut: 21 Feb 2022
Source: Study P204 Table 14.3.1.1.4.19 and Study P204 Table 14.3.1.1.4.20

In the younger age group (24 to 36 months, N=963), solicited ARs were more similar to placebo compared to older age groups. The most common solicited systemic ARs after any dose of mRNA-1273 was irritability/crying, followed by sleepiness and loss of appetite (Figure 21). Events were generally Grade 1 or Grade 2. Most solicited systemic ARs in the mRNA-1273 group occurred within the first 2 days after either dose.

Figure 21: Study 204 Solicited Systemic Adverse Reactions Other than Fever (Solicited Safety Set, 24 to 36 Months)



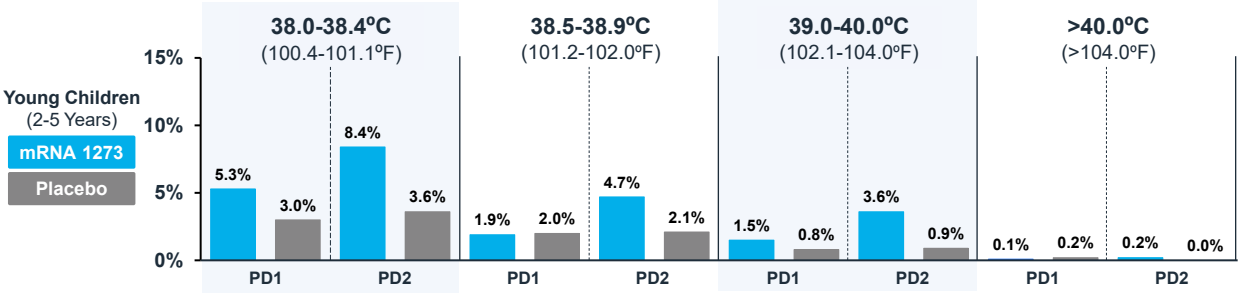
Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022; Source: Study P204 Table 14.3.1.1.4.19 and Study P204 Table 14.3.1.1.4.20

5.5.2.2.1 Analysis of Fever in (2 to 5 Years)

Fever was reported in both the mRNA-1273 and placebo groups and more frequently among mRNA-1273 recipients compared to placebo recipients. Among mRNA-1273 recipients, fever was more frequently after dose 2 than dose 1. Graphical representation

of the percentage of participants reporting temperatures ≥ 38°C to 38.9°C, ≥ 39°C to 40°C or > 40°C after each dose is provided in (Figure 22). In the mRNA-1273 group, most reported fevers were in the range of ≥ 38°C to 38.9°C with > 40°C temperature reported in 0.4% of participants after either dose.

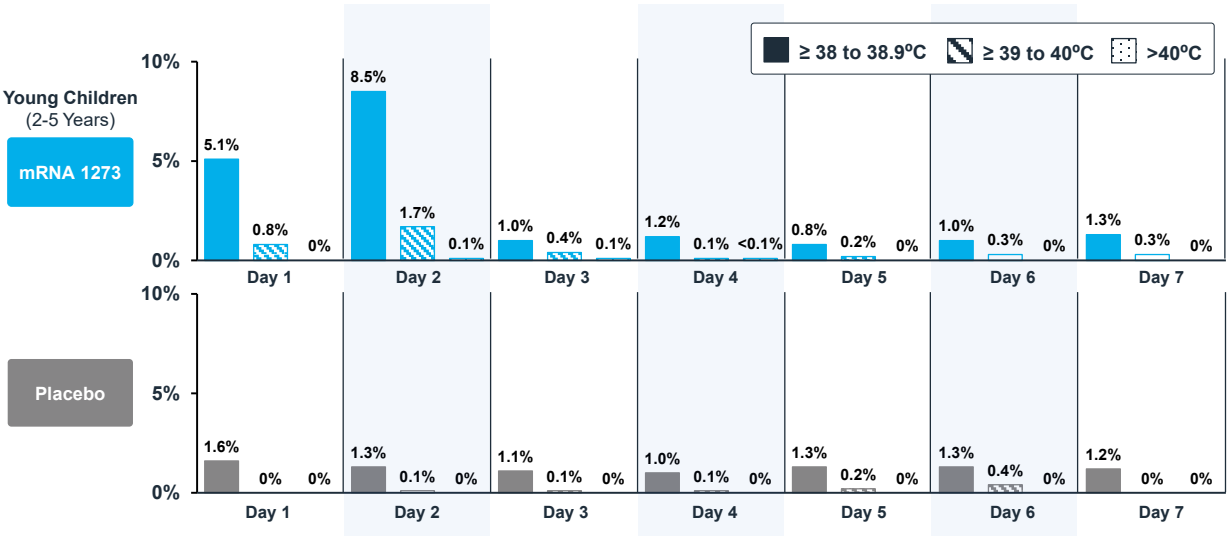
Figure 22: Study 204 Fevers within 7 days (Solicited Safety Set, 2 to 5 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Study P204 Table 14.3.1.1.1.2.1.2 and Table 14.3.1.1.2.2.1.2

In the mRNA-1273 group, fever was most commonly reported on Day 1 or Day 2 after vaccination. Beyond Day 2, fever rates were similar between the mRNA-1273 and placebo groups (Figure 23). A high background rate of fevers were observed in the placebo group, evidence of the prevalence of viral infections in the winter months over which this study was conducted.

Figure 23: Study 204 Fevers by Day and Temperature Post-Dose 2 (Safety Set, 2 to 5 Years)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Figure 6; Study P204 Table 14.3.1.6.5.2

Thirteen participants reported fever > 40°C: 11 participants in the mRNA-1273 group and 2 in the placebo group. Investigator inquiry determined that 3 of the 13 fever events were incorrectly reported as Grade 4, as none of these 3 participants recorded any elevated temperature. The 10 participants with confirmed Grade 4 fever events are discussed further: 8 (0.3%) in the mRNA-1273 group and 2 (0.2%) in the placebo group (Table 32). Grade 4 fever events in the mRNA-1273 recipients occurred after both dose 1 (3 of 8 events) and dose 2 (5 of 8 events).

Four of the 10 total participants reporting Grade 4 fever also reported concurrent AE including: 3 (of 8) in the mRNA-1273 group (URI; croup; bilateral viral pneumonia) and 1 (of 2) in the placebo group (COVID-19 infection). These concurrent AE may provide an additional explanation for fever.

Among the Grade 4 fever events, day of onset ranged from Day 1 to Day 5 post-vaccination with most starting on Day 2 or 3 after injection. Duration of the febrile episodes ranged from 1 to 4 days with most episodes lasting for 2 days.

Table 32: Study 204 Participants Reporting Fever > 40°C (2 to 5 Years)

Case #	Dose #	Start of any fever	Duration of any fever	Age (years)	Treatment	SARS-COV-2 Status at baseline	Report of Concurrent AE
1	Dose 1	D4	2 days	2	mRNA-1273	Positive	No
2	Dose 1	D3	3 days	2	mRNA-1273	Negative	No
3	Dose 1	D3	3 days	2	mRNA-1273	Negative	URI
4	Dose 2	D2	2 days	2	mRNA-1273	Positive	No
5	Dose 2	D2	4 days	4	mRNA-1273	Negative	Croup
6	Dose 2	D1	4 days	2	mRNA-1273	Negative	Bilateral viral pneumonia
7	Dose 2	D3	1 day	3	mRNA-1273	Negative	No
8	Dose 2	D2	2 days	2	mRNA-1273	Negative	No
9	Dose 1	D5	2 days	2	Placebo	Negative	SARS-CoV-2 infection
10	Dose 1	D2	2 days	3	Placebo	Negative	No

Abbreviations: SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; URI=upper respiratory infection
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Table 41

5.5.2.2.2 Solicited Systemic Adverse Reactions by Baseline Serostatus

An assessment of reactogenicity among participants with evidence of prior SARS-CoV-2 infection (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]) compared to those with no evidence of infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1) was conducted. In ages 2 to 5 years, 8.6% of participants had evidence of prior SARS-CoV-2 infection at baseline. Fever (temperature > 38°C) was the only systemic AR reported in a greater proportion of baseline SARS-CoV-2 positive vaccine participants compared to baseline SARS-CoV-2 negative vaccine participants. There were no notable differences in other reactogenicity events. Differences in ARs reported after the first dose between baseline seropositive

and seronegative recipients of mRNA-1273 were not observed to the same degree in this age group compared to older children and adolescents.

5.5.3 Unsolicited Adverse Events within 28 Days (2 to 5 Years)

Unsolicited AEs were reported at similar rates in the mRNA-1273 (40.0%) and placebo (37.5%) groups (Table 33).

Most unsolicited AEs in both groups reflect common childhood illnesses, such as URIs, which are particularly common in this age group and during the winter months (when this study and follow-up were conducted). Abdominal pain (including PTs of abdominal pain, abdominal pain upper, and abdominal discomfort) was observed in 0.7% of mRNA-1273 recipients and 0.4% of placebo recipients. Most events were non-specific, and no clear patterns in time to onset or etiology have been identified.

Unsolicited AE within 28 days after any dose assessed by the Investigator as related to study treatment were generally balanced between mRNA-1273 group (9.4%) and placebo (7.9%) groups.

There were 4 SAEs (0.1%) within 28 days of any dose in the mRNA-1273 group and 1 (< 0.1%) in the placebo group. None of the SAEs were considered related to study vaccine.

MAAEs within 28 days were also reported at similar rates in the two groups (21.8% and 21.9%) and tended to reflect events typical for this age group during the winter, such as URIs. The study required “illness visits” for URIs in order to allow for COVID-19 testing; these visits were then classified as MAAEs. MAAEs considered related to study vaccination were reported in a higher proportion of participants in the mRNA-1273 (1.0%) than in the placebo (0.3%) group, although rates were low in both groups. This imbalance mostly reflected events in the SOC of General disorders and administration site conditions.

No participant in either group was reported to have an AE leading to discontinuation from the study or study vaccine as of the data cutoff. After the data cut, an AE entry was updated as leading to discontinuation and subsequently the participant withdrew from the study (See Section 5.5.4.5).

