swissmedic

Réinfo Santé Suisse International
1800 Vevey

Berne, le 25 mai 2022

BGÖ338, Réinfosanté Suisse, Moderna (module 2.5), demande documentation

Mesdames, Messieurs,

En annexe, nous vous transmettons le résumé des études cliniques pour personnes ≥12 ans concernant le vaccin Spikevax de Moderna (module 2.5 « clinical overview) en vertu de la loi fédérale sur le principe de la transparence dans l'administration (LTrans, RS 152.3).
Pour votre information, Moderna n'a pas fait valoir de secrets professionnels, d'affaires ou de fabrication.
Le calcul et la perception des émoluments sera faite séparément (Art. 17 LTrans) ; cette partie de la demande est soumise à un émolument de frs. 100.- (art. 16 et annexe 1 ordonnance sur le principe de la transparence dans l'administration [OTrans, RS 152.31]).

Veuillez croire, Mesdames, Messieurs, à l'expression de nos sentiments distingués.

Swissmedic, Institut suisse des produits thérapeutiques
Division Médicaments 2
Conseiller à la transparence

Yves Amstutz, juriste

Conseiller à la transparence

Ronald Jermann, juriste

Annexe: ment.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Acronym	Definition
Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
bAb	binding antibodies
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CoVs	Coronaviruses
COVID-19	Coronavirus disease 2019
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GM	geometric mean
GMT	geometric mean titer
GMR	geometric mean ratio
IA	interim analysis
ID_{50}	50% inhibitory dose
IgG	immunoglobulin
IP	investigational product
iPSP	investigational pediatric study plan
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically-attended adverse events
MIS-C	multisystem inflammatory syndrome in children
mITT1	modified intent-to-treat 1
mRNA	messenger ribonucleic acid
MSD	MesoScale Discovery
MSD-ECL	MesoScale Discovery electrochemiluminescence
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NIM	noninferiority margin
NP	nasopharyngeal
PIP	paediatric investigation plan
PP	per-protocol
PSP	pediatric study plan
PsVNA	pseudotyped virus neutralizing assay
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SMQ	standard Medical Dictionary for Regulatory Activities queries
SOC	system organ class
Study P203	Study mRNA-1273-P203
Study P301	Study mRNA-1273-P301
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULOQ	upper limit of quantification
UTR	untranslated region
VE	vaccine efficacy

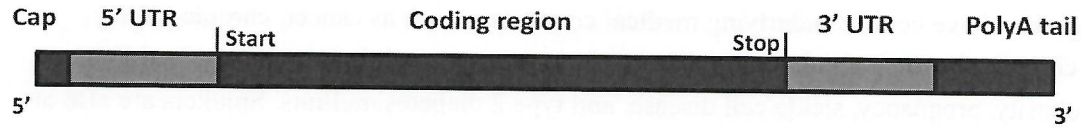
2.5.1 PRODUCT DEVELOPMENT RATIONALE

2.5.1.1 Pharmacologic Class of Agent

Moderna TX, Inc. (Sponsor) has developed a rapid response proprietary vaccine platform based on a messenger ribonucleic acid (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The estimated half-life for mRNA after injection is expected to be approximately 8 to 10 hours, before degradation by native RNases in the body. The duration of effect, however, also depends on the half-life of the expressed protein, which is expected to persist in the body for several days. mRNA vaccines are under investigation to induce immune responses against infectious pathogens such as cytomegalovirus (NCT03382405), hMPV and PIV3 (NCT03392389), Zika virus (NCT04064905), and influenza virus (NCT03076385 and NCT03345043).

A schematic of mRNA is provided in Figure 1. The mRNA in mRNA-1273 (also referred to as COVID-19 Vaccine Moderna herein) is chemically similar to naturally occurring mammalian mRNA, with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N1-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs (Rozenski et al 1999, Karikó et al 2005). This nucleoside is included in the mRNA in place of the normal uridine base to minimize indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors (Desmet and Ishii 2012). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Kozak 1991, Fechter and Brownlee 2005).

Figure 1: Structure of mRNA



Abbreviations: PolyA, polyadenylated; UTR, untranslated region.

The 3' untranslated region (UTR) is at the end of the open reading frame and is followed by a length of adenine-rich nucleotides, which is usually 50 to 250 nucleotides in length, the polyadenylated (polyA) tail. The polyA tail confers stability to the RNA molecule, plays a role in the termination of transcription, and participates in the export of the mRNA molecule from the nucleus and in initiation of translation of the target protein.

The coding region is between the 5' and 3' UTRs. The coding region contains a sequence of codons, the consecutive nucleotide triplets that encode for the individual amino acids and is read in the 5' to 3' direction. The coding region starts at an AUG nucleotide sequence and terminates in a stop codon.

2.5.1.2 Clinical/Pathophysiology of Condition

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV.

An outbreak of coronavirus disease 2019 (COVID-19) caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019, and the disease has since spread globally (WHO 2020a). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 Mar 2020. As of 14 May 2021, more than 160 million cases and over 3.3 million deaths worldwide have been attributed to the COVID-19 pandemic (WHO 2020a, WHO 2020b). Widespread community transmission of SARS-CoV-2 has been reported in the Americas, Europe, Africa, Asia and Southeast Asia, and Australia (WHO 2020a).

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (regardless of whether they are symptomatic) (Chen et al 2020, Licciardi et al 2020, Rothan and Byrareddy 2020, Shen et al 2020). Airborne transmission has been observed during certain medical procedures and in indoor, crowded, or poorly ventilated environments (WHO 2020c). Common symptoms of COVID-19 include fever and cough, and other symptoms include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, new loss of taste or smell, fatigue, body aches, congestion, nausea or vomiting, and diarrhea. Individuals at highest risk of COVID-19 and severe COVID-19 are older adults ($\geq$ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, serious heart conditions, compromised immune system, obesity, pregnancy, sickle cell disease, and type 2 diabetes mellitus. Smokers are also at increased risk for severe COVID-19 (CDC 2020a).

As with adults, hospitalization and death from COVID-19 occurs more frequently in children and adolescents with underlying conditions including asthma, chronic lung disease and cancer (Kim et al 2020). Children and adolescents present with a milder disease course compared with adults (Leidman et al 2021); a feature that makes assessment of incidence in this age group more challenging. However, although adolescents have milder disease than adults, they have

nasopharyngeal (NP) SARS-CoV-2 viral loads comparable to adults and accordingly, adolescents likely play an important role in community transmission (Sargent et al 2020).

A rare but serious condition associated with COVID-19 is multisystem inflammatory syndrome that often presents with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021b). Most cases occur in children 1 to 14 years of age, with a median age of 9 years. A total of 3185 cases and 36 deaths were reported to the Centers for Disease Control and Prevention (CDC) between May 2020 and March 2021 (CDC 2021b).

2.5.1.3 Therapeutic Rationale Supporting Investigation

The Sponsor's scalable mRNA/lipid nanoparticles (LNP) technology platform allowed for a rapid response to the pandemic, and was used to develop the COVID-19 Vaccine Moderna (mRNA-1273, also known by COVID-19 Vaccine Moderna outside of the US), a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes for the full-length SARS-CoV-2 spike protein, modified with 2 proline substitutions within the heptad repeat 1 domain (S2P) to stabilize the spike protein into a prefusion conformation. The CoV spike protein mediates attachment and entry of the virus into host cells (by binding to the angiotensin-converting enzyme 2 receptor followed by membrane fusion), making it a primary target for neutralizing antibodies that prevent infection (Corti et al 2015, Wang et al 2015, Yu et al 2015, Johnson et al 2016, Chen et al 2017, Wang et al 2018, Kim et al 2019, Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the prefusion conformation (Wrapp et al 2020).

2.5.1.3.1 Regulatory Status Worldwide

COVID-19 Vaccine Moderna has been authorized for emergency use in individuals 18 years of age and older in many countries as summarized in Table 1.

Table 1: COVID-19 Vaccine Moderna: List of Countries Where mRNA-1273 Is Authorized/Approved

Country	Date of Approval or Authorization	Type of Approval or Authorization
United States	18Dec2020	Emergency Use Authorization (FDA)
Canada	23Dec2020	Interim Order (Health Canada)
Israel	04Jan2021	Exceptional Use Authorization (MOH)

Country	Date of Approval or Authorization	Type of Approval or Authorization
European Union (member states)	06Jan2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA)
United Kingdom	31 Mar 2021	Conditional Marketing Authorisation (MHRA)
Switzerland	12Jan2021	Temporary Marketing Approval (SwissMedic)
Qatar	20Jan2021	Emergency Use Authorization (MOH)
Singapore	3 Feb 2021	Pandemic Special Access Route (PSAR) application
Paraguay	29 Dec 2020	Emergency Use Authorization for **all** COVID-19 vaccines authorized by FDA or EMA
Brunei	09 Apr 2021	Emergency Use Authorization by BDMCA
Taiwan	22 Apr 2021	Special Import Permit
Philippines	5 May 2021	Emergency Use Authorization
WHO	12 May 2021	Emergency Use Listing
Thailand	13 May 2021	Conditional Authorization for Emergency Use
South Korea	21 May 2021	Conditional Marketing Authorisation
Japan	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act

Abbreviations: BDMCA = Brunei Darussalam Medicines Control Authority; COVID-19 = coronavirus disease 2019; EC = European Commission; EMA = European Medicines Agency; EU = European Union; EUA = Emergency Use Authorization; FDA = United States Food and Drug Administration; MHRA = Medicines and Healthcare products Regulatory Agency; MOH = Ministry of Health; PDCD = Pharmacy and Drug Control Department; PMD = Pharmaceutical and Medical Devices; PSAR = Pandemic Special Access Route.

2.5.1.3.2 Epidemiology

At the start of the pandemic, the highest number of cases and deaths were in older age groups, particularly individuals aged 65 years and older reflecting increasing age as a dominant risk factor (Ayoub 2020, CDC 2021a, Hay 2020). While the greatest risk for severe disease and death remains in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease, the burden in the pediatric population is increasing (Leidman 2020, ECDC 2021a). Since the start of the pandemic, approximately 1.5 million cases of COVID-19 have been reported among adolescents 11 to 17 years of age (Oliver 2021). In the US, approximately 9,200 hospitalizations (more than 600 intensive care unit admissions and more than 200 deaths) have occurred in this age group (CDC 2021a). As of 18 Feb 2021 in the US, there was a 6% increase in pediatric COVID cases (169,718 cases) over a 2-week time period (between 04 Feb 2021 and 08 Feb 2021), with an overall incidence of 4,124 pediatric COVID-19 cases per 100,000 children in the population per year (between 16 Apr 2020 to 18 Feb 2021). During this time, the proportion of COVID-19–related hospitalizations was also shifting, as children comprise 1.2% to 3.0% of the total reported hospitalizations (AAP 2021).

The age distribution of US COVID-19 cases has been evaluated (from May to August 2020) based on 3 indicators: COVID-19-like illness-related emergency department visits, positive reverse transcription polymerase chain reaction (RT-PCR) results for SARS-CoV-2, and confirmed COVID-19 cases (Boehmer 2020). The authors reported an estimated mean COVID-19 incidence during this time period of 179.3 cases per 100,000 persons in individuals aged 10 to 19 years per year. Generally, the largest increase in incidence during this time period was observed in persons < 30 years of age.

2.5.1.3.3 Direct Medical Impact of COVID-19 On the Proposed Indicated Population

A recent report of COVID-19 trends in school-aged children in the US from 01 Mar 2020 to 19 Sep 2020 indicated that 63% of laboratory-confirmed cases of COVID-19 (positive SARSCoV2 test results) in school-aged children occurred in adolescents 12 to 17 years of age (Leeb 2020). During this time period, the average weekly incidence of infection was 37.4 cases per 100,000 in adolescents, compared with 19.0 cases per 100,000 in younger children. Among school-aged children with laboratory-confirmed COVID-19, 58% reported at least one symptom and 5% reported no symptoms; information on symptoms was missing or unknown for 37% of this population of school-aged children. Overall, in this same study, 1.2% of school-aged children with COVID-19 were hospitalized, 0.1% required intensive care unit admission, and < 0.01% died because of COVID-19. Furthermore, at least one underlying condition was reported in 3% of adolescents and 2% of younger children. Chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (neurologic or neurodevelopmental disorders, intellectual or physical disability, and vision or hearing impairment; 9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%) (Swedo 2020). Moreover, children and adolescents can manifest rare but serious multisystem inflammatory syndrome in children (MIS-C), often presenting with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021b).