Review of unsolicited AE of respiratory tract infection (RTI) within 28 days showed similar rates reported in the mRNA-1273 (8.1%) and placebo (9.2%) groups. Modest imbalances of selected RTI were investigated further. Accordingly, events of croup, respiratory syncytial virus (respiratory syncytial virus [RSV] infection, and pneumonia) were assessed in this age group as well as in the 6 to 23 month age group (Section 5.6.3). No differences in rates of croup were observed (0.6% mRNA-1273, 0.6% placebo) in this age group. Differences in rates of RSV infection (0.4% mRNA-1273, < 0.1% placebo) and pneumonia (0.3% mRNA-1273, 0% placebo) were observed. The reported events of RSV and pneumonia were typical in clinical

presentation, course, duration, and seasonal pattern and no trends in occurrence (post-dose 1 or 2, or in time to onset), intensity, or seriousness were identified. These findings should be interpreted in the context of a 3:1 randomization scheme, frequency of background rates in this age group, low reported rates in this study, and multiple comparisons without adjustment for multiplicity increasing the possibility that these imbalances occurred by chance.

Table 33: Study 204 Participants Reporting ≥ 1 Unsolicited Adverse Event within 28 Days after Any Dose (Safety Set, 2 to 5 Years)

Category, n (%)	mRNA-1273 25 µg N=3031		Placebo N=1007	
	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	1212 (40.0)	286 (9.4)	378 (37.5)	80 (7.9)
SAE	4 (0.1)	0	1 (< 0.1)	0
Fatal	0	0	0	0
Medically Attended AEs	662 (21.8)	30 (1.0)	221 (21.9)	3 (0.3)
Leading to Discontinuation - Vaccine	0*	0*	0	0
Leading to Discontinuation - Study	0*	0*	0	0
Severe	21 (0.7)	18 (0.6)	9 (0.9)	8 (0.8)
AESI – Any	5 (0.2)	2 (< 0.1)	1 (< 0.1)	1 (< 0.1)
AESI of MIS-C	0	0	0	0
AESI of Myocarditis/Pericarditis	0	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event

Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity Grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.

*One participant in the mRNA-1273 group had a case report form entry of "AE" as a basis for vaccine discontinuation, but "dose not changed" was recorded on the AE case report form. After the data cut, the entry was updated to indicate that investigational product was withdrawn.

Datacut: 21 Feb 2022

Source: Module 2.5 (< 6 yrs), Table 45

5.5.4 Unsolicited Adverse Events in the Entire Study Period (2 to 5 Years)

A cumulative summary of unsolicited AE in the overall study period (median follow-up of 2.5 months; 21 Feb 2022 data extraction) are described in the sections that follow and presented in Table 34. As no vaccine is available in this age group, blinded follow-up has continued for the entire period.

Table 34: Study 204 Unsolicited AEs in the Entire Study after Any Dose in Participants (Safety Set, 2 to 5 Years)

Category, n (%)	mRNA-1273 N=3,031		Placebo N=1,007	
	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	1561 (52)	290 (10)	512 (51)	82 (8.1)
SAE	9 (0.3)	0	2 (0.2)	0
Fatal	0	0	0	0
Medically Attended AEs	1002 (33)	31 (1.0)	334 (34)	3 (0.3)
Leading to Discontinuation - Vaccine	0*	0*	0	0
Leading to Discontinuation - Study	0*	0*	0	0
Severe	25 (0.8)	19 (0.6)	11 (1)	8 (0.8)
AESI – Any	5 (0.2)	2 (< 0.1)	1 (< 1)	1 (< 0.1)
AESI of MIS-C	0	0	0	0
AESI of Myocarditis/Pericarditis	0	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event.
*One participant in the mRNA-1273 group had a case report form entry of "AE" as a basis for vaccine discontinuation, but "dose not changed" was recorded on the AE case report form. After the data cut, the entry was updated to indicate that investigational product was withdrawn.
Datacut: 21 Feb 2022
Source: Study P204 Table 14.3.1.7.2.2

5.5.4.1 SAEs in the Entire Period (2 to 5 Years)

SAEs are summarized first for the period within 28 days of any injection and subsequently for the entire study period (cumulatively). As the study was still blinded as of the data cutoff, SAEs in both the mRNA-1273 and placebo groups throughout the study are described.

SAE reported within 28 days

In the period within 28 days after injection, a total of 5 participants reported an SAE, 4 (0.1%) in the mRNA-1273 group and 1 (< 0.1%) in the placebo group. None of these SAE were considered related by the Investigator. All SAE reported within 28 days are described below in Table 35.

Table 35: Study 204 SAEs within 28 Days of any Injection (Safety Set, 2 to 5 Years)

Treatment group	Age (years)	Sex	Preferred Term	Post Dose #	TTO in days	Causality per Investigator	Additional Information
mRNA-1273 25 µg	2	M	Adenovirus infection	2	3	Not Related	Overnight admission
mRNA-1273 25 µg	3	F	Metapneumovirus infection	1	8	Not Related	Child has history of broncho-pulmonary dysplasia and asthma. Admitted for labored breathing, treated with salbutamol and Dexamethasone
mRNA-1273 25 µg	2	M	Pneumonia viral, Bronchial hyperreactivity, Respiratory distress	1	13–14	Not Related	Admitted x 2 days for increased WOB. Treated with Salbutamol and Dexamethasone
mRNA-1273 25 µg	4	M	Seizure	2	22	Not Related	Diagnosed with possible atypical seizure
Placebo	2	M	Abdominal wall abscess	2	28	Not Related	s/p hernia repair. Abscess at surgical site.

Abbreviation: TTO=time to onset.
Datacut: 21 Feb 2022
Source: Study P204 Listing 16.2.7.5.2

SAE reported in the entire study period

Cumulatively, from study start (median follow-up 2.5 months post-dose 2; 21 Feb 2022 data extraction), a total of 11 participants reported SAEs, including the 5 participants reporting SAE within 28 days (summarized above). Rates of SAEs were infrequent in both mRNA-1273 (9 participant; 0.3%) and placebo (2 participants; 0.2%) groups and none were assessed by Investigators as related. Reported SAEs largely reflected common childhood infections or were related to preexisting conditions. No new trends or patterns were identified among reported SAEs.

SAE reported within 28 days of any injection are summarized in the section above; those reported beyond 28 days are summarized in Table 36.

Table 36: Study 204 Serious Adverse Events Beyond 28 days after Any injection (2 to 5 Years)

Treatment group	Age (years)	Sex	Preferred Term	Post Dose #	TTO in days	Causality per Investigator	Additional Information
mRNA-1273 25 µg	2	F	Urinary tract infection	2	38	Not Related	Admitted for 3 days.
mRNA-1273 25 µg	3	M	Epstein-Barr virus infection	2	52	Not Related	Admitted for two days with fever, headache, sore throat, pharyngitis, dehydration, found to have acute EBV infection via serology; Treated with IV fluids, pain medications, Decadron. AE of COVID-19 1 month prior.
mRNA-1273 25 µg	4	F	Humerus fracture	2	53	Not Related	Fell down while chased by a dog
mRNA-1273 25 µg	3	F	Rhinovirus infection	2	75	Not Related	Admitted for 1 day, tested negative for COVID-19, positive for Rhinovirus; Chest Xray read as normal
Placebo	2	F	Rhinovirus infection &Asthma	2	83	Not Related	Admitted to ICU x 1 day with respiratory distress, Rhinovirus positive, COVID-19 negative, treated with prednisolone and albuterol
mRNA-1273 25 µg	2	M	Bronchial hyperreactivity	2	96	Not Related	Admitted x 1 day with wheezing, treated with albuterol and Decadron Tested negative for Influenza, RSV and COVID-19,

Abbreviation: TTO=time to onset.
Datacut: 21 Feb 2022
Source: Study P204 Listing 16.2.7.5.2

5.5.4.2 *Deaths in the Entire Study Period (2 to 5 Years)*

No deaths have been reported in Study 204 2 to 5 year age group.

5.5.4.3 *MAAEs in the Entire Study Period (2 to 5 Years)*

Rates of participants reporting MAAEs in the overall study period were balanced between the mRNA-1273 and placebo groups (33% vs 34%, respectively). Most events were viral URIs, which, per protocol, led to illness visits to exclude a diagnosis of COVID-19, thus causing such events to qualify as MAAEs. Differences between groups largely reflected carry-over of events reported within the 28 day period (ie, events of reactogenicity within the SOC General Disorders and Administrative Site Conditions).

5.5.4.4 *AESI in the Entire Study Period (2 to 5 Years)*

Cumulatively, from study start (median follow-up 2.5 months post-dose 2; 21 Feb 2022 data extraction), a total of 6 participants reported AESIs: 5 (0.2%) in the mRNA-1273 and 1 (< 0.1%) in the placebo group. Two AESIs in in the mRNA-1273 group were considered related by the Investigators - a 3 year old male reported erythema multiforme 3 days post-dose 2 mRNA-1273 which resolved the following day and a 4 year old male reported chest pain (not considered to be an AESI per protocol) 5 days post-dose 2 which resolved the same day. The participant reporting chest pain was evaluated by a cardiologist; electrocardiogram and high sensitivity were within normal limits. The AESI reported in a placebo participant (Henoch-Schonlein purpura in a 3 year old female 3 days post-dose 2 of placebo) also was considered related by the Investigator.

As of the data cutoff, no confirmed events of myocarditis or pericarditis have been reported in Study 204 in the 2 to 5 years old age group.

Enhanced surveillance (regular telephone safety calls) was implemented in Study 204 to solicit symptoms included in the CDC working definition of myocarditis and pericarditis. If any symptoms were reported, the Investigators evaluated the children. Additionally, to identify potential cases, this safety database was then evaluated by (i) aggregate analysis of the Cardiomyopathy SMQs and by (ii) analysis of PT included in the CDC definition. No cases meeting the CDC definition of myocarditis or pericarditis were identified from this surveillance activity.

5.5.4.5 *Discontinuation from Investigational Product or Study Participation in the Overall Period in Participants 2 to 5 Years*

One participant in the mRNA-1273 group had a case report form entry of “AE” as a basis for vaccine discontinuation, but “dose not changed” was recorded on the AE case report form. Accordingly, this participant does not appear in Table 34. After the data cut, the entry was updated to indicate that investigational product was withdrawn and the participant withdrew from the study. The participant was a 4-year-old-male with an AE of

urticaria (urticaria on torso and wrists) occurring on the day of dose 1 of mRNA-1273. The event resolved within 2 days and was considered related by the Investigator.

5.5.4.6 Other Events of Interest Reported after the 21 Feb 2022 Data Extraction

After the 21 Feb 2022 data extraction, 2 additional SAE (both also AESI) were reported into the live database. An SAE of MIS-C was reported in a 2-year-old female placebo recipient 113 days post-dose 2 who had been diagnosed with SARS-CoV-2 infection approximately 5 weeks earlier. An SAE of Kawasaki Disease was reported in a 2-year-old male mRNA-1273 recipient 4 days after diagnosis with adenovirus infection and 79 days post-dose 2 mRNA-1273. The Investigators did not consider either event to be related to vaccination.

5.6 Overview of Safety in Study 204 Participants 6 to 23 Months of Age

5.6.1 Duration of Follow-up and Data Cutoff Date

Safety data for participants 6 to 23 months of age in Study 204 derive from the blinded phase, with a median follow-up of 2.4 months (68 days) post-dose 2 (21 Feb 2022 data extraction).

5.6.2 Solicited Adverse Reactions

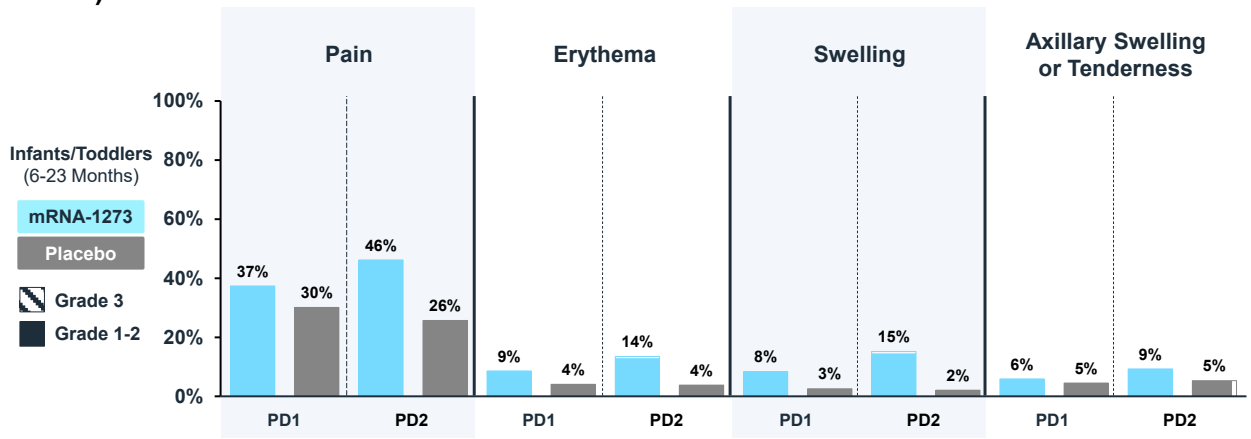
5.6.2.1 Solicited Local Adverse Reactions (6 to 23 Months)

Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness.

Solicited local ARs were more common in the mRNA-1273 group than in the placebo group after either dose (Figure 24). Pain was the most commonly reported solicited AR. Most solicited local ARs were Grade 1 and 2 in mRNA-1273 recipients; no Grade 4 solicited local ARs were reported.

Most solicited local ARs in the mRNA-1273 group occurred within 1 day. Local ARs had a median duration of 2–3 days in the mRNA-1273 group.

Figure 24: Study 204 Solicited Local Adverse Reactions (Solicited Safety Set, 6 to 23 Months)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Table 59

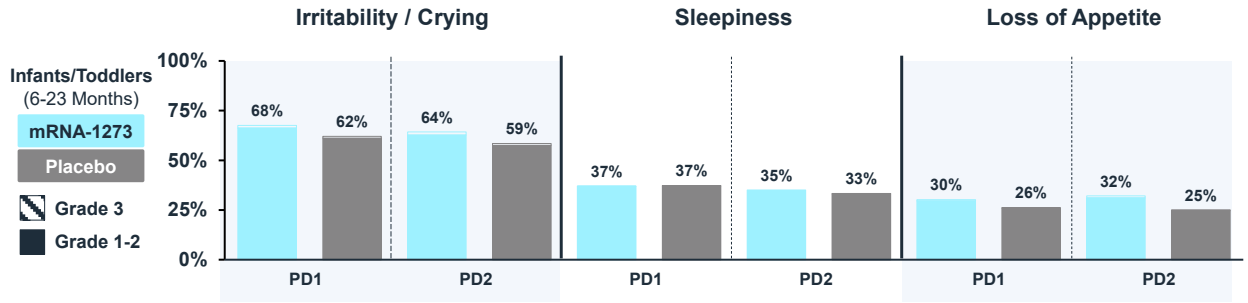
5.6.2.2 Solicited Systemic Adverse Reactions (6 to 23 Months)

For participants 6 to 23 months old, the solicited systemic ARs assessed were fever, irritability/crying, sleepiness, and loss of appetite (the same assessments as for 24 to 36 months old participants).

Similar to the 24 to 36 month age group, solicited ARs in the 6 to 23 month age group were more similar to placebo. The most common solicited systemic ARs after any dose of mRNA-1273 was irritability/crying, followed by sleepiness and loss of appetite (Figure 25). Events were generally Grade 1 or Grade 2. Most solicited systemic ARs in the mRNA-1273 group occurred within the first 2 days after either dose with a median duration of 3 days.

Fever was reported in 22% of participants receiving mRNA-1273. The only Grade 4 solicited systemic ARs reported were fevers (discussed further in Section 5.6.2.2.1).

Figure 25: Study 204 Solicited Systemic Adverse Reactions (Solicited Safety Set, 6 to 23 Months)

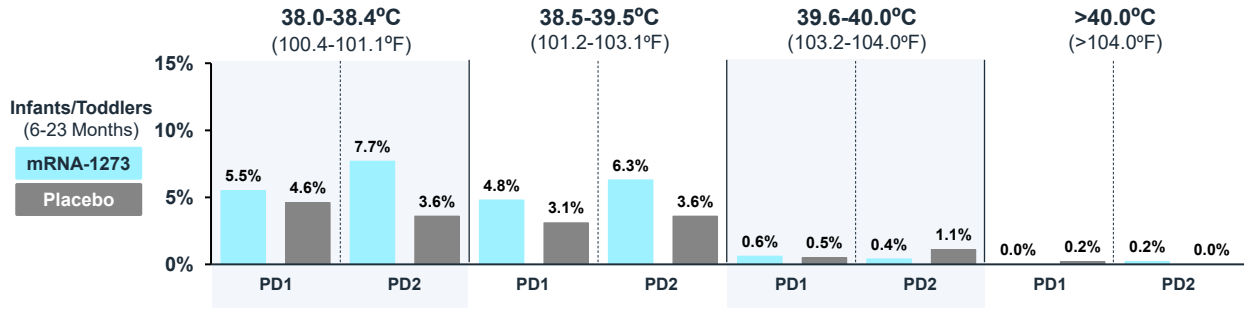


Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Table 61

5.6.2.2.1 Analysis of Fever in Part 2 (6 to 23 Months)

Fever was reported in both treatment groups, after any dose, at a higher frequency in the mRNA-1273 group than the placebo group. A higher frequency of fever after dose 2 than dose 1 was observed. Graphical representation of the percentage of participants reporting temperatures after each dose is provided in (Figure 26). In the mRNA-1273 group, most reported fevers were in the range of ≥ 38 to 39.5°C with only rare cases of fever > 40°C (0.2%) after either dose in both treatment groups.

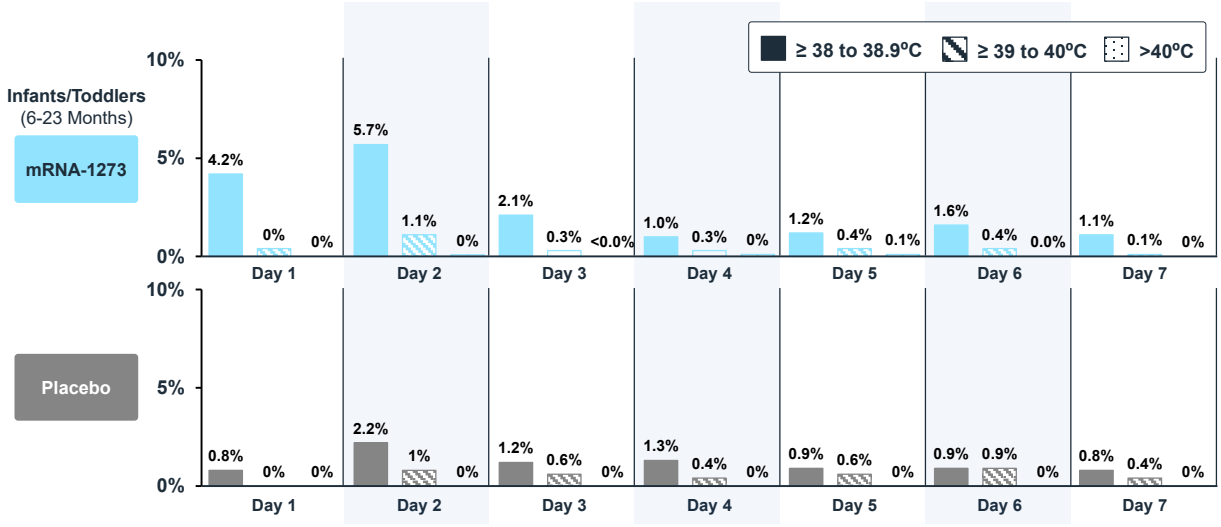
Figure 26: Study 204 Fevers within 7 Days (Solicited Safety Set, 6 to 23 Months)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Study P204 Table 14.3.1.6.4.2 and Table 14.3.1.6.5.2

Most fevers were reported in the mRNA-1273 group and occurred on Day 1 and 2 after either dose. Fevers (after any dose) lasted for a median of 1 day. Beyond Day 2, fever rates were similar between the mRNA-1273 and placebo groups, reflecting a high background rate of fevers observed in the placebo group, analogous to the observation in the 2 to 5-year-old age group (Figure 27).