2.5.1.3.4 Social Impact and Transmission At School

Evidence is emerging to suggest that children and adolescents may be disproportionately contributing to the number of new cases, as schools re-open for varying degrees of in-person learning (CDC 2021a, SAGE 2020). As of 30 May 2021, the US Centers for Disease Control and Prevention (CDC) reported over 3.3 million cases of COVID-19 in children less than 18 years of age (12.4% of all cases in US) and 437 deaths (< 0.1% of all deaths in US) (CDC 2021a). In the United Kingdom, a population-based cohort among 9,334,392 adults aged ≤ 65 years indicated an increased risk of reported SARS-CoV-2 infection and COVID-19 outcomes among adults

living with children of any age during Wave 2, relative to Wave 1 (hazard ratio 1.06 (95% confidence interval [CI] 1.05 to 1.08) (Forbes 2021). During Wave 3 in Europe, widespread community transmission of SARS-CoV-2 variants with high transmissibility increased the possibility of transmission in schools and subsequently to households (ECDC 2020, Somekh 2021). This increased transmission of variants could lead to school closures due to actual or anticipated school-specific outbreaks in order to decrease the impact of COVID-19 upon students as well as to mitigate the risk of increased community transmission (Davies 2021).

As the COVID-19 vaccination program initially targeted older age groups, the number of new COVID-19 cases has started to increase in the remaining unvaccinated age groups. As of 01 May 2021, the incidence of COVID-19 cases in 14- to 17-year olds was 133 per 100,000 population, and the incidence in 6- to 13-year olds was 84 per 100,000 cases, which is now greater than the incidence of COVID-19 cases in the > 65 age group (CDC 2021a).

A Swedish study compared transmission rates from students in lower-secondary schools (14-16 years of age), with transmission from students in upper-secondary schools (17-19 years of age) during the study period. These lower-secondary schools remained closed, while the upper-secondary schools had been opened. The study found a small increase in the risk of SARS-CoV-2 infection in parents of lower-secondary school students (OR: 1.17, 95% CI: 1.03-1.32), but double the risk for lower-secondary school teachers versus upper-secondary school teachers (OR: 2.01, 95% CI: 1.52-2.67) (Vlachos 2021). Another study applied data collected in Europe and China to the United States, in order to estimate the impact of different age groups in driving and sustaining the epidemic (Monod 2021). The study concluded that school opening is indirectly associated with a 26% increase in SARS-CoV-2 transmission (Monod 2021).

During the COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control infection; therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, is infected household contacts. Indeed, a retrospective cohort study of high school students, parents and siblings of students, and school staff conducted in France in early April 2020, suggests that there was little to no transmission from infected students to other students or school staff; rather, a high prevalence of antibodies against SARS-CoV-2 among families suggests familial clustering of COVID-19 cases (Ezeanolue 2020).

Although it is possible that children with COVID-19 may be infectious for a shorter period of time (Han 2020, Lee 2020), the viral load of asymptomatic and symptomatic cases does not appear to differ (Lee 2020, Hurst 2020), infectious virus is cultured from both, and the likelihood of successfully culturing virus is unrelated to age (Singanayagam 2020). Children might,

therefore, play a role in community transmission, given the large number of contacts children have in childcare centers and schools (Hyde 2020). Indeed, a recent report described an adolescent (13-year-old female), having only nasal congestion, who was the index case in an outbreak of COVID-19 across 4 states (Schwartz 2020). Infection of this primary individual led to 11 subsequent cases during July and August 2020 in 5 households, all linked to a family gathering, suggesting that adolescents can serve as the source of COVID-19 outbreaks within families, even when their symptoms are mild, as in this case.

2.5.1.3.5 Other Indirect Impact Upon This Population

Although much focus of the pandemic's impact has been upon its direct medical consequences (measured in disease incidence, morbidity and mortality), these measures underestimate the pandemic's toll on young people. The indirect impact of the COVID-19 pandemic on children and adolescents has been substantial due to stressors, school closures, and loss of household income and social supports, and include suicide-related behaviors and ideation, as well as child maltreatment and hospitalizations due to child maltreatment (Swedo 2020, Usher 2020, Baron 2020, ECDC 2021b, UNICEF 2020).

2.5.1.3.6 Importance of Vaccinating the Adolescent Population

Immunization with a safe and effective COVID-19 vaccine is a critical component of the nation's strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning. Several regulatory authorities have authorized the COVID-19 Vaccine Moderna (Table 1) and the Janssen COVID-19 Vaccine to prevent COVID-19 in persons aged ≥ 18 years. Currently, the Pfizer COVID-19 Vaccine is the only vaccine authorized to prevent COVID-19 in persons aged ≥ 12 years of age. Although no vaccines are approved to prevent COVID-19, Veklury (remdesivir) has been approved for the treatment of COVID-19 in a hospitalized setting, and Emergency Use Authorizations have been granted for bamlanivimab + etesevimab for the treatment of mild to moderate COVID-19, and for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19.

Overall, the evidence suggests that the burden of COVID-19 has begun to increase in younger age groups. Moreover, children and adolescents can manifest rare but serious MIS-C, often presenting with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021b). Studies of NP viral load confirm comparable levels in adolescents and adults, indicating that children and adolescents can transmit SARS-CoV-2 to their unvaccinated household contacts. Adolescents, who are often mobile and

may demonstrate lower compliance with nonpharmaceutical interventions such as mask-wearing and social distancing, also likely represent a segment of the population contributing to sustained community transmission of SARS-CoV-2 and may spread SARS-CoV-2 within households. As the COVID-19 pandemic continues and more transmissible variants become dominant, Moderna proposes that COVID-19 Vaccine Moderna should qualify for emergency use in persons ≥12 through < 18 years of age, as a part of the world's action plan to curb the pandemic.

2.5.1.4 Summary of the Clinical Development Program and Timing of Application

The development of the mRNA-1273 vaccine is being expedited given the current global public health emergency, although it is important to note that Phase 1, Phase 2, and Phase 3 development are ongoing, and no steps have been eliminated. The ongoing and planned studies with mRNA-1273 are presented in Table 2.

Table 2: Clinical Summary Table of Ongoing and Planned Studies With mRNA-1273

Study Number (Country)/ Status	Participants/Age Groups / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	BLA and CSR Data Cutoff Points
mRNA-1273-P301 (US)/ Ongoing	Healthy adults Age groups: ≥ 18 years (n = 30,000) Dose groups: Placebo (n = 15,000) mRNA-1273 100 µg (n = 15,000)	Phase 3, randomized, stratified, observer-blind, placebo-controlled	100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart	Interim CSR: Efficacy: -Interim efficacy analysis (11 Nov 2020 data cutoff/ DS1) - Primary efficacy analysis (25 Nov 2020 data cutoff/ DS2) - Supplemental efficacy results from the final blinded efficacy analyses for the primary and secondary efficacy endpoints based on the blinded phase. Immunogenicity: - bAb and nAb in a subset of participants Safety: - Safety data from the final blinded analyses based on the blinded phase will be included in the CSR. A CSR addendum summarizing the additional safety data from the unblinded phase of the study to bring the aggregate median follow-up period to 6 months post dose 2 will be provided.
mRNA-1273-P201 (US)/ Ongoing	Healthy adults Age groups: Cohort 1: ≥ 18 to < 55 years (n = 300) Cohort 2: ≥ 55 years (n = 300) Dose groups: Placebo (n = 200)	Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation	50 or 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart	Interim CSR: Efficacy: Not applicable Immunogenicity: Day 57 Safety: Day 57

Study Number (Country)/ Status	Participants/Age Groups / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	BLA and CSR Data Cutoff Points
	mRNA-1273 50 µg (n = 200), mRNA-1273 100 µg (n = 200)			
mRNA-1273-101 (DMID Study 20-0003) (US)/ Ongoing	Healthy adults Age groups: 18 to 55 years (n = 75), 56 to 70 years (n = 40), ≥ 71 years (n = 40) mRNA-1273 dose groups: 10 µg (n = 15)[a], 25 µg (n = 35), 50 µg (n = 35), 100 µg (n = 35), 250 µg (n = 35)[b]	Phase 1, open-label, dose-ranging	25, 50, 100, or 250 µg mRNA-1273 2 IM doses, 28 days apart	Interim CSR: Efficacy: Not applicable Immunogenicity: Day 119 (included in CSR) Safety: Range of 13 to 26 weeks post dose 2 (included in CSR) Day 209 safety and immunogenicity data provided as a CSR addendum
mRNA-1273-P203 (US)/ Ongoing	Healthy adolescents Age group: 12 to < 18 years N = 3,000 planned mRNA-1273 n = ~2000 placebo n = ~1000	Phase 2/3, randomized, observer-blind, and placebo-controlled	100 µg mRNA-1273 or placebo (2:1) 2 IM doses, 28 days apart	Safety: Day 57 (1-month post dose 2) for full cohort (2:1) Efficacy/Immunogenicity: Day 57 serum antibody (Ab) response in a subset of 550 participants (2:1)
mRNA-1273-P204 (US)/Ongoing	Healthy pediatrics Part 1: Age groups: 6 to < 12 years (n = 150) 2 to < 6 years (n = 150) 6 months to < 2 years (n = 450) mRNA-1273 dose groups: 25 µg (n = 150), 50 µg (n = 300), 100 µg (n = 300), Part 2: Age groups: 6 to < 12 years (n = 2,000)	A Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation, and randomized, observer-blind, placebo-controlled expansion	25, 50, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart	NA

Study Number (Country)/ Status	Participants/Age Groups / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	BLA and CSR Data Cutoff Points
	2 to < 6 years (n = 2,000) 6 months to < 2 years (n = 2,000) mRNA-1273 selected dose (n = 4,500) Placebo (n = 1,500)			
mRNA-1273-901 (US)/ Ongoing	Adults Age group: ≥ 18 years Real world effectiveness study	Observational cohort study	Dosed under EUA 100 µg mRNA-1273 2 IM doses, 28 days apart	NA
mRNA-1273-P304 (US)/ Planned	Adult liver and kidney transplant recipients and healthy control participants. Age group: ≥ 18 years (n = 120) mRNA-1273 100 µg (n = 120)	Phase 3b, open-label	100 µg mRNA-1273 2 IM doses, 28 days apart	NA
mRNA-1273-902 (Global)/ Planned	Pregnant women Age group: ≥ 18 years	Prospective, observational pregnancy exposure registry	Dosed under EUA 100 µg mRNA-1273 2 IM doses, 28 days apart	NA

Abbreviations: bAb = binding antibody; BLA= Biologics License Application; CSR = clinical study report; DMID = Division of Microbiology and Infectious Disease; DS = data snapshot; EUA = Emergency Use Authorization; IM = intramuscular; NA = not applicable; nAb = neutralizing antibody; US = United States.

[a] In Study DMID 20-0003, Cohort 13 (10 µg mRNA-1273, 18-55 years, n = 15) was not enrolled.

[b] In Study DMID 20-0003, dosing at the 250-µg level was discontinued after Cohort 3 (18-55 years, n = 15) and prior to enrollment in Cohort 6 (56-70 years, n = 10) and Cohort 9 (≥ 71 years, n = 10).

This submission intends to extend the emergency use of mRNA-1273 to include vaccination of persons ≥12 to < 18 years of age to prevent COVID-19 based on the following: 1) safety and efficacy data, which includes a median of 53 days follow-up after dose 2 in the Phase 2/3 Study mRNA-1273-P203 (Study P203); and 2) immunogenicity data from Study P203 and from the ≥ 18 to ≤ 25 years age group from Study mRNA-1273-P301 (Study P301) to infer vaccine effectiveness (Study P203, Table 1.4).

As the present submission is intended to support the emergency use of the vaccine in adolescents, this section focuses on the ongoing clinical studies included to support the expanded use of mRNA-1273 in adolescents aged ≥ 12 years.

2.5.1.4.1 Study mRNA-1273-P203

Study P203 (ClinicalTrials.gov Identifier: NCT04649151) is an ongoing, two-part (Part A and Part B), Phase 2/3, randomized, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents aged ≥ 12 to < 18 years. 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 < 18 years age group. Vaccine effectiveness is inferred based either upon: (i) proportion of study participants with serum Ab levels (on study Day 57) that meet or exceed an Ab level conferring protection from COVID-19, or in the absence of such an accepted threshold of protection, (ii) by demonstrating noninferiority of both the (a) geometric mean (GM) value of serum Ab and (b) the seroresponse rate from adolescent participants - with both measures compared with those obtained from young adults (≥ 18 to ≤ 25 years) enrolled in the ongoing adult study (Study P301). Comparing Ab levels and seroresponse rates from adolescents in Study P203 to young adults in the pivotal adult study (P301), in which clinical endpoint efficacy against COVID-19 was successfully demonstrated, allowed immunobridging of the 2 populations and allowed vaccine effectiveness to be inferred in children between ≥ 12 and < 18 years of age.

Additionally, secondary study endpoints assessed the effect of mRNA-1273 on COVID-19 and asymptomatic infection as measured by RT-PCR testing of mucosal samples and serologic assessment of SARS-CoV-2 infection. For this study, baseline SARS-CoV-2 status was determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1:

- Positive SARS-CoV-2 status at baseline was defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibodies (bAb) specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before Day 1.

- Negative status at baseline was defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before Day 1.

Study participants are randomly assigned to receive 2 injections (28 days apart) of either 100 µg of mRNA-1273 vaccine or placebo in a 2:1 randomization ratio (Part A, the Blinded Phase of

Study P203). All study subjects are followed for tolerability, safety and have blood collected at prespecified timepoints for immunogenicity assessments. In addition, data regarding the occurrence of COVID-19 and of asymptomatic SARS-CoV-2 infections is collected. Surveillance for COVID-19 symptoms is conducted by regular biweekly telephone calls or eDiary prompts starting at enrollment. For the purpose of this document, the occurrence of asymptomatic infection was assessed by means of NP swabs obtained on Study Days 29 and 57 and serology for SARS-CoV-2 infection on Study Day 57.

Upon availability of a COVID-19 vaccine authorized for emergency use in adolescents, the study transitioned to Part B, the Open-label Observational Phase of this study. In this Part, participants who are age-eligible for a COVID-19 vaccine authorized for emergency use, could request unblinding and those having received placebo could seek the authorized vaccine. Upon unblinding, previous placebo recipients who seek alternative vaccine are removed from study. A data snapshot for this submission was triggered (date: 08 May 2021) based on the availability of immunogenicity data from Study P203, with a median study follow-up duration of 53 days after dose 2, based on a total of 3,732 participants (3,726 participants randomized and receiving dose 1, with 1,240 on placebo and 2,486 on mRNA-1273).

Unless otherwise specified, summary statements included in this submission based on safety, efficacy, and immunogenicity data at the time of the data snapshot (08 May 2021), refer to the entire adolescent population (≥ 12 to < 18 years old) in Study P203. The clinical database for Study P203 is monitored, reconciled, and cleaned on an ongoing basis, and the dataset date (data snapshot date 08 May 2021) refers to the date the data were extracted from the database.

The primary safety objective of Study P203 is to evaluate the safety and reactogenicity of 100 μg of mRNA-1273 vaccine administered in 2 doses 28 days apart, as assessed by the following primary endpoints:

- solicited local and systemic adverse reactions (ARs) through 7 days after each dose
- unsolicited adverse events (AEs) through 28 days after each dose
- medically-attended adverse events (MAAEs) through the entire study period
- serious adverse events (SAEs) through the entire study period
- adverse events of special interest (AESI) of MIS-C through the entire study period
- vital sign measurements
- physical examination findings

The data snapshot (dated 08 May 2021) includes safety data for all enrolled adolescents aged ≥ 12 through < 18 years (ie, including those not yet reaching 2 months (56 days) follow-up after dose 2). Therefore, Section 2.5.5 presents Study P203 safety data for a total of 1,561 participants who reached at least 2 months (56 days) of follow-up after dose 2, of which 1,087 (69.6%) participants received the 100-µg dose of mRNA-1273 (Table 3). Safety data presented in this submission includes all solicited AR and all unsolicited AE data, including MAAEs, SAEs and AESIs, for all enrolled adolescents through the data snapshot (safety results are presented in Section 2.5.5). Per-protocol, clinically significant physical examination findings identified during any study visit should be reported as MAAEs.

The primary immunogenicity objective of Study P203 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 (aged ≥ 12 through < 18 years) to the young adult (≥ 18 to ≤ 25 year of age) cohort in Study P301, where efficacy was demonstrated (Section 2.5.4.2.1.1). At the time of the analysis, no correlate or threshold conferring protection had been established. As prespecified, effectiveness was inferred by demonstrating noninferiority of both the (i) GM value of serum neutralizing Ab (nAb) and (ii) the seroconversion rate from adolescent participants compared with those from young adults (aged ≥18 to ≤ 25 years) enrolled in the ongoing Phase 3 efficacy study (Study P301) (Study P203 Protocol Amendment 1 Module 5.3.5.1). Statistical methods and success criteria for noninferiority are provided in Section 2.5.4.2.1.1.

The primary study endpoint was based on results obtained from a pseudotyped virus neutralizing assay (PsVNA) 50% inhibitory dose (ID_{50}). The PsVNA ID_{50} assay yields results which fall in the middle of the dynamic range of the dilution response curve. The immunogenicity analyses were based on the Per-Protocol Set for immunogenicity that included baseline SARS-CoV-2 negative participants with no major protocol deviations that impact critical data. For the PsVNA ID_{50} assay, seroresponse was defined as a change from below the lower limit of quantification (LLOQ) at baseline to greater than or equal to (≥) the LLOQ, or a 3.3-fold rise for those with ≥ LLOQ at baseline (Module 5.3.5.1 for Study P203 statistical analysis plan [SAP]). Data from confirmatory testing of the anti-Spike bAb using the MesoScale Discovery electrochemiluminescence (MSD-ECL) and enzyme-linked immunosorbent assay (ELISA) were also generated and are provided in Module 5.3.5.1 for Study P203.

A descriptive summary of mRNA-1273 efficacy against COVID-19, asymptomatic SARS-CoV-2 infection, and SARS-CoV-2 infection (regardless of symptoms) of the data snapshot (08 May 2021) is provided in this submission (Section 2.5.4.2.2). The Study P203 Protocol Amendment 1 (Study P203 in Module 5.3.5.1) includes the assessment of COVID-19 cases

utilizing 2 case definitions: (i) the "P301 case definition" used in the adult clinical endpoint efficacy trial, and (ii) the "CDC case definition", requiring only one symptom (and laboratory confirmation), reflecting the less symptomatic disease more common in adolescence. Assessments were performed starting 14 days after dose 1 or 14 days after dose 2 (CDC 2020b) to expand the number of cases available for analyses as of the time of the data snapshot. These analyses were performed using the Per-Protocol (PP) efficacy Set or the Modified Intent-to-Treat 1 (mITT1) Set (Section 2.5.4.1.1.3). Definitions of COVID-19 cases, asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection (regardless of symptoms) are provided in Section 2.5.4.2.2.

2.5.1.4.2 Study mRNA-1273-P301

Study P301 (ClinicalTrials.gov Identifier: NCT04470427) is an ongoing pivotal randomized, observer-blind, placebo-controlled, stratified study to evaluate efficacy, immunogenicity, and safety in adults ≥ 18 years of age that supported the indication of COVID-19 Vaccine Moderna in adults. The adult submission from the first interim analysis included a median of 49 days of safety follow-up from dose 2. The primary analysis included a median of 2 months of safety follow-up from dose 2, was also provided. In this study, more than 30,000 participants were randomized and > 96.7% participants received dose 2 of mRNA-1273.

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study P301. The primary efficacy endpoint was met at an interim analysis (IA, data snapshot date of 11 Nov 2020): mRNA-1273 prevented symptomatic COVID-19 disease starting 14 days after dose 2 of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the mRNA-1273 group and 90 cases in the placebo group). The vaccine efficacy (VE) was 94.5% (95% CI: 86.5%, 97.8%; one-sided *p* value to test the null hypothesis of VE ≤ 30% was < 0.0001) at the IA. This result was confirmed for the primary analysis at data snapshot 2 (dated 25 Nov 2020) of Study P301. At the primary analysis, the VE was 94.1% with 95% CI: 89.3%, 96.8%) based on 196 adjudicated cases (11 cases in the mRNA-1273 group and 185 cases in the placebo group).

The safety and reactogenicity of a 2-dose regimen of mRNA-1273 100 µg (compared with a 2-dose regimen of placebo) administered 28 days apart, was assessed in participants 18 years of age and older at increased risk for acquiring COVID-19 based on occupation or location and living circumstances. Reactogenicity (solicited local and/or systemic ARs) was observed in the majority of participants in the mRNA-1273 group, and generally increased after dose 2. The rates of local and systemic reactions were higher in the mRNA-1273 group than in the placebo group after each dose. The majority of solicited ARs in the mRNA-1273 group were grade 1 to grade 2

in severity and generally resolved within 3 days or less. The incidence rates of unsolicited AEs and severe AEs during the 28 days after each dose were also generally similar in participants who received mRNA-1273 and those who received placebo.

Deaths and SAEs were reported at a similar incidence in the mRNA-1273 and placebo groups. There was no evidence of vaccine enhanced disease; indeed, fewer cases of severe COVID-19 (and less severe COVID-19) were observed in participants who received mRNA-1273 than in those who received placebo.

In this submission to support adolescent (aged ≥ 12 to < 18 years) use of the COVID-19 Vaccine Moderna, immunogenicity data from young adults (aged ≥ 18 to ≤ 25 years) in Study P301, based on a database lock date of 04 May 2021, were used as a comparator group to infer vaccine effectiveness in adolescents aged ≥ 12 to <18 years (Study P203) (Section 2.5.4.2.1). A summary of the Study P301 population used for the immunogenicity data from a subset of young adults analysis is provided in Section 2.5.4.1.2.

2.5.1.4.3 Timing of Application

The present submission intends to extend the existing indication of the use of the COVID-19 Vaccine Moderna in persons aged ≥ 18 years to persons ≥ 12 years of age for the prevention of COVID-19.

A data snapshot for this submission was triggered (date: 08 May 2021) based on the availability of immunogenicity data from Study P203, resulting in a median study follow-up duration of 53 days after dose 2. This analysis included a total of 3,732 participants (3,726 participants randomized and received study treatment, with 1,240 participants randomized to placebo and 2,486 participants randomized to mRNA-1273).

2.5.1.5 Adherence to Current Standard Research Approaches in the Design, Conduct, and Analysis of Studies

The clinical development of mRNA-1273 has been expedited to address the ongoing global public health emergency resulting from the SARS-CoV-2 pandemic (and assigned by the World Health Organisation to the highest public health emergency status). The Study P203 and Study P301 protocols and Statistical Analysis Plans have been designed in accordance with both United States Food and Drug Administration (FDA) general guidance on COVID-19 vaccine development (DHHS 2020) and product-specific guidance. Study P301 data were extensively discussed with European Medicines Agency, Health Canada, as well as other Agencies as part of the authorization pathway developed to expedite regulatory approval in each country. These

studies are also conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines and applicable ICH GCP Guidelines. Study P203 is part of the approved pediatric plan in place in the United States (investigational pediatric study plan, iPSP) and European Union (paediatric investigational plan, PIP). Study P203 was conducted with oversight by a Data Safety Monitoring Board (DSMB) and Study P301 was conducted with oversight by an independent DSMB and adjudication committee.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

During clinical development of mRNA-1273, the Sponsor is evaluating immunogenicity by assessing changes from baseline in SARS-CoV-2-specific bAb and nAb titers.