Figure 27: Study 204 Percentage of Participants Reporting Fevers by Temperature over Time after Dose 2 (Safety Set, 6 to 23 Months)



Abbreviations: PD1=post-dose 1; PD2=post-dose 2
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Figure 7; Study P204 Table 14.3.1.6.5.2

Four participants in the mRNA-1273 group and one participant in the placebo group had fever > 40°C after any dose. In the mRNA-1273 group, one event was reported after dose 1, and the other 3 were reported after dose 2. There were reports of concurrent URIs in the 3 children who reported fevers after dose 2. One placebo recipient reported a fever over 40°C after dose 1; this participant also had a concurrent AE of 'viral rash' reported at the time of fever (Table 37).

Table 37: Study 204 Participants Reporting a Fever > 40 C (6 to 23 Months)

Case #	Dose #	Start of any fever	Duration of any fever	Age at enrollment	Treatment	Baseline SARS-CoV-2 status	Report of Concurrent AE
1	Dose 1	D4	4 days	17 months	mRNA-1273	Negative	No
2	Dose 2	D2	4 days	13 months	mRNA-1273	Negative	URI
3	Dose 2	D4	7 days	13 months	mRNA-1273	Negative	URI (twin of #4)
4	Dose 2	D4	3 days	13 months	mRNA-1273	Negative	URI (twin of #3)
5	Dose 1	D6	6 days	19 months	Placebo	Negative	Viral rash

Abbreviations: AE=adverse event; D=day; URI=upper respiratory infection.
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Table 63

5.6.2.2.2 Solicited Systemic Adverse Reactions by Baseline Serostatus

An assessment of reactogenicity among participants with evidence of prior SARS-CoV-2 infection (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]) compared to those with no evidence of infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1) was conducted. In ages 6 to 23 months, 6.1% participants had evidence of prior SARS-CoV-2 infection at baseline. Fever (temperature > 38°C) was the only systemic AR reported in a greater proportion of baseline SARS-CoV-2 positive vaccine participants compared to baseline SARS-CoV-2 negative vaccine participants. There were no notable differences in other reactogenicity events. Differences ARs reported after the first dose between baseline seropositive and seronegative recipients of mRNA-1273 not observed to the same degree in this age group compared to older children and adolescents.

5.6.3 Unsolicited Adverse Events within 28 Days (6 to 23 Months)

The most commonly reported unsolicited AE in either group were upper URIs (which are common in this age group during the winter months when this study and follow-up were conducted), irritability, pyrexia, and teething. In general, unsolicited AEs reported in the mRNA-1273 group were similar in nature and frequency to those in the placebo group.

Unsolicited AE reported within 28 days after any dose assessed by the Investigator as related to study treatment were reported in 16.6% of mRNA-1273 recipients and 12.1% of placebo recipients (Table 38). Differences are primarily attributed to those in SOC of Skin and Cutaneous disorders and General disorders and administration site conditions (ie, reactogenicity events).

There were 8 SAEs (0.5%) within 28 days after any dose in the mRNA-1273 group and none in the placebo group. One participant was reported to have a related SAE. SAEs are discussed below (Section 5.6.4.1).

MAAEs were reported at similar frequency in the two groups: 27.6% in the mRNA-1273 group and 27.3% in the placebo group. MAAEs in general reflected events typical for this age group during the winter months when the study was conducted (eg, URIs). The study required “illness visits” for any respiratory tract symptoms to assess for potential COVID-19 cases. MAAEs considered related to study vaccination were reported in 1.3% of vaccine recipients and 0.5% of placebo recipients; differences largely attributed to systemic reactogenicity events of pyrexia, irritability, and decreased appetite.

One participant in each group was reported to have an AE leading to discontinuation from study vaccine; the placebo group participant was also discontinued from the study.

Review of unsolicited AEs of URI within 28 days of injection showed similar rates reported in mRNA-1273 (10.3%) and placebo (12.2%) groups. Modest imbalances of

selected URI were investigated further. Accordingly, events of croup, RSV infection and pneumonia were assessed in this 6 to 23 month age group (and in the older 2 to 5 year age group; Section 5.5.2.2.2). Differences were observed in rates of croup (1.3% mRNA-1273, 0.3% placebo), RSV infection (0.8% mRNA-1273, 0.5% placebo) and pneumonia (0.2% mRNA-1273, 0 placebo). The reported events of croup, RSV and pneumonia were typical in clinical presentation, course, duration and seasonal pattern and no trends in occurrence (post-dose 1 or 2, or in time to onset), intensity or seriousness were identified. These findings should be interpreted in the context of a 3:1 randomization scheme, frequency of background rates in this age group, low reported rates in this study, and multiple comparisons without adjustment for multiplicity increasing the possibility that these imbalances occurred by chance.

Table 38: Participants Reporting ≥ 1 Unsolicited Adverse Event within 28 Days after Any Dose (Safety Set, 6 to 23 Months)

	mRNA-1273 25 µg (N=1761)		Placebo (N=589)	
Category, n (%)	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	869 (49.3)	292 (16.6)	284 (48.2)	71 (12.1)
Nonserious	868 (49.3)	292 (16.6)	284 (48.2)	71 (12.1)
Serious	8 (0.5)	1 (< 0.1)	0	0
Fatal	0	0	0	0
Medically attended	486 (27.6)	23 (1.3)	161 (27.3)	3 (0.5)
Leading to discontinuation from study vaccine	1 (< 0.1)	1 (< 0.1)	1 (0.2)	0
Leading to discontinuation from participation in the study	0	0	1 (0.2)	0
Severe	21 (1.2)	12 (0.7)	4 (0.7)	3 (0.5)
Special Interest (AESI)	3 (0.2)	2 (0.1)	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special s of age
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity Grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs), Table 67 Study P204 Table 14.3.1.7.1.2

Febrile seizures occur in up to 5% of young children at some time (Duffy et al 2017), with a peak incidence between 14 and 18 months (Centers for Disease Control and Prevention 2020). There were 4 reports of febrile seizure among mRNA-1273 recipients in Study 204 overall, all occurring in the 6 to 23 month group. All 4 are presented here for completeness although one occurred in a timeframe beyond 28 days after any dose and one was reported in a participant enrolled in the open-label (Part 1) phase. Table 39, below, presents the clinical details of each event. Of the 4 participants with febrile seizure, only 1 was considered related to study treatment by the Investigator (reported 2 days post-dose 1 mRNA-1273 in a 17 month old child); this child was reported with a maculopapular truncal rash 2 days after the event of febrile seizure was reported. The child had a subsequent seizure associated with fever reported 6 weeks after the initial

seizure but remained in the study and received dose 2 without incident. The 3 other events were reported in 3 children 10–66 days after vaccination and were not considered by the Investigator to be vaccine related. Two of these children had concurrent AEs of viral infections. The third was diagnosed with a periodic fever syndrome. All 4 events were also reported as SAEs (described below).

Table 39: Study 204 Time to Onset of Reported Febrile Seizures (Safety Set, 6 to 23 Months)

Age at Enrollment	Sex	Time to Onset	Related per Investigator	Concurrent AEs
17 months	Female	2 days PD1	Yes	Fever to 103.1°F; maculopapular rash on trunk 2 days post event*
16 months	Male	10 days PD2	No	Fever to 102.2°F; maculopapular rash on trunk, urticaria bilateral cheeks, URI, bilateral otitis media
19 months	Male	21 days PD2	No	Fever to 101ºF, diagnosed with Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome (PFAPA) after data cut
17 months	Female	66 days PD2	No	Fever to 101.5ºF, considered likely viral by ER physician

Abbreviations: ER=emergency room; PD=post-dose 1; PD2=post-dose 2; URI=upper respiratory infection
*Post 21 Feb 2022 data cut this child experienced another febrile seizure ~6 weeks later; received Dose 2 with antipyretics – no events reported
Datacut: 21 Feb 2022
Source: Module 2.5 (< 6 yrs)

5.6.4 Unsolicited Adverse Events in the Entire Study Period (6 to 23 Months)

A cumulative summary of unsolicited AE in the entire study period (median follow-up of 2.5 months; 21 Feb 2022 data extraction) are described in the sections that follow and presented in Table 40. As no vaccine is available in this age group, blinded follow-up has continued for the entire study period.

Table 40: Study 204 Unsolicited AEs in the Entire Study Period after Any Dose in Participants (Safety Set, 6 to 23 Months)

Category, n (%)	mRNA-1273 N=1761		Placebo N=589	
	Any AE	Related to Vaccination	Any AE	Related to Vaccination
All	1022 (58.0)	298 (16.9)	348 (59.1)	72 (12.2)
SAE	15 (0.9)	2 (0.1)	1 (0.2)	0
Fatal	0	0	0	0
Medically Attended AEs	678 (38.5)	26 (1.5)	242 (41.1)	5 (0.8)
Leading to Discontinuation - Vaccine	2 (< 0.1)	1 (< 0.1)	1 (0.2)	0
Leading to Discontinuation - Study	1 (< 0.1)	0	1 (0.2)	0
Severe	27 (1.5)	15 (0.9)	5 (0.8)	3 (0.5)
AESI – Any	4 (0.2)	2 (0.1)	1 (0.2)	0
AESI of MIS-C	0	0	0	0
AESI of Myocarditis/Pericarditis	0	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; MIS-C=Multisystem Inflammatory Syndrome in Children; SAE=serious adverse event
Datacut: 21 Feb 2022
Source: Study P204 Table 14.2.1.7.2.2

5.6.4.1 SAEs in the Entire Study Period (6 to 23 Months)

SAEs are summarized first for the period within 28 days of any injection and subsequently for the entire study period (cumulatively). As the study was still blinded as of the data cutoff, SAEs in both the mRNA-1273 and placebo groups throughout the study are described.

SAE reported within 28 days

In the period within 28 days of any injection, a total of 8 participants in the mRNA-1273 group reported 9 SAEs that were reported after any dose; none were reported in the placebo group. Table 41 below summarizes these events. One participant (reporting SAE of pyrexia and febrile seizure) had an SAE considered related to study treatment.