In Phase 1 Study 20-0003, vaccine-induced neutralizing activity was assessed by PsVNA (performed by the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center), and by live wild-type SARS-CoV-2 virus plaque reduction neutralization (PRNT) assay (performed by the Vanderbilt University Medical Center). Binding Ab titers were assessed using an anti-S ELISA, and a Mesoscale Discovery (MSD) multiplex serological assay to test for immunoglobulin G (IgG) antibodies to 3 antigens related to SARS-CoV-2 (Spike, Nucleocapsid, and RBD). These experimental assays were developed using a fit-for-purpose approach.

Assays used in later phases were qualified or validated. A qualified micronucleus (MN) assay (performed by Battelle) and qualified anti-Spike ELISA (performed by PPD) were used to test samples from Study mRNA-1273-P201. A panel of validated assays was used to assess immunogenicity in Study mRNA-1273-P301. These assays included anti-Spike ELISA, Mesoscale Discovery (MSD) multiplex serological assay was used to test for IgG antibodies to 3 antigens related to SARS-CoV-2 (Spike, Nucleocapsid, and receptor-binding domain [RBD]) performed at VIP and PPD, and PsVNA at Duke University.

In Study P203, IgG bAbs were assessed via the validated anti-S ELISA, validated Mesoscale Discovery (MSD) assay (performed by PPD). For the assessment of nAb titers, a validated PsVNA (developed and performed by Duke University) was used.

Of note, for the immunogenicity analysis of P203 adolescents compared to P301 young adults (≥ 18 to ≤ 25 years old), the samples from the P203 adolescents and P301 young adults selected for this analysis were tested concurrently at PPD vaccine for anti-Spike ELISA and MSD multiplex, and Duke University for PsVNA.

Although the MSD for Study P301 was performed at a different laboratory with a different protocol for Study P203, the sponsor performed a concordance test and determined that the 2 MSD assays are equivalent.

Validation reports supporting the bioassays discussed in this submission are provided in Study P203, Module 5.3.1.4.

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 Study Populations

2.5.4.1.1 Study mRNA-1273-P203

2.5.4.1.1.1 Study Duration and Disposition

A total of 3,732 participants were randomly assigned to receive injections of either 100 µg of mRNA-1273 vaccine or a placebo control in a 2:1 randomization ratio (2,773 participants aged ≥12 to < 16 years and 959 participants aged ≥ 16 to < 18 years). The dosage and dosing schedule was identical to that administered to adults in Study P301 (100 ug), with each dose of the 2-dose vaccination regimen assigned to be administered 28 days apart (Table 3). As of 08 May 2021 (data snapshot date), 2,486 (99.9%) participants in the mRNA-1273 group and 1,240 (99.8%) participants in the placebo group received dose 1, and 2,480 (99.6%) participants in the mRNA-1273 group and 1,222 (98.3%) participants in the placebo group received dose 2 (Table 3). In the mRNA-1273 group and the placebo group, the median follow-up time after dose 1 was 83.5 days and 82.0 days, respectively, and the median follow-up time after dose 2 was 53 days and 51 days, respectively (Table 3).

At the time of the data snapshot (08 May 2021), 245 participants (6.6%) had discontinued the study, with the most frequently reported reason for discontinuation from the study of withdrawal of consent by participant. There had been more discontinuations from the study occurring in the placebo group than the mRNA-1273 group (188 [15.1%] vs 57 [2.3%] participants). This is consistent with Part B of the protocol, in which unblinded participants that received vaccine are encouraged to stay in the study for long-term safety follow-up while those that received placebo

are withdrawn from the study to receive vaccines available under emergency use. Additionally, one (< 0.1%) participant in the mRNA-1273 group discontinued from the study due to an AE and one (< 0.1%) additional participant in the mRNA-1273 group discontinued from study vaccine due to an AE. These events are described in Section 2.5.5.2.6.3.1.

Table 3: Participant Disposition in Study mRNA-1273-P203

	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 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)
COVID-19 Non-infection related	2 (<0.1)	13 (1.0)	15 (0.4)
Other	25 (1.0)	89 (7.2)	114 (3.1)
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)
Safety Set[a]	N=2486	N=1240	N=3726
Completed 2 doses	2479 (99.7)	1222 (98.5)	3701 (99.3)
Median follow-up post dose 2 (days)[b]	53.0	51.0	53.0
Completed at least 1 month follow-up post dose 2	2452 (98.6)	1173 (94.6)	3625 (97.3)
Completed at least 2 months follow-up post dose 2	1087 (43.7)	474 (38.2)	1561 (41.9)
Solicited Safety Set[c]	N=2485	N=1240	N=3725
First Dose Solicited Safety Set	2482 (99.8)	1238 (99.8)	3720 (99.8)
Second Dose Solicited Safety Set	2478 (99.7)	1220 (98.4)	3698 (99.2)
Full Analysis Set[d]	N=2486	N=1240	N=3726
mITT Set[e]	N=2167	N=1075	N=3242
mITT1 Set for Efficacy[f]	N=2163	N=1073	N=3236
Excluded from mITT1 Set for Efficacy	326 (13.0)	170 (13.68)	496 (13.29)
Reason for exclusion			
Randomized but not dosed	3 (0.12)	3 (0.24)	6 (0.16)
Positive or missing baseline SARS-CoV-2 status	319 (12.82)	165 (13.27)	484 (12.97)
Received incorrect vaccination	4 (0.16)	2 (0.16)	6 (0.16)
PP Set for Efficacy[g]	N=2139	N=1042	N=3181

	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Excluded from PP Set for Efficacy	350 (14.06)	201 (16.17)	551 (14.76)
Reason for exclusion			
Randomized but not dosed	3 (0.12)	3 (0.24)	6 (0.16)
Positive or missing baseline SARS-CoV-2 status	319 (12.82)	165 (13.27)	484 (12.97)
Discontinued study treatment or participation without receiving dose 2	2 (0.08)	13 (1.05)	15 (0.40)
As of cutoff date[h], not received dose 2 and passed window of +14 days	1 (0.04)	0	1 (0.03)
Received incorrect vaccination	4 (0.16)	2 (0.16)	6 (0.16)
Received dose 2 out of window	21 (0.84)	18 (1.45)	39 (1.05)
Immunogenicity Subset[i]	N=374	–	–
PP Immunogenicity Subset[j]	N=340	–	–
Excluded from PP Immunogenicity Subset[k]	34 (9.1)	–	–
Reason for exclusion			
Positive baseline SARS-CoV-2 status	26 (7.0)	–	–
Received dose 2 out of window	8 (2.1)	–	–

Abbreviations: Ab = antibody; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; 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.

Note: Percentages are based on the number of participants (N) for each analysis set, except for exclusions from mITT1 Set for Efficacy and PP Set for Efficacy where N is based on the Randomized Set.

a The Safety Set consists of all randomized participants who received any study injection.

b Study duration from second injection is 0 day for participants who did not receive dose 2.

c The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.

d The FAS consists of all randomized participants who received at least 1 dose of IP. Numbers are based on planned treatment group.

e The mITT Set consists of 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) before the first dose of IP, ie, all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.

f The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A was not as randomized). Numbers are based on planned treatment group.

g The PP Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of dose 2; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group.

h For Study P203, data cutoff refers to the data snapshot date (08 May 2021).

i The Immunogenicity Subset consists of participants in the FAS who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.

j The PP Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of dose 2; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.

k A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.

Source: Study P203, Table 1.1; Table 1.2; Table 1.4; Table 1.2.3.

2.5.4.1.1.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics were in general balanced between the mRNA-1273 and placebo groups in Study P203 (Table 4).

Table 4: Demographic and Baseline Characteristics in Study mRNA-1273-P203 (Safety Set)

Characteristic	mRNA-1273 (N=2486) n (%)	Placebo (N=1240) n (%)	Total (N=3726) n (%)
Sex			
Female	1203 (48.4)	608 (49.0)	1811 (48.6)
Male	1283 (51.6)	632 (51.0)	1915 (51.4)
Age			
16 to <18 years	648 (26.1)	311 (25.1)	959 (25.7)
12 to <16 years	1838 (73.9)	929 (74.9)	2767 (74.3)
Race			
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	2085 (83.9)	1041 (84.0)	3126 (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			
Hispanic or Latino	280 (11.3)	152 (12.3)	432 (11.6)
Not Hispanic or Latino	2188 (88.0)	1076 (86.8)	3264 (87.6)
Not reported	17 (0.7)	10 (0.8)	27 (0.7)
Unknown	1 (<0.1)	2 (0.2)	3 (<0.1)
Race and Ethnicity Group[a]			
White non-Hispanic	1857 (74.7)	912 (73.5)	2769 (74.3)
Communities of Color	625 (25.1)	325 (26.2)	950 (25.5)
Missing	4 (0.2)	3 (0.2)	7 (0.2)
Body Mass Index			
<30 kg/m^2	2316 (93.2)	1146 (92.4)	3462 (92.9)
≥30 kg/m^2	170 (6.8)	94 (7.6)	264 (7.1)

Characteristic	mRNA-1273 (N=2486) n (%)	Placebo (N=1240) n (%)	Total (N=3726) n (%)
Positive baseline SARS-CoV-2 status[b]	147 (5.9)	69 (5.6)	216 (5.8)
Negative baseline SARS-CoV-2 status[c]	2167 (87.2)	1075 (86.7)	3242 (87.0)
Missing baseline SARS-CoV-2 status	172 (6.9)	96 (7.7)	268 (7.2)

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

Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.

[a] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.

[b] 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.

[c] Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.

Source: Study P203, Table 1.3.

2.5.4.1.1.3 Analysis Sets

Analysis sets from Study P203 that are referenced in this EUA amendment are defined in Table 5. A complete list of analysis sets with corresponding definitions are provided in the Study P203 SAP Version 2.0 (Study P203, Module 5.3.5.1). The number of participants in each analysis set discussed in this submission document are presented in Table 3.

Table 5: mRNA-1273-P203 Analysis Sets

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
FAS	All randomized participants who received at least 1 injection of IP.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The Immunogenicity Subset consists of: • a subset of participants in the FAS, and • have baseline (Day 1) SARS-CoV-2 status available, and • have baseline and at least one post-injection antibody assessment for the analysis endpoint.
Per-Protocol Immunogenicity Subset	A subset of participants in the FAS will be 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

Analysis Set	Description
	data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
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 have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
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.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline.
Modified Intent-to-Treat 1 (mITT1) Set	All participants in the mITT Set excluding those who received the wrong treatment.

Abbreviations: AR = adverse reaction; COVID-19 = coronavirus disease 2019; FAS = full analysis set; IP = investigational product; mITT1 = modified intent-to-treat 1; PP = Per-Protocol.
Source: Study P203 SAP Version 2.0 in Module 5.3.5.1.

2.5.4.1.2 Study mRNA-1273-P301

This section discusses the Study P301 Immunogenicity Subset used as the comparator for the primary immunogenicity endpoint in Study P203 (Section 2.5.4.2.1).

2.5.4.1.2.1 Disposition

Samples from 340 participants aged ≥ 18 to ≤ 25 years in the mRNA-1273 group from Study P301 were randomly selected from all participants in that age group in the mRNA-1273 group in Study P301 to be used in the comparator arm with P203 adolescents in the mRNA-1273 group selected for the immunogenicity subset, the analysis is refer to as the Study P203 immunobridging analysis. The Per-Protocol Immunogenicity Subset is used for the immunobridging analysis.

Of the 340 selected participants from the Study P301 mRNA-1273 group, 35 were excluded from the PP Immunogenicity Subset for the following reasons: baseline SARS-CoV-2 positive or

missing (17 participants), did not receive dose 2 per schedule (16 participants), or received dose 2 outside of [21, 42] days after dose 1 (2 participants).

Of the 374 mRNA-1273 participants in P203 selected for the Immunogenicity Subset, 34 were excluded from the PP Immunogenicity Subset for the following reasons: baseline SARS-CoV-2 positive or missing (26 participants), or received dose 2 outside of [21, 42] days after dose 1 (8 participants).

2.5.4.1.2.2 Demographics and Baseline Characteristics

In the PP Immunogenicity Subset including Study P203 and P301 participants, proportions of males and females were similar between P203 and P301 young adults (Table 6).

In the PP Immunogenicity Subset, the mean and median ages were 14.4 years and 14.0 years, respectively, for Study P203 participants and 22.3 years and 23.0 years, respectively, for Study P301 young adults (Study P203, Table 1.3.2).

A total of 20.3% of Study P203 participants were from communities of color (78.5% were non-Hispanic white) (Table 6). Of note, 51.8% of Study P301 young adults were from communities of color which was numerically higher than in that in all Study P301 mRNA-1273 participants who received at least one dose (37.1%, FAS, PA, 25 Nov 2020) (Study P203, Table 1.3.2). Please note, for Study P301 the intention was to enroll a representative population from communities of color that have been disproportionately affected by COVID-19.

The percentages of participants with ≥ 30 kg/m^2 BMI were 7.1% in P203 and 23.3% in Study P301 young adults.

Table 6: Demographic and Baseline Characteristics in Study mRNA-1273-P203 (Participants Aged ≥ 12 to < 18 Years) and Study mRNA-1273-P301 (Participants Aged ≥ 18 to ≤ 25 Years) (Per-Protocol Immunogenicity Subset)

Characteristic	P203 mRNA-1273 (N = 340) n (%)	P301 mRNA-1273 (N = 305) n (%)
Sex		
Female	162 (47.6)	157 (51.5)
Male	178 (52.4)	148 (48.5)

Characteristic	P203 mRNA-1273 (N = 340) n (%)	P301 mRNA-1273 (N = 305) n (%)
Age		
16 to <18 years	101 (29.7)	–
12 to <16 years	239 (70.3)	–
Race		
American Indian or Alaska Native	0	3 (1.0)
Asian	15 (4.4)	30 (9.8)
Black or African American	4 (1.2)	34 (11.1)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
White	285 (83.8)	211 (69.2)
Other	7 (2.1)	8 (2.6)
Multiracial	19 (5.6)	14 (4.6)
Not reported	6 (1.8)	3 (1.0)
Unknown	4 (1.2)	0
Ethnicity		
Hispanic or Latino	26 (7.6)	81 (26.6)
Not Hispanic or Latino	304 (89.4)	222 (72.8)
Not reported	9 (2.6)	0
Unknown	1 (0.3)	2 (0.7)
Race and ethnicity group[a]		
White non-Hispanic	267 (78.5)	147 (48.2)
Communities of color	69 (20.3)	158 (51.8)
Missing	4 (1.2)	0
Body mass index		
<30 kg/m^2	316 (92.9)	233 (76.4)
≥30 kg/m^2	24 (7.1)	71 (23.3)
Positive baseline SARS-CoV-2 status[b]	0	0
Negative baseline SARS-CoV-2 status[c]	340 (100)	305 (100)

Abbreviations: COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Note: Percentages are based on the number of participants in the Immunogenicity Subset (N).
[a] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
[b] 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.
[c] Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.
Source: Study P203, Table 1.3.2.

2.5.4.2 Vaccine Effectiveness and Efficacy

This section contains an overview of immunogenicity and efficacy data for the ongoing Study P203. Refer to Module 5.3.5.1 for the comprehensive set of Study P203 efficacy tables, figures, and listings (TFLs).

2.5.4.2.1 Immunogenicity

The primary immunogenicity objective of Study P203 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 either,

1. evaluating against an accepted Ab threshold of protection against COVID-19 in Study P301 **or**, if an accepted Ab threshold is not established (Section 2.5.4.2.1.1),
2. establishing noninferiority of adolescent (≥ 12 to < 18 years of age; Study P203) to adult (≥ 18 to ≤ 25 years; Study P301) values for the coprimary endpoints of serum Ab levels **and** seroresponse rates.

An overview of Study P203 and Study P301 is summarized in Section 2.5.1.4.1 and Section 2.5.1.4.2, respectively.

2.5.4.2.1.1 Statistical Methods

At the time the analysis for this submission was performed, when the median study follow-up was 53 days after dose 2 (08 May 2021 data snapshot), an immunogenicity correlate of protection had not been established (Section 2.5.4.2.1).

Therefore, the primary objective to infer efficacy of mRNA-1273 in adolescents was evaluated by comparing the immune response to mRNA-1273 as measured by GM values/titers of serum Ab and seroresponse rate in P203 with those obtained from young adults (≥ 18 to ≤ 25 years of age) in P301 using the Per-Protocol Immunogenicity Subset.

The study is considered to meet the primary immunogenicity objective if the noninferiority based on both GM titer (GMT) and seroresponse rate at Day 57 is demonstrated at a 2-sided alpha of 0.05, in P203 participants on mRNA-1273 compared with those in Study P301 young adults on mRNA-1273. The null hypotheses based on GMT and seroresponse and the criterion of study success: noninferiority based on the ratio of GMT (Study P203 vs Study P301 young adults) with a noninferiority margin (NIM) of 1.5 AND a point estimator of GMT > 0.8; AND non-inferiority based on difference of seroresponse rate (Study P203 – Study P301 young adults) with a NIM of 10% AND a point estimator of difference in seroresponse rate > -5.0% are described in Table 7.

Table 7: Coprimary Endpoints to Demonstrate Immunogenicity Noninferiority

	Coprimary endpoint 1[a]	Coprimary endpoint 2[a]
	Ab GM at Day 57	*Ab seroresponse rate at Day 57*
Null Hypothesis	H^1_0: immunogenicity response to mRNA-1273 as measured by Ab GM at Day 57 is inferior in adolescents (≥ 12 to < 18 years of age) receiving mRNA-1273 compared with that in young adults (≥ 18 to ≤ 25 years of age) receiving mRNA-1273 using Phase 3 Study P301 data.	H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in adolescents (≥ 12 to < 18 years of age) receiving mRNA-1273 compared with that in adults (≥ 18 to ≤ 25 years of age) using mRNA-1273 Study P301 data.
Noninferiority Criteria	• The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5. • The GMR[b] point estimate > 0.8 (minimum threshold).	• The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and • The seroresponse rate difference point estimate > -5% (minimum threshold).

Abbreviations: Ab = antibody; CI = confidence interval; GM = geometric mean; GMR = geometric mean ratio

[a] The primary immunogenicity objective was considered met if noninferiority was demonstrated based on both coprimary endpoints.

[b] The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this study, Study P203, at Day 57 compared with the GM value of young adults (≥ 18 to ≤ 25 years of age) on mRNA-1273 in Study P301.

Immunogenicity to mRNA-1273 was assessed using 3 immunogenicity assays. The definition of seroresponse was based on assay-specific performance characteristics, as described in Table 8. Note that PsVNA ID_{50} was used as the basis for the primary immunogenicity objective (to infer efficacy in adolescents).

Table 8: Assay-specific Definitions of Seroresponse for Assays of Interest

Assay Name	Category	Test Name/ Description	Definition of Seroresponse
Pseudovirus (PsVNA)	nAb	PsVNA ID_{50}	baseline < LLOQ: ≥ LLOQ baseline ≥ LLOQ: 3.3-fold rise
		PsVNA ID_{80}	baseline < LLOQ: ≥ LLOQ baseline ≥ LLOQ: 2.3-fold rise
Anti-Spike ELISA	bAb	Anti-Spike ELISA	baseline < LLOQ: ≥ LLOQ baseline ≥ LLOQ: 4.6-fold rise
MSD multiplex	bAb	Anti-Spike	baseline < LLOQ: ≥ LLOQ baseline ≥ LLOQ: 1.9-fold rise

Abbreviations: bAb = binding antibodies; ELISA = enzyme-linked immunosorbent assay; ID_{50} = 50% inhibitory dose; ID_{80} = 80% inhibitory dose; LLOQ = lower limit of quantitation; MSD = MesoScale Discovery; nAb = neutralizing antibody; PsVNA = pseudotype-based neutralization assay.
Note: PsVNA ID_{50} is used as the basis to establish noninferiority.

For each assay, the seroresponse rate was defined as the rate in participants achieving seroresponse based on assay-specific seroresponse definition. The difference in seroresoponse rate is defined as seroresponse rate in Study P203 mRNA-1273 participants minus that in Study P301 young adults in mRNA-1273.

2.5.4.2.1.2 Results

2.5.4.2.1.2.1 Disposition

In Study P203, immunogenicity was assessed at baseline (Day 1) and 28 days after the second dose (Day 57). A total of 374 participants on mRNA-1273 in Study P203 and 340 young adults on mRNA-1273 group were selected for the Immunogenicity Subset. The PP Immunogenicity Subset is the analysis population used for the immunogenicity analysis, and included 340 mRNA-1273 recipients in Study P203 (adolescents) and 305 mRNA-1273 recipients in Study P301 (young adults) (Section 2.5.4.1.1.3).

2.5.4.2.1.2.2 Demographics and Baseline Characteristics

Participant demographics and baseline characteristics in Study P203 is summarized in Section 2.5.4.1.1.3; subject demographics and baseline characteristics in Study P301 is summarized in Section 2.5.4.1.2.2.

2.5.4.2.1.2.3 Coprimary Endpoints

Table 9 summarizes the analysis of the differences in immune response at Day 57 for adolescents in Study P203 compared to young adults aged ≥ 18 to ≤ 25 years in Study P301 for serum Ab level (PsVNA ID50 assay) and seroresponse.

The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the 1.5-fold noninferiority criterion (ie, lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb seroresponse rates at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the 10% noninferiority criterion (lower bound of the 95% of the seroresponse rate difference is > -10%).

Since both coprimary endpoints met the prespecified success criteria for noninferiority (Section 2.5.4.2.1.1), the primary immunogenicity objective is considered to have been met.

In general, the analyses by age group (Study P203, Table 2.1.1.3.2); baseline SARS-CoV-2 status (Study P203, Table 2.1.1.3.3); and gender, race, and body mass index (Study P203, Table 2.1.1.3.4) yielded similar results. Anti-Spike bAb assay data using the MesoScale Discovery (MSD) Platform and ELISA were also generated and confirmed the findings of the analyses based on the ID_{50} assay (Module 5.3.5.1 for Study P203 immunogenicity TFLs). Similarly, assessment of the PsVNA results applying a cutoff of 80% inhibitory dose (ID_{80}), showed similar results with a GMR of adolescents to young adults at Day 57 of 1.117 (95% CI:

0.991, 1.26) and difference in seroresponse rate again of 0.2 (95% CI: -1.8, 2.4) (Study P203, Table 2.1.1.3.1 and Table 2.1.2.3.1).