Table 41: Study 204 Serious Adverse Events within 28 Days of Any Injection (6 to 23 Months)

Treatment group	Age	Sex	PT	Post Dose #	TTO (days)	Causality per Investigator	Additional Information
mRNA-1273 25 µg	**17 months**	**F**	**Pyrexia Febrile convulsion**	**1**	**1 2**	**Related**	Fever to 103.1°F, maculo-papular rash on trunk 2 days post febrile seizure event
mRNA-1273 25 µg	18 months	M	Mastoiditis	1	3	Not Related	Diagnosed in the setting of severe adenovirus infection. Admitted for 5 days
mRNA-1273 25 µg	12 months	F	Metapneumovirus infection	1	4	Not Related	Admitted x 3 days
mRNA-1273 25 µg	12 months	F	Electrolyte imbalance	1	8	Not Related	Imbalance secondary to dehydration in the setting of RSV bronchiolitis. Admitted to hospital x1 day,
mRNA-1273 25 µg	12 months	F	Rhinovirus infection	1	8	Not Related	Presented with high fever (106°F), tachypnea and cough. Admitted to hospital x 1 day
mRNA-1273 25 µg	23 months	F	Foreign body in respiratory tract	1	15	Not Related	Removed by bronchoscopy
mRNA-1273 25 µg	19 months	F	Bronchiolitis	1	17	Not Related	Admitted x 2 days for increased WOB. Treated with salbutamol and Dexamethasone, NP swab negative for COVID-19, influenza A & B, & RSV, CXR with peribronchial cuffing
mRNA-1273 25 µg	19 months	M	Febrile convulsion	1	21	Not Related	Fever to 101ºF, diagnosed with PFAPA** after data extraction date

** Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome
Abbreviations: RSV=Respiratory syncytial virus; TTO=time to onset.
Datacut: 21 Feb 2022
Source: Study P204 Listing 16.2.7.5.2

SAE reported in the entire study period

Cumulatively, from study start (median follow-up 2.4 months post-dose 2; 21 Feb 2022), a total of 16 participants reported 18 SAEs, including the 8 participants reporting 9 SAEs within 28 of injection days (summarized above). In total, 15 (0.9%) participants in the mRNA-1273 group reported AEs, and 1 (0.2%) placebo participants in the placebo group reported 5 SAEs. Two of these participants had events considered related: one SAE of pyrexia and febrile convulsion has been described above (SAE reported within 28 days). The other SAE considered related was new-onset Type 1 diabetes mellitus and diabetic ketoacidosis in a 1-year-old female reported 37 days post dose 2. This child has a significant family history of diabetes mellitus and a recent URI. Assessed as related, the Investigator also noted that the event is “more likely caused by a genetic predisposition to pre-diabetes and viral upper respiratory tract infection that occurred prior to second dose of study vaccine.”

SAE reported with 28 days of injection are summarized in the section above; those reported beyond 28 days are summarized below in Table 42.

Table 42: Study 204 SAEs Beyond 28 Days After Any Injection (6 to 23 Months)

Treatment group	Age at enrollment (months)	Sex	PT	Post Dose #	TTO (days)	Causality per Investigator	Additional Information
Placebo	15 months	M	Bronchiolitis Rhinovirus infection Acute respiratory failure	1	29	Not Related	Required high flow oxygen via nasal cannula. Admitted for 3 days.
mRNA-1273 25 ug	14 months	M	Asthma	2	31	Not Related	History of eczema and chronic cough Admitted for 3 days.
mRNA-1273 25 ug	11 months	M	Erythema multiforme	1	35	Not Related	Erythema multiforme after peanut exposure.
mRNA-1273 25 ug	20 months	M	Adenovirus infection	1	35	Not Related	Admitted for prolonged fever. Positive adenovirus PCR. MIS-C and Kawasaki were ruled out.
mRNA-1273 25 ug	15 months	F	Diabetic ketoacidosis Type 1 diabetes mellitus	2	37	Related	Strong family history of diabetes, upper respiratory infection around the time of dose 2
mRNA-1273 25 ug	18 months	M	Gastroenteritis viral	2	43	Not Related	Presented with vomiting. Admitted for 2 days
mRNA-1273 25 ug	22 months	F	Croup infectious	2	43	Not Related	Event started after adenoidectomy and turbinate reduction
mRNA-1273 25 ug	17 months	F	Febrile convulsion	2	66	Not Related	Temperature 101.5 recorded in the Emergency Department, otherwise reassuring exam. Child was not admitted

Abbreviations: MIS-C=Multisystem Inflammatory Syndrome in Children; PCR=polymerase chain reaction; TTO=time to onset.
Datacut: 21 Feb 2022
Source: Study P204 Listing 16.2.7.5.2

5.6.4.2 Deaths in the Entire Study Period (6 to 23 Months)

No deaths have been reported in Study 204 6 to 23 months age group.

5.6.4.3 MAAEs in the Entire Study Period (6 to 23 Months)

Rates of participants reporting MAAEs in the overall study period were generally balanced between the mRNA-1273 (38.5%) and placebo (41.1%) groups and largely - reflect MAAE associated symptoms of URIs that prompted an illness visit per protocol (thus qualifying as MAAEs). Rates of MAAEs considered related by the Investigator were reported in 1.5% of mRNA-1273 and 0.8% of placebo recipients. Differences between groups largely reflected carry-over of events reported in the within 28 day period (ie, events of systemic reactogenicity including pyrexia, irritability and decreased appetite).

5.6.4.4 AESI in the Entire Study Period (6 to 23 Months)

Cumulatively, from study start (median follow-up 2.4 months post-dose 2; 21 Feb 2022 data extraction), a total of 5 participants reported an AESI: 4 (0.2%) in the mRNA-1273 and 1 (0.2%) in the placebo group. Two AESIs in the mRNA-1273 group were considered related by the Investigators. Of the 2 related AESIs, one was also reported as an SAE (pyrexia and febrile convulsion in a 17 month old); the other reported AESI considered related is described here.

An AESI of “mild liver injury” (verbatim term) was reported in a 9-month-old female in the mRNA-1273 group occurring 2 days after dose 2. The infant’s mother was taking a medication known to be associated with hepatic injury and secreted in breast milk and accordingly, infant liver function tests (LFTs) were regularly monitored. LFTs were known to be previously elevated and blood collection 2 days post-dose 2 showed additional elevation. This blood collection also occurred within a week of an AE of viral gastro-enteritis in the infant The Investigator considered the AESI related to study treatment as there was a temporal association between dose 2 and elevated LFTs.

Enhanced surveillance (regular telephone safety calls) was implemented in Study 204 to solicit symptoms included in the CDC working definition of myocarditis and pericarditis. If any symptoms were reported, the Investigators evaluated the children. Additionally, to identify potential cases, this safety database was then evaluated by (i) aggregate analysis of the Cardiomyopathy SMQs and by (ii) analysis of PT included in the CDC definition. No cases meeting the CDC definition of myocarditis or pericarditis were identified from this surveillance activity.

5.6.4.5 Discontinuation from Investigational Product or Study in the Entire Period (6 to 23 Months)

A total of 3 participants reported AE leading to discontinuation of vaccine: 2 (< 0.1%) in the mRNA-1273 and 1 (0.2%) in the placebo group. Of the 2 participants reporting AE leading to discontinuation of vaccine in the mRNA-1273 group, one was considered

related – a 1 year old male reported an unsolicited AE of (mild) urticaria on the day of dose 1. No other AE leading to discontinuation (study or vaccine) were considered related.

5.7 Safety Conclusions

The tolerability and safety of mRNA-1273 (primary endpoint) was evaluated in > 10,800 infants, toddlers, children, and adolescents. The two-dose primary series of mRNA-1273 was generally safe and well tolerated, based on a median of 2.4 to 11.1 months of follow-up. The safety profile in children was consistent with that observed in adults in clinical trials as well as in post-marketing surveillance. All participants in Study 203 and 204 will continue to be followed until one year after their last dose.

In all age groups, pain was the most common solicited local AR; local ARs were mostly Grade 1 and 2 in severity and lasted 2–3 days. Solicited ARs in all age groups were most common post-dose 2 than post-dose 1. In adolescents and older children, headache and fatigue were the most common. ARs were mostly Grade 1 or Grade 2 and had a median duration of 2–3 days. Among infants, toddlers, and young children, fatigue and irritability/crying were the most common ARs. In this age group, ARs also were Grade 1 or Grade 2 and had a median duration of 2–3 days. There were few Grade 4 ARs among vaccine recipients and ever was the only Grade 4 AR reported in more than 1 participant.

Some solicited ARs were reported more frequently after the first dose in baseline seropositive recipients of mRNA-1273 compared to baseline seronegative recipients of the vaccine. The difference was no longer evident after the second dose. The difference was noted mostly in older children and adolescents (6 to 17 years).

Fever (temperature ≥ 38°C) was observed in 12% of adolescents and ~25% of infants, toddler, and children (6 months to 11 years) who received vaccine. Most fevers occurred within 2 days of vaccination, with a median duration of 1 day. Beyond Day 2 (after any dose) fever rates were similar between the mRNA-1273 and placebo groups, suggesting that fever due to vaccination is largely limited to the first two days after vaccination. These findings are consistent with those of the World Health Organization and CDC, which report that fever is the most commonly reported AE post-vaccination in all age groups (infants to adults), across all vaccines (Zhou et al 2003) and typically occurs 1 to 4 days post-vaccination. Fevers > 40°C were rare, occurring only in the 2–5 year (0.4%) and the 6–23 month (0.2%) groups. Fever > 40°C also was of short duration and the children often had symptoms of concurrent viral infections.

One concern regarding post-vaccination fever is the occurrence of febrile seizures. One febrile seizure occurred in a child proximal to dose 1 which was considered related by the Investigator. Up to 5% of young children are expected to have a febrile seizure at some time in their life (Duffy et al 2017). Febrile seizures typically occur between 6 months and 5 years, peak between 14–18 months (CDC 2020) and are often

associated with common childhood illnesses (URIs, otitis media, roseola). Indeed, among the 4 children reported with febrile seizures in Study 204, 3 had evidence of concurrent viral infections (including the child with the febrile seizure considered related) and one was diagnosed with a periodic fever syndrome.