Table 9: Analysis of Serum Antibody Level and Seroresponse at Day 57 by Pseudovirus Neutralization Assay (ID50): ANCOVA Model (Per-Protocol Immunogenicity Subset for SARS-CoV-2-specific nAb)

Serum antibody level Pseudovirus Neutralization (ID_{50})	**Study P203: ≥ 12 to < 18 Years GLSM 95% CI N= 340**	**Study P301: ≥ 18 to ≤ 25 Years GLSM 95% CI N= 305**	**GMR Study P203 vs. Study P301 95% CI**	**Met Success Criteria[a]?**
	1401.670 1276.300, 1539.355	1301.312 1176.979, 1438.780	1.077 0.939, 1.236	Yes
Seroresponse by Pseudovirus Neutralization (ID_{50})	**Study P203: ≥ 12 to < 18 Years n (%) 95% CI N= 340**	**Study P301: ≥ 18 to ≤ 25 Years n (%) 95% CI N= 305**	**Difference in Seroresponse Rate 95% CI**	**Met Success Criteria[b]?**
	336 (98.8) 97.0, 99.7	292 (98.6) 96.6, 99.6	0.2 -1.8, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least square; n = number of subjects with non-missing data at the corresponding timepoint; ULOQ = upper limit of quantification

[a] The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

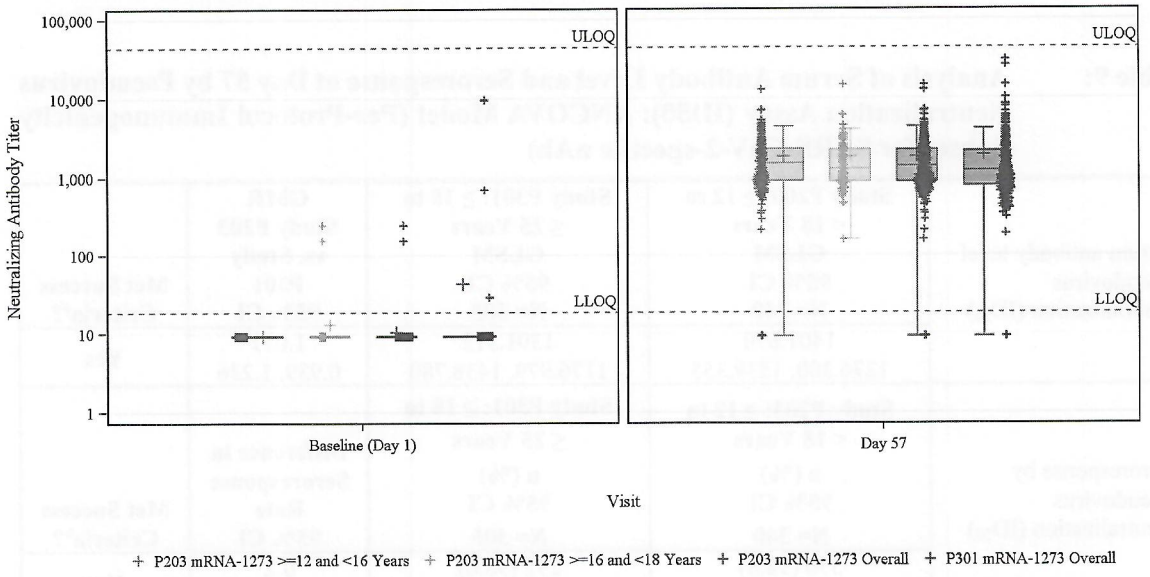
[b] The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Notes:

- The ULOQ for selected P301 participants tested previously was different.
- Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
- The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resultant LS means, difference of LS means, and 95% CI were back-transformed to the original scale for presentation.

Sources: Study P203, Table 2.1.1.3.1 and Table 2.1.2.3.1.

Figure 2: Box Plot of Pseudovirus Neutralizing Antibody ID50 (Per-Protocol Immunogenicity Set)



Abbreviations: LLOQ = lower limit of quantification; P203 = Study mRNA-1273-P203; P301 = Study mRNA-1273-P301
ULOQ = upper limit of quantification.
Note: Antibody values reported as below the LLOQ (18.5) are replaced by 0.5 x LLOQ. Values greater than the ULOQ (45118) are replaced by the ULOQ if actual values are not available.

2.5.4.2.2 Clinical Efficacy

In addition to the primary immunobridging analysis, VE was assessed against COVID-19 and SARS-CoV-2 infections (asymptomatic and with or without symptoms) in adolescents. Methods used were the same as those employed for adults ≥ 18 years (Study P301). Vaccine efficacy was assessed against COVID-19 meeting the following case definitions: (i) the "P301 case definition" used in the adult efficacy study, based on either at least 2 prespecified systemic symptoms or at least 1 respiratory symptom and a positive RT-PCR and (ii) the "CDC case definition" based on at least 1 prespecified clinical symptom and a positive RT-PCR. Use of the "P301 case definition" allowed alignment of VE assessment with that in the pivotal adult study (Study P301). Use of the "CDC case definition", defined by a single symptom, tailored the assessment of VE to adolescents known to have milder clinical presentation than adults. Cases were assessed in both the PP Efficacy Set (received both planned doses) and the mITT1 set (received at least one dose as randomized), both of which exclude subjects with evidence of previous SARS-CoV-2 infection at baseline (Table 4).

Assessment using the PP Efficacy Set is consistent with the analysis set used in the pivotal adult study. Assessments using the mITT1 Set in Study P203 allowed a longer observation period for

case occurrence (starting 14 days after the first dose), allowing expanded assessment of cases at the time of the data snapshot. The analyses presented in this submission thus maintain the stringent assessment of the pivotal adult efficacy study ("P301 case definition" in the PP Set) but also employ assessments more aligned with the epidemiology and pathophysiology of COVID-19 in adolescents ("CDC case definition" in the mITT1 set).

Definitions of COVID-19 cases and SARS-CoV-2 infections used in Study P203 and included in this submission are presented in Table 10. An overview of Study P203 is provided in Section 2.5.1.4.1. The definition of the efficacy endpoints used in Study P203 are generally aligned with those in Study P301 based on data collected in respective studies.

Table 10: Case Definitions in Study mRNA-1273-P203

Endpoint	Definition
COVID-19 "P301 case definition"	COVID-19 case will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms as follows: • A positive post-baseline PCR result **AND** • At least 2 systemic symptoms: Fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** • At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
COVID-19 "CDC case definition"	At least one symptom from a prespecified list of COVID-19 symptoms derived from the CDC case definition (CDC 2020b) • Systemic symptoms: fever (temperature > 38°C/≥ 100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea, **AND** • At least one positive RT-PCR for SARS-CoV-2.
SARS-CoV-2 Infection (regardless of symptoms)	A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline • bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, **OR** • Positive RT-PCR test.
Asymptomatic SARS-CoV-2 infection	• Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. • Absent of COVID-19 symptoms. • **AND** at least one from below[a]: • bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that

Endpoint	Definition
	becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, **OR** • Positive RT-PCR test at scheduled or unscheduled/illness visits.

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 19; IP = investigational product; NP = nasopharyngeal; RT-PCR = reverse-transcriptase polymerase chain reaction; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2
Source: Study P203 protocol amendment 1 in Module 5.3.5.1.
[a] At this analysis (08 May 2021), results from scheduled RT-PCR tests at Day 29 and Day 57, and from scheduled serology tests at Day 57 were considered.

This submission, prepared at the time of the data snapshot (08 May 2021), includes a descriptive analysis of VE against COVID-19 cases and infections as defined above (Table 10) and occurring (i) 14 days or more after dose 2, and (ii) 14 days or more after dose 1. Surveillance for COVID-19 symptoms was conducted via biweekly telephone calls or eDiary prompts starting at enrollment. Results are discussed both as case splits and incidence per 1,000 person-years to accommodate for the 2:1 vaccine:placebo randomization ratio.

For the analysis of VE in Study P203 aligning with that in the pivotal adult efficacy study, the COVID-19 "P301 case definition" was utilized and the observed VE against confirmed cases occurring 14 days or more after dose 2 was 100.0%. The case split was 0 cases in the mRNA-1273 group and 4 cases in the placebo group (Table 11). Applying a stringent case definition and limiting cases counted to those occurring post dose 2, the lower bound of the 95% CI around the point estimate was nonetheless 28.9%. These results, using criteria matching those in the adult efficacy study, are consistent with results obtained in that pivotal study.

VE analyses were also conducted using the COVID-19 "CDC case definition", requiring only one symptom and reflecting the paucity of symptoms more common in adolescence. Using this CDC case definition, more cases were observed than when the more stringent "P301 case definition" was employed. VE against cases occurring 14 days or more after dose 2 was 93.3% (95% CI: 47.9%, 99.9%) (Table 11). The case split was 1 case (1.94 cases/1000 person-years) in the mRNA-1273 group and 7 cases (28.981/1000 person-years) in the placebo group.

The VE analysis using the "CDC case definition" was expanded by counting cases starting 14 days after dose 1 (mITT1 set), to accommodate the less symptomatic profile of disease in this age group. Vaccine efficacy in this analysis was 92.7% (95% CI: 67.8, 99.2) (Table 11). The case split was 2 cases in the mRNA-1273 group (3.828 per 1,000 person-years) and 13 cases in the placebo group (52.473 per 1,000 person-years).

Results of VE against COVID-19, defined using either the "P301 case definition" or the "CDC case definition", and conducted starting 14 days after dose 1 or dose 2 were all similar to the

94.1% VE observed 14 days post dose 2 in the pivotal P301 study. Thus, using measures capturing cases defined by at least 1 or by at least 2 clinical symptoms (measured starting after 1 or 2 doses) all VE analyses were consistent with that observed in Study P301 and the lowest lower bound of the 95% CI of all analyses nonetheless exceed 28%.

Analysis of VE against asymptomatic SARS-CoV-2 infection (defined in Table 10) was also conducted based on data available at the time of the data snapshot (08 May 2021). VE against asymptomatic SARS-CoV-2 infection based on testing starting 14 days after dose 1 (mITT1 Set) was 59.5% (95% CI: 28.4, 77.3%), with a case split of 25 cases (48.076/1,000 person-years) in the mRNA-1273 group and 25 (118.828/1,000 person-years) in the placebo group (Study P203, Table 2.6.2.1). VE against asymptomatic SARS-CoV-2 infection occurring at least 14 days after dose 2 (PP Set for Efficacy) was 39.2% (95% CI, -0.247, 0.697).

VE was also assessed against all SARS-CoV-2 infection (regardless of symptoms). VE starting 14 days after dose 1 was 69.8 % (95% CI, 0.499, 0.821). Limiting the analysis to events based on confirmatory testing starting 14 days after dose 2 (PP set for Efficacy), VE was 55.7% (95% CI, 0.168, 0.764), with a case split of 22 cases (42.856/1000 person-years) in the mRNA-1273 group, compared with 23 cases (with 96.649/1000 person-years) in the placebo group (Table 11).

Secondary endpoints including COVID-19 cases at the participant level are presented in Study P203, Listing 2.2.1.

Table 11: Summary of Key Secondary Efficacy Endpoint Analysis Results in Study mRNA-1273-P203

Set	Endpoint	mRNA-1273 (N = 2,162)	Placebo (N = 1,073)
PP[a]	**P301 case definition[b] starting 14 days after dose 2**		
	Cases, n	0	4
	Incidence rate per 1,000 person-years (95% CI)[c]	0 (NE, 7.149)	16.525 (4.503, 42.311)
	VE based on incidence rate (95% CI)[d]	1.00 (0.289, NE)	
mITT1[e]	**CDC case definition[f] of COVID-19 starting 14 days after dose 1**		
	Cases, n	2	13
	Incidence rate per 1,000 person-years (95% CI)[c]	3.828 (0.464, 13.830)	52.473 (27.939, 89.730)
	VE based on incidence rate (95% CI)[d]	0.927 (0.678, 0.992)	

Set	Endpoint	mRNA-1273 (N = 2,162)	Placebo (N = 1,073)
	CDC case definition[f] of COVID-19 starting 14 days after dose 2		
PP[a]	Cases, n	1	7
	Incidence rate per 1,000 person-years (95% CI)[c]	1.940 (0.049, 10.808)	28.981 (11.652, 59.711)
	VE based on incidence rate (95% CI)[d]	0.933 (0.479, 0.999)	
	SARS-CoV-2 infection[g] starting 14 days after dose 1		
mITT1[e]	Cases, n	27	42
	Incidence rate per 1,000 person-years (95% CI)[c]	51.922 (34.217, 75.543)	172.120 (124.049, 232.656)
	VE based on incidence rate (95% CI)[d]	0.698 (0.499, 0.821)	
	SARS-CoV-2 infection[g] starting 14 days after dose 2		
PP[a]	Cases, n	22	23
	Incidence rate per 1,000 person-years (95% CI)[c]	42.856 (26.857, 64.884)	96.649 (61.267, 145.021)
	VE based on incidence rate (95% CI)[d]	0.557 (0.168, 0.764)	
	Asymptomatic SARS-CoV-2 infection[h] starting 14 days after dose 1		
mITT1[e]	Cases, n	25	29
	Incidence rate per 1,000 person-years (95% CI)[c]	48.076 (31.112, 70.969)	118.828 (79.581, 170.657)
	VE based on incidence rate (95% CI)[d]	0.595 (0.284, 0.773)	
	Asymptomatic SARS-CoV-2 infection[h] starting 14 days after dose 2		
PP[a]	Cases, n	21	16
	Incidence rate per 1,000 person-years (95% CI)[c]	40.908 (25.323, 62.532)	67.230 (38.428, 109.178)
	VE based on incidence rate (95% CI)[d]	0.392 (-0.247, 0.697)	

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; n = number of events; N = number of participants; NE = not evaluable; mITT1 = Modified Intent-to-Treat-1; PP = Per-Protocol Efficacy Set; RT-PCR = reverse transcription polymerase chain reaction; VE = vaccine efficacy.