Since April 2021, an association between myocarditis and/or pericarditis and COVID-19 COVID mRNA vaccine exposure has been reported in case series, followed by passive surveillance systems and several observational studies, primarily among young adult males after dose 2. Both passive reporting as well as observational studies characterize these as very rare events associated with the administration of COVID-19 mRNA vaccines. Cases are typically mild; individuals tend to recover within a short time following standard treatment and rest (Gargano et al 2021).

No confirmed events of myocarditis or pericarditis were reported in Studies 203 or 204. Safety surveillance for myocarditis and pericarditis was enhanced by the inclusion in regular and routine safety calls to solicit for possible symptoms included in the CDC case definition of myocarditis and pericarditis. The enriched safety database was assessed for potential cases of myocarditis or pericarditis by several approaches including assessment of AE PT included in the CDC case definition. No participants in Study 203 or 204 met the criteria for CDC Working Case Definition for Acute Myocarditis and Acute Pericarditis (Gargano et al 2021).

In the participants randomized to mRNA-1273, there were no deaths, cases of MIS-C, observed in any age group; within 28 days of vaccination, no related SAEs were observed in children or adolescents; 1 related SAE of fever/seizure was reported in the 6 to 23 month group. Careful assessment of the safety database obtained in Studies 203 and 204 was performed to exclude the identification of emergent safety concerns. This included assessment of common diseases of childhood for rate of occurrence, severity and proximity to vaccination. Common events including respiratory tract infections and febrile seizures were evaluated and found to be typical in clinical presentation, course, duration and seasonal pattern, without trends in time to occurrence, intensity or seriousness. The overall safety profile observed in this study was consistent with the known safety profile to date observed in clinical trials and post-marketing surveillance of the use of mRNA-1273 in adults.

6 POST-AUTHORIZATION SAFETY UPDATE

Summary

- As of the end of 15 Apr 2022, over 1 billion doses of mRNA-1273 had been delivered to more than 100 countries, and an estimated total of 633 million doses of mRNA-1273 have been administered.
- It is estimated that approximately 281 million individuals received a first dose, 225 million received a second dose, and 126 million received a third or more dose.
- mRNA-1273 vaccine is considered to be well tolerated and with an acceptable safety profile.
- The 3 most common events reported cumulatively for mRNA-1273 in the post-authorization data by PT were headache (5.6%), pyrexia (5.5%), and fatigue (4.8%).
- Events of myocarditis and pericarditis primarily occur in young adult males shortly after the second dose of the vaccine with a time to onset of less than 7 days. The clinical course indicates that most cases are mild (in contrast to COVID-19 associated myocarditis) and resolve rapidly with conservative management.

Cumulatively, as of the end of 15 Apr 2022, more than one billion doses of mRNA-1273 had been delivered to over 100 countries, and an estimated total of 633 million doses of mRNA-1273 have been administered.

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that approximately 281 million individuals received a first dose, 226 million received a second dose, and 126 million received a third or more dose. Based on post-marketing data sources from literature, safety database, routine pharmacovigilance, and signal management, mRNA-1273 vaccine is considered to be well tolerated and with an acceptable safety profile. Moderna prioritizes the identification and characterization of emergent safety concerns occurring under real-world conditions and takes this responsibility especially seriously given the number of vaccine doses that have been administered worldwide based on the authorized indications, and the role that mRNA-1273 and other COVID-19 vaccines have as essential contributors to the control of the COVID-19 pandemic.

The post-authorization safety data show that mRNA-1273 vaccine is well tolerated, and the safety profile is similar to that observed during clinical trials. The 3 most common events reported cumulatively for mRNA-1273 by PT were headache, pyrexia, and

fatigue. The safety profile of the mRNA-1273 vaccine is closely monitored on a continuous basis.

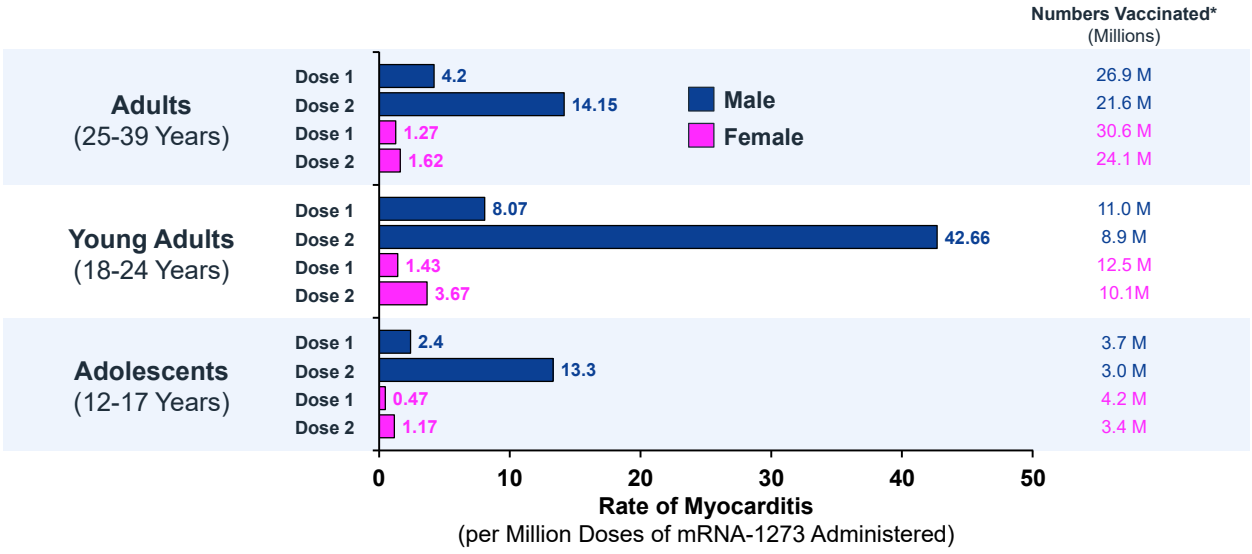
6.1 Summary of Post-Authorization Myocarditis Data

A cumulative review of post-authorization safety data received as of 15 Apr 2022 showed that events of myocarditis and pericarditis continue to primarily occur in young adult males 12–39 years old, shortly after the second dose of the vaccine with a time to onset of 2 to 4 days (Figure 28).

At the time that reports were submitted, a large proportion of the myocarditis and pericarditis events received were reported as either resolved or resolving, including 7 events reported as resolved with sequelae. In general, events of myocarditis following vaccination with an mRNA COVID-19 vaccine are typically milder in severity than viral myocarditis (Ling et al 2022; Patel et al 2022; Woo et al 2022).

Cumulatively, as of 15 Apr 2022, there have been no reports received of myocarditis or pericarditis following the use of mRNA-1273 in children less than 12 years old although the use of the vaccine in this population has been limited. The majority of the myocarditis and pericarditis events in adolescents were reported as resolved or resolving. There have been no fatal reports in adolescents due to myocarditis or pericarditis.

Figure 28: Reporting Rates of Myocarditis within 7 Days After Dose 1 and 2 per Million Doses Administered of mRNA-1273 Stratified by Age and Sex – Moderna Global Safety Database



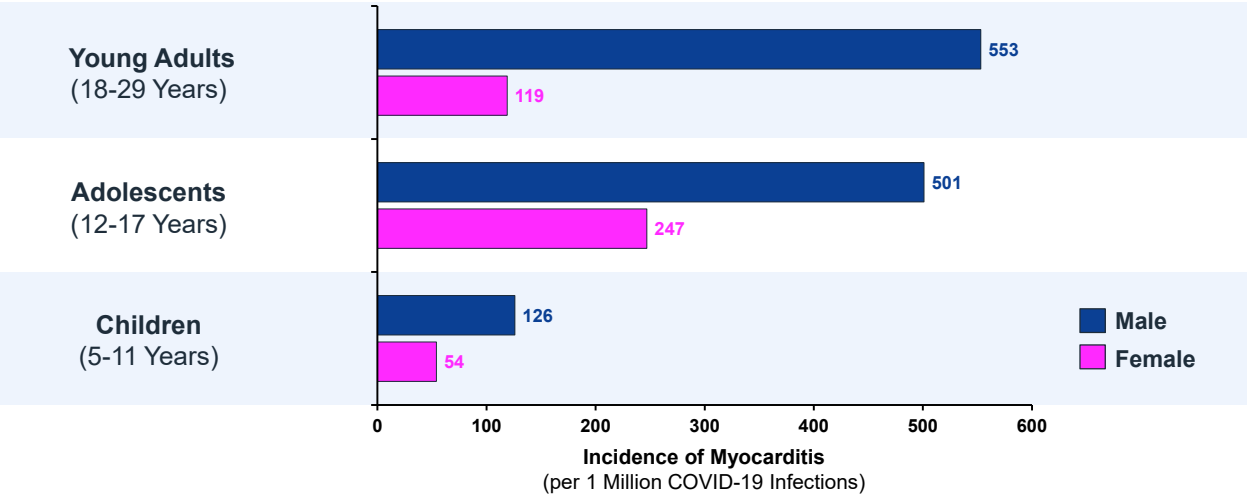
*Numbers vaccinated estimated from 15 Apr 2022
Source: 2022 Moderna Bi-Monthly Summary Safety Reports

As the passive and observational surveillance data, along with case reports, continue to accumulate, a better understanding of the clinical profile of patients experiencing myocarditis/ pericarditis following exposure to a COVID-19 mRNA vaccine is being formed. Most cases follow an uncomplicated course. Individuals may be briefly hospitalized before being discharged with conservative management consisting of NSAID +/- colchicine and rest. Cases typically resolve without any cardiac MRI-detectable consequence (Manfredi et al 2022).

Recently published data from a health care organization in Israel estimated the incidence of myocarditis due to COVID-19 infection as 11.0 cases per 100 000 persons (95% CI: 5.6–15.8), compared to the nearly five-fold lower incidence of myocarditis observed following the 2nd dose of mRNA-1273 (highest IR) at 2.17 per 100,000 person-days (95% CI: 1.55-3.04) (Wong 2022). Myocarditis cases related to COVID-19 infection revealed a higher mortality rate and rate of severe complications compared to myocarditis cases following vaccination with a COVID-19 mRNA vaccine (Patel et al 2022). Moreover, infection with SARS-CoV-2 has more adverse events beyond myocarditis, including many carrying significant risk for death.