[a] The PP Set for Efficacy is defined as all participants in the FAS who meet all the following criteria: received planned doses of study vaccination, had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) at baseline, and had no major protocol deviations that impact key or critical efficacy data.

[b] Defined as symptomatic disease and positive RT-PCR results.

[c] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[d] Vaccine efficacy 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.

[e] mITT1 Set for Efficacy defined all participants in the mITT Set (defined as all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline), excluding those who received the wrong treatment.

[f] Defined as the presence of at least one symptom from a list of COVID-19 symptoms using the CDC case definition (CDC 2020b), and a positive nasopharyngeal swab or saliva sample for SARS-CoV-2 RT-PCR, in baseline negative SARS-CoV-2 participants.

[g] SARS-CoV-2 infection defined in participants with negative SARS-CoV-2 at baseline as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR positive RT-PCR counted starting 14 days after the second dose of investigational product.

[h] Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) counted starting at Day 57 or later, OR positive RT-PCR.
Source: Study P203, Table 2.5.2.1; Table 2.6.2.1; Table 2.8.1.1; Table 2.8.2.1; Table 2.5.1.1; Table 2.6.1.1; Table 2.7.1.1.

2.5.5 OVERVIEW OF SAFETY

This section contains a summary of the key safety data for Study P203 in adolescent participants aged ≥ 12 to < 18 years. An overview of Study P203 is provided in Section 2.5.1.4. Safety population is presented in Table 5. A complete set of safety TFLs are provided in Study P203, Module 5.2.5.1.

The 08 May 2021 data snapshot included a median study follow-up duration of 53 days (approximately 2 months) after dose 2 (Study P203, Table 1.4). The median study duration from randomization for participants was similar between the mRNA-1273 group and the placebo group.

Both solicited local and systemic ARs were more commonly reported by participants in the mRNA-1273 group and systemic AR generally increased after dose 2. While the majority of these solicited ARs were grade 1 or grade 2, there was a higher frequency of grade 3 or higher solicited reactions in the mRNA-1273 group than in the placebo group after dose 1 and dose 2 (Table 12). The majority of the solicited ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after any dose and generally persisted for a median of 1 to 3 days. The frequency of reported solicited ARs were generally similar and there were no notable differences in the reported rates of unsolicited AEs observed between participants aged ≥ 12 to < 16 years and participants aged ≥ 16 to < 18 years (Study P203, Table 3.2.1.1). Overall, local reactogenicity was higher and systemic reactogenicity was lower to mRNA-1273 in adolescents compared with that observed in the adult mRNA-1273 P301 study.

Unsolicited treatment-emergent AEs (TEAE) up to 28 days after any dose were more common in the mRNA-1273 group than in the placebo group (Table 12). Imbalances in unsolicited TEAEs up to 28 days after any dose was primarily attributable to events related to reactogenicity. The incidence of MAAEs within 28 days of injection was generally similar between the mRNA-1273 and placebo groups. The incidence of unsolicited severe TEAEs and serious TEAEs in the 28 days after any dose was low overall and generally similar in participants who received mRNA-1273 and those who received placebo (Table 12). Unsolicited treatment-emergent adverse events (TEAE), including MAAEs, up to 28 days after any dose assessed by the Investigator as related to study treatment were more frequently reported in the mRNA-1273 group than in the placebo group.

There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, and no cases of MIS-C reported during the entire study period (Study P203, Listing 3.4, Listing 3.8, and Listing 4).

Table 12: Safety Overview in Study mRNA-1273-P203 (Safety Set)

Participants reporting at least one	**mRNA-1273**	**Placebo**
Solicited adverse reactions	**n/N1 (%)**	**n/N1 (%)**
Solicited adverse reaction within 60 minutes after vaccination	1134/2,485 (45.6)	527/1,240 (42.5)
Dose #1	776/2,482 (31.3)	355/1,238 (28.7)
Dose #2	684/2,478 (27.6)	326/1,220 (26.7)
Solicited local adverse reaction within 7 days	2431/2,485 (97.8)	602/1,240 (48.5)
Dose #1	2339/2,482 (94.2)	455/1,238 (36.8)
Dose #2	2314/2,478 (93.4)	398/1,220 (32.6)
Grade 3 or 4 solicited local adverse reaction (any dose)	344/2,485 (13.8)	4/1,240 (0.3)
Solicited systemic adverse reaction within 7 days	2284/2,485 (91.9)	830/1,240 (66.9)
Dose #1	1701/2,482 (68.5)	687/1,238 (55.5)
Dose #2	2134/2,478 (86.1)	561/1,220 (46.0)
Grade 3 or 4 systemic adverse reaction (any dose)	414/2,485 (16.7)	58/1,240 (4.7)
Unsolicited adverse events	**n/N (%)**	**n/N (%)**
Unsolicited adverse event up to 28 days after any dose	510/2,486 (20.5)	197/1,240 (15.9)
Non-serious unsolicited adverse event	509/2,486 (20.5)	196/1,240 (15.8)
Related non-serious unsolicited AE	312/2,486 (12.6)	72/1,240 (5.8)
Severe non-serious unsolicited AE	2/2,486 (<0.1)	0
Related severe non-serious unsolicited AE	0	0
Medically-attended adverse event up to 28 days after any dose	156/2,486 (6.3)	81/1,240 (6.5)
Related MAAE	19/2,486 (0.8)	5/1,240 (0.4)
SAE up to 28 days after any dose	2/2,486 (<0.1)	1/1,240 (<0.1)
Related SAE	0	0
AESI (MIS-C)	0	0
Related AESI (MIS-C)	0	0
Deaths	0	0
AE leading to discontinuation of the vaccine up to 28 days after any dose	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically-attended adverse event; MIS-C = multisystem inflammatory syndrome in children; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety subjects (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set consists of all randomized participants who received any study dose. The Solicited Safety Set consists of all participants who were randomized and received any study dose and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who

received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.
Source: Study P203, Table 3.1.2.1; Table 3.1.2.2; Table 3.1.2.3; Table 3.1.1.1; Table 3.1.1.2; Table 3.1.1.3; Table 3.2.1.3; Table 3.2.1.1.

2.5.5.1 Solicited Adverse Reactions

Solicited local and systemic ARs with an onset within 7 days after each dose (ie, the day of injection and the 6 subsequent days) were assessed. Solicited ARs were recorded daily using an eDiary, which was unchanged from the eDiary used in the Study P301 submission for adults aged ≥ 18 years. The solicited ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness, as well as fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. The eDiary solicited daily participant reporting of ARs using a structured checklist. Participants recorded such occurrences in an eDiary on the day of each investigational product (IP) injection and for the 6 days after the day of dosing (Day 1 through Day 7). If an AR persisted beyond Day 7, the participant was prompted to continue to record until resolution. Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Refer to the Study P203 protocol amendment 1 in Module 5.3.5.1 for additional details on the collection of ARs.

2.5.5.1.1 Solicited Local Adverse Reactions

Solicited local ARs occurred more frequently in the mRNA-1273 group than in the placebo group after dose 1 and dose 2 (Table 13). Pain was the most common solicited local AR after dose 1 and dose 2 (93.1% and 92.4% of participants, respectively, in the mRNA-1273 group) (Table 13). Grade 3 solicited local ARs reported in ≥ 5% of participants in any treatment group included pain after dose 1 and dose 2 (5.4% and 5.1%, respectively, of participants in the mRNA-1273 group vs < 0.1% and 0.2% of participants, respectively, in the placebo group). There were no grade 4 solicited local ARs reported in the study (Table 13).

The majority of the solicited local ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after each dose (Study P203, Table 3.1.2.1 and Table 3.1.2.2) and generally persisted for a median of 3 days (Study P203, Table 3.1.3.1 and Table 3.1.3.2).

There was a higher incidence of participants who reported solicited local ARs that persisted beyond 7 days in the mRNA-1273 group than in the placebo group, with a higher incidence of participants after the first dose (6.4% vs 1.2%, respectively) compared with dose 2 (1.6% vs

0.7%, respectively) in both treatment groups (Study P203, Table 3.1.4.1 and Table 3.1.4.2). The incidence of any local AR that occurred at Day 8 or beyond was higher in the mRNA-1273 group (7.1% and 1.7%) than in the placebo group (1.2% and 0.7%) after dose 1 and dose 2, respectively (Study P203, Table 3.1.5.2). This was primarily due to ARs of axillary swelling or tenderness that started within 7 days of the injection and continued beyond 7 days. The incidence of solicited ARs with onset after Day 7 after any dose, while low overall for all participants (1.4%), was higher in participants that received mRNA-1273 (1.9%) than in participants that received placebo (0.3%). More participants reported solicited local ARs (0.9%) with onset after Day 7 after any injection than reported solicited systemic ARs (0.6%) with onset after Day 7 after any injection. No participants in the placebo group and 1.3% of participants in the mRNA-1273 reported solicited local ARs with onset after Day 7 after any injection. The most commonly reported solicited ARs with onset after Day 7 after any injection in the mRNA-1273 group were local ARs of erythema (0.7%), swelling (0.4%), and axillary swelling or tenderness (0.4%) (Study P203, Table 3.1.5.1).

Table 13: Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants Aged ≥ 12 to < 18 Years (Solicited Safety Set)

	Dose 1		Dose 2	
Event	**mRNA-1273 N = 2482 n (%)**	**Placebo N = 1238 n (%)**	**mRNA-1273 N = 2478 n (%)**	**Placebo N = 1220 n (%)**
Any local adverse reaction	N1 = 2482	N1 = 1238	N1 = 2,478	N1 = 1,220
Any	2,339 (94.2)	455 (36.8)	2,314 (93.4)	398 (32.6)
Grade 3	170 (6.8)	1 (<0.1)	220 (8.9)	3 (0.2)
Grade 4	0	0	0	0
Pain	N1 = 2482	N1 = 1238	N1 = 2,478	N1 = 1,220
Any	2,310 (93.1)	431 (34.8)	2,290 (92.4)	370 (30.3)
Grade 3[a]	133 (5.4)	1 (<0.1)	126 (5.1)	3 (0.2)
Grade 4[a]	0	0	0	0
Erythema (redness)	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	334 (13.5)	8 (0.6)	484 (19.5)	11 (0.9)
Grade 3[b]	21 (0.8)	0	72 (2.9)	0
Grade 4[b]	0	0	0	0

Event	Dose 1		Dose 2	
	mRNA-1273 N = 2482 n (%)	Placebo N = 1238 n (%)	mRNA-1273 N = 2478 n (%)	Placebo N = 1220 n (%)
Swelling (hardness)	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	403 (16.2)	12 (1.0)	509 (20.5)	12 (1.0)
Grade 3[b]	27 (1.1)	0	56 (2.3)	0
Grade 4[b]	0	0	0	0
Axillary swelling or tenderness	N1 = 2,481	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	578 (23.3)	101 (8.2)	519 (21.0)	61 (5.0)
Grade 3[c]	10 (0.4)	0	7 (0.3)	0
Grade 4[c]	0	0	0	0

Abbreviation: AR = adverse reaction.

Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

[a] Pain Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[b] Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis.

[c] Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2.

2.5.5.1.2 Solicited Systemic Adverse Reactions

Solicited systemic ARs were also more common in the mRNA-1273 group than in the placebo group (Table 14) and were more common after dose 2 compared to dose 1 in the mRNA-1273 group (Table 14). After any dose, the most common solicited systemic ARs were headache, fatigue, myalgia and chills (Study P203, Table 3.1.1.3). The majority of solicited systemic ARs were grade 1 to grade 2 in severity; however, there was a higher occurrence of grade 3 or higher solicited systemic reactions in the mRNA-1273 group than in the placebo group. Three participants in the mRNA-1273 group experienced at least one grade 4 solicited systemic AR, including one participant each with grade 4 solicited systemic AR of fever, headache and nausea/vomiting. Grade 3 or higher solicited systemic ARs reported in ≥ 5% of participants in any treatment group included fatigue (7.6% of participants in the mRNA-1273 group vs 0.8% of participants in the placebo group) and myalgia (5.2% of participants in the mRNA-1273 group vs 0.2% of participants in the placebo group) after dose 2 (Table 14). There was a higher incidence of reports of fever in the mRNA-1273 group than in the placebo group and the incidence of reports of fever increased after dose 2 in the mRNA-1273 group. (Study P203, Table 3.1.1.3).