Reporting rates of myocarditis associated with SARS-CoV-2 infections in children, adolescents, and young adults are summarized in Figure 29.

Figure 29: Reporting Rates of Myocarditis Associated with SARS-CoV-2 Infections



Source: (Block et al 2022). Block, J. P. et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination — PCORnet, United States, January 2021–January 2022. Mmwr Morbidity Mortal Wkly Rep 71, (2022).

Based on the analysis of all the safety data available as of 15 Apr 2022, the Sponsor considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of mRNA-1273, and the benefits for mRNA-1273 far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.

7 PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN

Several PASS in the US and EU are included in the Risk Management Plan addressing long-term safety information as well as characterization of the important and potential identified risks included in the safety profile of mRNA-1273. The previously endorsed PASS assessing the risk of individual AESI (US PASS protocol mRNA-1273-P903 and EU PASS mRNA-1273-P904) have been expanded to capture any use of mRNA-1273 observed, including among children and adolescents. Analyses in these studies will quantify the incidence of vaccine-associated AESI, including myocarditis, by age, sex, and mRNA-1273 dose, and will utilize both historical cohort and self-controlled risk interval methods to assess absolute and relative risks. Further, new analyses currently in development will characterize the natural history, clinical course, short and long-term outcomes, and risk factors for myocarditis temporally associated with mRNA-1273.

In addition, the long-term safety and effectiveness of mRNA-1273 in Studies 203 and 204 will continue to be captured until study completion.

Table 43 summaries the studies included as post-authorization commitments.

Table 43: Post-Authorization Commitment Studies

Study Title and Number	Purpose of the Study
Phase I, Open-Label, dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (Division of Microbiology and Infectious Diseases Protocol No. 20-0003 [NCT04283461])	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. Immunoglobulin enzyme-linked immunosorbent assay (ELISA) at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.
A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years (mRNA-1273-P201)	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow-up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster.
A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls (mRNA-1273-P304)	Safety and reactogenicity and AEs for 12 months after receiving 2 or 3 doses of SARS-CoV-2 mRNA-1273 vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.
Post-Authorisation 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 (mRNA-1273-P903)	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort. -Assessment of observed versus expected rates. -Self-controlled risk interval analyses for AEs that meet specific threshold criteria.

Study Title and Number	Purpose of the Study
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (mRNA-1273-P904)	The overarching research question of this study: Is the occurrence of each AESI among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax?
Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries (mRNA-1273-P905)	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?
Moderna mRNA-1273 Observational Pregnancy Outcome Study (mRNA-1273-P902)	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy; evaluate infant outcomes.
Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US (mRNA-1273-P901)	Evaluate the vaccine effectiveness of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality).
Natural history and clinical outcomes of vaccine-associated myocarditis (mRNA-1273-P910)	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults
Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) (mRNA-1273-P911)	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (SPIKEVAX).

Abbreviations: AE=adverse event; AESI=adverse event of special interest

8 PATH FORWARD: CONTINUED FOLLOW-UP

As the pandemic has continued to evolve, both studies 203 and 204 have been amended to offer booster doses to participants who received a 2-dose primary series of mRNA-1273.

All study participants in Study 203 are eligible for a 50 µg booster dose. As of 03 Jun, approximately 1400 adolescents 12 to 17 years of age have received a booster dose. In Study 204 participants 6 to 11 years of age (Part 1 and Part 2), are eligible for a 25 µg booster dose of mRNA-1273 at least 6 months after dose 2. Approximately 1700 participants have received a booster dose as of 03 Jun 2022. Study 204 was also updated to offer a booster dose of mRNA-1273 for all participants (Part 1) 6 months to 5 years of age, at least 6 months after dose 2, before the participants reached the end of study. As of 03 Jun, a total of 180 participants 6 months – 5 years who received a primary series (25 µg or 50 µg) have received a 10 µg booster dose.

Follow-up for all participants in Studies 203 and 204 will continue through 12 months after last dose.

As new variants of concern have emerged, the Sponsor has developed modified vaccines in response to circulating strains. The Sponsor has developed mRNA-1273.214, a bivalent vaccine consisting of the mRNA that encodes for the prefusion stabilized spike glycoprotein of both the SARS-CoV-2 original isolate and the Omicron variant. The total mRNA dosage of mRNA-1273.214 is identical to mRNA-1273 for a specific use/indication (with a 50/50 mix of the 2 mRNAs), ie, a booster dose of mRNA-1273 for adults is 50 µg, and the corresponding dosage of mRNA-1273.214 for the same use is 50 µg total (25 µg mRNA-1273 + 25 µg mRNA-1273.214).

An ongoing Phase 2 study is assessing superiority of a 50 µg booster dose of mRNA-1273.214 as compared to a 50 µg booster dose of mRNA-1273 in adults. Should the data be positive, the Sponsor believes mRNA-1273.214 will be the best candidate for the upcoming boosters in the fall in the context of the current circulating Omicron variants and other related emerging variants.

As such, the Sponsor has decided to offer children 6 months to 5 years the option to rollover from Study 204 to a newly designed study, Study 306, an Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years to test a 10 µg booster dose of this modified bivalent vaccine.

9 BENEFITS AND RISKS CONCLUSIONS

9.1 Benefit-Risk Analysis Evaluation

The benefits and risks of the proposed indications are evaluated within the context of the COVID-19 pandemic. COVID-19 cases, hospitalizations and sequelae from COVID-19 and SARS-CoV-2 infection in children (eg, MIS-C and "long-COVID-19") have increased during outbreaks of variants of concern, including Delta and Omicron. Vaccination with safe and efficacious vaccines targeting SARS-CoV-2 is an essential public health tool for control of the pandemic. The benefits of preventing COVID-19 disease, hospitalization, and associated sequelae, including MIS-C, in children 6 months to 17 years of age, must be weighed against the risks associated with exposure to mRNA-1273.

In the adult clinical development program, two doses of 100 µg mRNA-1273 demonstrated 93.2% efficacy against COVID-19 in more than 30,000 participants over a median observation period of over 5.3 months (El Sahly et al 2021). The safety profile of the adult primary series of mRNA-1273 has been well characterized in clinical studies, including 15,184 adults exposed to mRNA-1273 in Study 301. In addition, the overall safety profile of this vaccine is now well described, with more than 633 million vaccine doses having been administered globally (as of 15 Apr 2022).

Across the full pediatric program, the effectiveness of mRNA-1273 has been demonstrated from 6 months to 17 years. In Studies 203 and 204 the pre-specified co-primary immunogenicity objectives were met in all age groups, demonstrating non-inferiority to young adults (18 to 25 years of age) in the pivotal efficacy trial, Study 301. The GMT ratio of nAb titers as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a two-dose primary series (two doses of 100 µg in adolescents, two doses of 50 µg mRNA-1273 in older children and two doses of 25 µg of mRNA-1273 in younger children and infants/toddlers) (Figure 1).

The efficacy of mRNA-1273 was assessed as a secondary objective in the pediatric program, and was evaluated in the randomized, blinded parts of each study. VE in adolescents was demonstrated in Study 203 while the original SARS-CoV-2 strain was circulating. Study 204 allowed evaluation of VE against the Delta variant in older children and against the Omicron variant in younger children and infants/toddlers. VE in each pediatric or adolescent population was highly consistent to efficacy of mRNA-1273 observed in adults in the placebo-controlled pivotal adult Study 301 conducted when the original strain prevailed, and effectiveness observed during periods of Delta or Omicron circulation from the real-world effectiveness study (Table 25) (Tseng et al 2022a; Tseng et al 2022b).

Vaccine effectiveness data show that despite the epitope divergence from the original strain, mRNA-1273 continues to protect adults against severe outcomes associated with Omicron, including hospitalization and death (VE ~ 80%) (Tseng et al 2022a; Tseng et

al 2022b). Although severe COVID-19-related outcomes are rare in children, one case of MIS-C and one case of long COVID were observed in placebo recipients in the 2 to 5 and 6 to 11 year age groups, respectively. It is expected that the successful immunobridging would similarly predict protection from severe outcomes among children and adolescents 6 months to 17 years. Data from the Omicron wave continue to show that the vast majority of hospitalizations are occurring in unvaccinated individuals (Figure 3) (Minnesota Department of Health 2022; New York State 2022; Utah 2022; Virginia Department of Health 2022). It is particularly important to offer a vaccination option to children younger than 5 years old for whom there is not vaccine currently authorized.

The tolerability and safety of mRNA-1273 (co-primary endpoint) was evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who received at least 1 dose of mRNA-1273. mRNA-1273 in these age groups was generally safe, well tolerated, and no new safety signals were identified.

The overall safety profile of two doses of mRNA-1273 observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as post-marketing surveillance. The profile of mRNA-1273 in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of mRNA-1273 in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections.

Since April 2021, myocarditis and/or pericarditis following COVID-19 mRNA vaccine exposure have been reported in passive surveillance systems, scientific literature, and observational studies, as very rare events, with a higher incidence in young males (12 to 39 years old) and a short symptom onset (typically 2 to 4 days following a second dose). Cases are typically mild; individuals tend to recover within a short time following conservative treatment and rest (Gargano et al 2021).

No cases of myocarditis or pericarditis were reported in Studies 203 and 204. Enhanced surveillance via a phone script and search strategies of the database did not identify any additional cases meeting the CDC case definition. Across both studies only a single potential case of myocarditis was reviewed by the cardiac endpoint adjudication committed. This single case of chest pain in an adolescent was adjudicated as not meeting the CDC case definition.

Since December 2020, mRNA-1273 and other COVID-19 vaccines have been available, under EUA in the US and approved worldwide. As of 15 Apr 2022, more than 633 million doses of mRNA-1273 had been administered. Consistent with clinical study data,

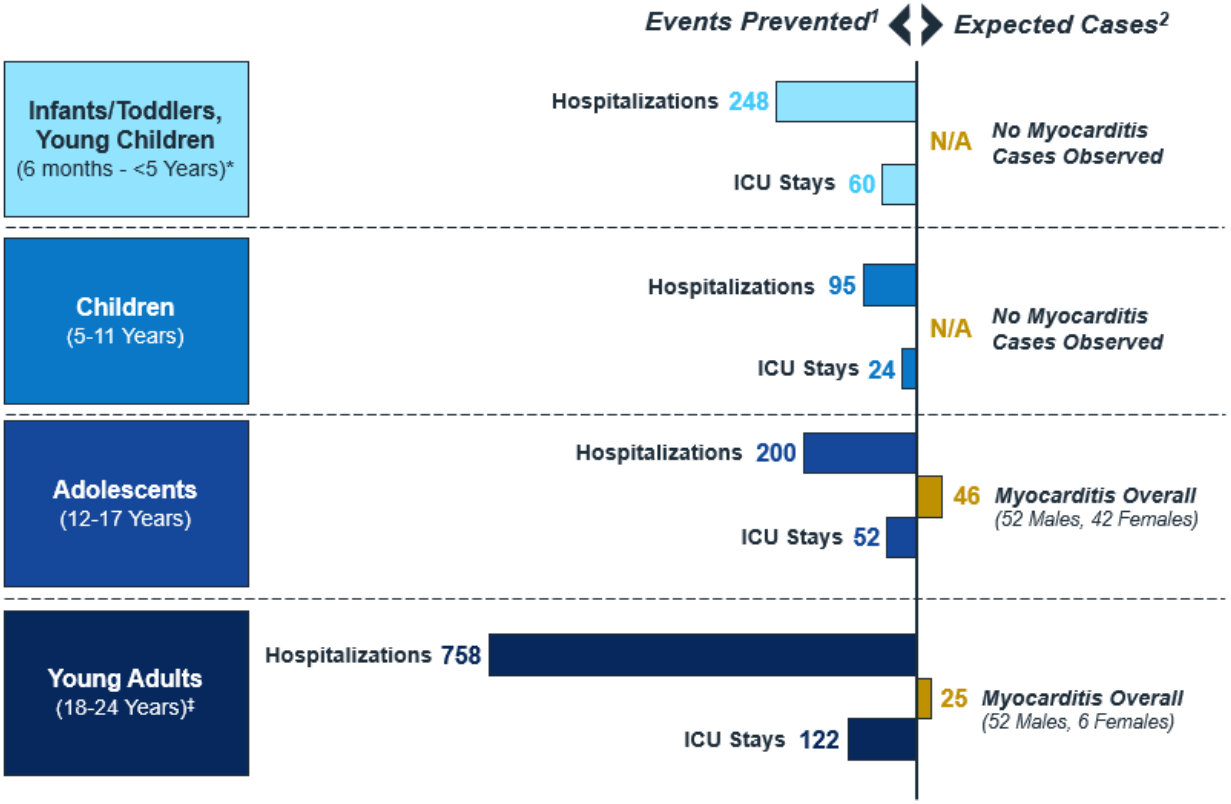
the safety profile of the mRNA-1273 vaccine is closely monitored on a continuous basis through post-market surveillance and a range of post-approval studies. The post-authorization safety data show that mRNA-1273 vaccine is well tolerated.

Benefit-risk was also evaluated using a model estimating COVID hospitalizations prevented and expected myocarditis cases per million 2nd doses of mRNA-1273. This model was generated using published methods (Funk et al 2022) and publicly available data from CDC Wonder, COVID Data Tracker and COVID-NET. Age-specific COVID hospitalization rates for each age group were extracted for the week ending 02 Apr 2022, which was the most recent data available, accounting for data lag. The benefit assessment model assumed a 5-month benefit period with vaccine effectiveness against hospitalization of 72% based on UK data during the Omicron period (United Kingdom Health Security Agency 2021). The benefits and risks are scaled based on administration of 1 million doses (see Appendix: Benefit-Risk Assessment Methodology in Section 11.2 for detailed approach). Data from the 18 to 24 year old age group are the most robust, as more than 77 million adults in the US have been fully vaccinated on label with mRNA-1273. Based on these assumptions, 758 hospitalizations and 122 ICU stays would be prevented per million 2nd doses of mRNA-1273 in this age group (Figure 30). Using the same model to estimate the number of hospitalizations prevented in the pediatric age groups, 248, 95, and 200 hospitalizations would be prevented per million 2nd doses of mRNA-1273 in children aged 6 months to 5 years, 6 to 11 years, and 12 to 17 years, respectively.

Expected myocarditis case data were sourced from the Moderna US PASS, using a 7-day risk window after mRNA-1273 administration. The PASS study captures data from more than 140 million US individuals and currently includes more than 50,000 children and adolescents vaccinated with mRNA-1273 (off-label use). Among young adults ages 18 to 24 years, the expected number of myocarditis cases per 1 million 2nd doses of mRNA-1273 would be 25. No myocarditis cases have been observed in children < 12 years, and 2 cases have been reported in adolescents 12 to 17 years of age. Based on these data, the expected number of myocarditis cases per 1 million 2nd doses of mRNA-1273 among adolescents 12 to 17 would be 46.

Based on this modeling, the benefits of preventing hospitalizations with mRNA-1273 in these populations outweigh the potential risks, including that of vaccine-associated myocarditis.

Figure 30: mRNA-1273 Benefit-Risk Assessment



Abbreviation: ICU=intensive care unitSource: 1. CDC Wonder; COVID Data Tracker; COVID-Net ; 2. Moderna US PASS – query 09 May 2022 (HealthVerity); 3. UK Health Security Agency, 2021

9.2 Conclusions

Based on the cumulative evidence, the overall benefit-risk evaluation of the mRNA-1273 vaccine remains favorable. There is an urgent unmet medical need to prevent COVID-19 cases, COVID-related hospitalizations, sequelae from COVID-19 (eg, MIS-C and "long-COVID-19"), and deaths in children. The immunogenicity, efficacy, and safety, data from Studies 203 and 204 support administration of mRNA-1273 as two-dose primary series administered 28 days apart of 100 µg in adolescents 12 to 17 years of age, 50 µg doses in children 6 to 11 years of age, and 25 µg in children 6 months to 5 years of age. Based on the totality of the data and the compelling unmet medical need, Moderna seeks EUA in all of these age groups.

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11 APPENDICES

11.1 Appendix: Specified Adverse Events of Special Interest

Adverse Event	Additional Notes
Anosmia, ageusia	New-onset COVID-associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	Including but not limited to events of atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	Including but not limited to events of autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	Include any event of appendicitis
Rhabdomyolysis	New-onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	Including but not limited to new events of acute respiratory distress syndrome and respiratory failure.
Coagulation disorders	Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	Include events with idiopathic or autoimmune etiologies Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast, etc.) Include all cases that meet the following criteria : • Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/L) within 48 hours; OR • Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR • Urine volume ≤ 0.5 mL/kg/hour for 6 hours
Acute liver injury	Include events with idiopathic or autoimmune etiologies Exclude events with clear alternate etiology (trauma, infection, tumor, etc.) Include all cases that meet the following criteria • 3-fold elevation above the upper normal limit for alanine transaminase (ALT) or aspartate aminotransferase (AST) OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or gamma-glutamyl transferase (GGT) or alkaline phosphatase (ALP)

Adverse Event	Additional Notes
Dermatologic findings	Chilblain-like lesions Single organ cutaneous vasculitis Erythema multiforme Bullous rashes Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms and fixed drug eruptions
Multisystem inflammatory disorders	Multisystem inflammatory syndrome in adults (MIS-A) Multisystem inflammatory syndrome in children (MIS-C) Kawasaki's disease
Thrombocytopenia	Platelet counts < 150×10^9/L Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome (Hemolysis-Elevated Liver enzymes-Low Platelets)
Acute aseptic arthritis	New-onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma)
New-onset of or worsening of neurologic disease	Including but not limited to: o Guillain-Barré Syndrome o Acute disseminated encephalomyelitis o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	Anaphylaxis as defined per protocol.
Other syndromes	Fibromyalgia Postural Orthostatic Tachycardia Syndrome Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) Myasthenia gravis

11.2 Appendix: Benefit-Risk Assessment Methodology

The benefit-risk assessment methodology was as follows:

The benefit assessment was generated using methodology outlined in Funk et al, and used publicly available data sources to estimate:

a. the projected 2021 US population (CDC Wonder)

b. the population vaccinated with at least 1 dose of any COVID vaccine (CDC COVID Data Tracker) to ultimately identify the population at risk (ie, the unvaccinated population)

c. COVID infection and hospitalization rates (CDC COVID-NET)

    i. Age-specific estimates were extracted because combined gender and age estimates for COVID infection and hospitalization rates were not publicly available.

    ii. Hospitalization rates from the week ending 02 April 2022 were utilized as this was the most recent week of data available (accounting for an approximate 6-week data lag). Hospitalization rates for the 18 to 24 age group corresponding to the projected 2021 US population from CDC Wonder and the population vaccinated (CDC COVID Data Tracker) were not publicly available. The COVID-NET rate reported for the 18 to 29 age group was used instead.

    iii. The proportion of ICU stays or deaths among COVID hospitalizations was summarized from COVID-NET data 01 Mar 2020 to 31 Mar 2022. Estimates were not available for ages 5 to 11 years and 12 to 17 years, specifically; instead, the estimate for ages 5 to 17 years was used for both age groups. Likewise, estimates for 18 to 24 were not available; the closest age category of 18–49 was used instead (CDC COVID-NET).

    iv. All data sources were accessed 22 May 2022.

2. Benefit model assumptions and parameters tested:

    a. The rate of hospitalization was assumed to be constant over a 5- month period (the estimated length of vaccine protection).

    b. The following parameters were tested in the model:

        i. Length of duration of protection: 5-months (150 days)

        ii. Doses: set at 1 million

        iii. Vaccine effectiveness against hospitalization: 72% based on UK data during the Omicron period.

3. Expected myocarditis case data was sourced from the Moderna US Post-Authorization Safety Study:
    a. Database used: HealthVerity which comprised secondary, de-identified individual-level medical and pharmacy claims data and includes more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems.
    b. Risk of myocarditis was assessed using a 7-day risk window after Spikevax administration.

The benefits and risk are scaled based on administration of 1 million 2nd doses.