The majority of the solicited systemic ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after each dose (Study P203, Table 3.1.2.1 and Table 3.1.2.2) and

generally persisted for a median of 2 days (Study P203, Table 3.1.3.1 and Table 3.1.3.2). The incidence of participants who reported solicited systemic ARs that persisted beyond 7 days was similar between the mRNA1273 and placebo groups, with a lower incidence after dose 2 in both treatment groups (4.7% vs 3.1% after dose 1 and dose 2, respectively, in the mRNA1273 group and 5.2% vs 2.6% after dose 1 and dose 2, respectively, in the placebo group) (Study P203, Table 3.1.4.1; Table 3.1.4.2). The incidence of participants who reported solicited systemic ARs with onset after Day 7 after any dose was higher in participants who received mRNA-1273 (0.7%) than participants who received placebo (0.3%). The most frequently reported solicited systemic ARs with onset after Day 7 after any dose were headache and fatigue (Study P203, Table 3.1.5.1).

Use of antipyretic or analgesic medications within 28 days post dose in the mRNA-1273 group was higher than the placebo group and occurred more frequently after dose 2 in the mRNA-1273 group (Table 14).

Table 14: Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Does, by Maximum Severity, Participants ≥ 12 to < 18 Years (Solicited Safety Set)

Event	Dose 1		Dose 2	
	mRNA-1273 N = 2482 n (%)	Placebo N = 1238 n (%)	mRNA-1273 N = 2478 n (%)	Placebo N = 1220 n (%)
Any systemic AR	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,701 (68.5)	687 (55.5)	2,134 (86.1)	561 (46.0)
Grade 3	108 (4.4)	36 (2.9)	340 (13.7)	25 (2.0)
Grade 4	0	0	3 (0.1)	1 (<0.1)
Fever[a]	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,219
≥38.0°C	63 (2.5)	12 (1.0)	302 (12.2)	12 (1.0)
38.0°C to 38.4°C	36 (1.5)	9 (0.7)	162 (6.5)	6 (0.5)
38.5°C to 38.9°C	18 (0.7)	2 (0.2)	93 (3.8)	4 (0.3)
39°C to 40.0°C	9 (0.4)	1 (<0.1)	46 (1.9)	1 (<0.1)
>40.0°C	0	0	1 (<0.1)	1 (<0.1)
Headache	N1 = 2,480	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,106 (44.6)	477 (38.5)	1,739 (70.2)	370 (30.3)
Grade 3[b]	56 (2.3)	17 (1.4)	112 (4.5)	14 (1.1)
Grade 4[b]	0	0	1 (<0.1)	0
Fatigue	N1 = 2,481	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,188 (47.9)	453 (36.6)	1,679 (67.8)	353 (28.9)
Grade 3[c]	33 (1.3)	18 (1.5)	188 (7.6)	10 (0.8)
Grade 4[c]	0	0	0	0

Event	Dose 1		Dose 2	
	mRNA-1273 N = 2482 n (%)	Placebo N = 1238 n (%)	mRNA-1273 N = 2478 n (%)	Placebo N = 1220 n (%)
Myalgia	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	668 (26.9)	205 (16.6)	1154 (46.6)	153 (12.5)
Grade 3[c]	24 (1.0)	10 (0.8)	129 (5.2)	3 (0.2)
Grade 4[c]	0	0	0	0
Arthralgia	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	371 (15.0)	143 (11.6)	716 (28.9)	113 (9.3)
Grade 3[c]	15 (0.6)	5 (0.4)	57 (2.3)	2 (0.2)
Grade 4[c]	0	0	0	0
Nausea/vomiting	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	281 (11.3)	110 (8.9)	591 (23.9)	106 (8.7)
Grade 3[d]	2 (<0.1)	0	2 (<0.1)	0
Grade 4[d]	0	0	1 (<0.1)	0
Chills	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	456 (18.4)	138 (11.1)	1,066 (43.0)	97 (8.0)
Grade 3[e]	4 (0.2)	1 (<0.1)	11 (0.4)	0
Grade 4[e]	0	0	0	0
Use of antipyretic or pain medication	N = 2482	N = 1,238	N = 2,478	N = 1,220
Any	748 (30.1)	118 (9.5)	1,242 (50.1)	108 (8.9)

Abbreviation: AR = adverse reaction.

Note: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received at least 1 dose of IP and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days. Medications were collected on the eDiary.

[a] Fever is defined as: Grade 1 = 38 to 38.4°C; Grade 2 = 38.5 to 38.9°C; Grade 3 = 39 to 40°C; Grade 4 = greater than 40°C.

[b] Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[c] Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[d] Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; Grade 4 requires emergency room visit or hospitalization for hypotensive shock.

[e] Chills: Grade 3 prevents daily activity and requires medical intervention; Grade 4 requires emergency room visit or hospitalization.

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2; Table 1.7.1; Table 1.7.2.

2.5.5.1.3 Subgroup Analyses of Solicited Adverse Reactions

2.5.5.1.3.1 Age Group

Solicited ARs were generally similar between participants aged ≥ 12 to < 16 years and participants aged ≥ 16 to < 18 years (Study P203, Table 3.1.1.1, Table 3.1.1.2, Table 3.1.1.3, Table 3.1.2.1, Table 3.1.2.2, Table 3.1.2.3, Table 3.1.3.1, Table 3.1.3.2, Table 3.1.3.3, Table 3.1.4.1, Table 3.1.4.2, Table 3.1.4.3, Table 3.1.5.1, Table 3.1.5.2).

2.5.5.1.3.2 Baseline SARS-CoV-2 Status

In Study P203, 3,242 (87.0%) participants had negative SARS-CoV-2 status at baseline, 216 (5.8%) participants had positive SARS-CoV-2 status at baseline, and 268 (7.2%) participants had a missing SARS-CoV-2 status at baseline (Safety Set, Table 1.3). The relatively small number of baseline SARS-CoV-2 positive participants limits the interpretation of differences in reactogenicity by baseline SARS-CoV-2 status. The incidence of solicited local ARs after any dose in participants negative for SARS-CoV-2 at baseline was 98.1% in the mRNA-1273 group and 48.7% in the placebo group (Study P203, Table 3.1.1.9). In baseline positive participants, the incidence was 94.6% and 42.0%, respectively, after any dose (Study P203, Table 3.1.1.9). Overall, the frequency of solicited local ARs appeared comparable for baseline positive and baseline negative participants after dose 1 with the exception of axillary swelling and tenderness (Study P203, Table 3.1.1.7 and Table 3.1.1.8). The incidence of axillary swelling and tenderness after dose 1 was 39.5% in baseline positive participants in the mRNA-1273 group and 22.5% in the baseline negative participants that received mRNA-1273. After dose 2, the incidence of solicited local ARs appeared slightly higher in baseline negative participants than baseline positive participants receiving mRNA-1273. The severity of solicited local ARs seemed similar in baseline positive and baseline negative participants after any dose.

The incidence of solicited systemic ARs after any dose in participants negative for SARS-CoV-2 at baseline was 91.7% in the mRNA-1273 group and 68.1% in the placebo group (Study P203, Table 3.1.1.9). In baseline positive participants, the incidence of solicited systemic SAR after any dose was 93.9% in the mRNA-1273 group and 55.1% in the placebo group (Study P203, Table 3.1.1.9). Overall, after dose 1, the incidence of solicited systemic ARs appeared higher for baseline positive participants in the mRNA-1273 group (87.1%) than in the baseline negative participants in the mRNA-1273 group (67.6%) (Study P203, Table 3.1.1.7). After dose 1, baseline positive participants receiving mRNA-1273, compared to baseline negative participants receiving mRNA-1273, had a higher incidence of fever (19.7% vs 1.5%), headache (70.1% vs 43.4%), fatigue (70.1% vs 46.4%), myalgia (42.9% vs 25.8%), arthralgia (24.5% vs

14.1%), nausea/vomiting (20.4% vs 11.0%), and chills (49.0% vs 16.8%) (Study, Table 3.1.1.7). After dose 1, the severity of solicited systemic ARs appeared higher in baseline positive participants receiving mRNA-1273 than baseline negative participants receiving mRNA-1273. After dose 2, the incidence of solicited systemic ARs was slightly higher in baseline negative participants receiving mRNA-1273 than in baseline positive participants receiving mRNA-1273 but overall appeared more generally similar.

2.5.5.2 Unsolicited Adverse Events

Unsolicited AEs were collected during the 28 days after each IP dose (ie, the day of injection and 27 subsequent days). Adverse events leading to discontinuation from IP and/or study participation, SAEs, AESIs, MAAEs and pregnancies are being collected from Day 1 through the entire study period or until last day of study participation.

Refer to the Study P203 protocol for additional details on the collection of unsolicited AEs.

2.5.5.2.1 Summary of Unsolicited Adverse Events

Unsolicited TEAE up to 28 days after any dose were more common in participants in the mRNA-1273 group (20.5%) compared to participants in the placebo group (15.9%) (Table 15). More unsolicited TEAEs were assessed by the Investigator as related to study treatment in the mRNA-1273 group than the placebo group. (12.6% vs 5.8%, respectively).

The incidence of unsolicited severe TEAEs in the 28 days after any dose was low (5 [0.1%] participants overall), and generally similar in the mRNA-1273 group (4 [0.2%]) compared with the placebo group (1 [<0.1%] participant) (Table 15). No unsolicited severe TEAEs within 28 days of any dose were assessed by the Investigator as related to the IP (Table 15).

The incidence of MAAEs within 28 days of any dose was generally similar between the mRNA-1273 group (156 [6.3%] participants) and the placebo group (81 [6.5%] participants; Table 15). The incidence of MAAEs within 28 days of any dose assessed by the Investigator as related to study treatment was higher in participants that received mRNA-1273 (19 [0.8%] participants) compared with placebo (5 [0.4%] participants) (Table 15).

The incidence of SAEs was similar in the mRNA-1273 group (< 0.1%) and placebo group (< 0.1%) up to 28 days after any injection (Table 15). There were no SAEs assessed as related to study vaccine.

One participant in the mRNA-1273 group discontinued from study vaccine and 1 participant in the mRNA-1273 group discontinued the study due to MAAEs that were assessed as not related to IP (Table 15 and Study P203, Listing 3.6). There is a discrepancy between the disposition analysis and the analysis for unsolicited AEs leading to discontinuation from study vaccine because the action taken field in electronic data capture (EDC) was "dose not changed" at the time of the data snapshot.

There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, and no cases of MIS-C reported during the entire study period (Table 15).

Table 15: Summary of Unsolicited TEAE up to 28 Days After Any Injection in Participants Aged ≥ 12 to < 18 Years (Safety Set)

	Placebo (N = 1,240) n (%)	mRNA-1273 (N = 2,486) n (%)	Total (N = 3,726) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination			
All	197 (15.9)	510 (20.5)	707 (19.0)
Serious	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Fatal	0	0	0
Medically-Attended	81 (6.5)	156 (6.3)	237 (6.4)
Leading to discontinuation from study vaccine	0	0	0
Leading to discontinuation from participation in the study	0	1 (< 0.1)	1 (< 0.1)
Severe	1 (< 0.1)	4 (0.2)	5 (0.1)
Special interest of MIS-C	0	0	0
Unsolicited TEAEs related to study vaccination			
All	72 (5.8)	312 (12.6)	384 (10.3)
Serious	0	0	0
Fatal	0	0	0
Medically-attended	5 (0.4)	19 (0.8)	24 (0.6)
Leading to discontinuation from study vaccine	0	0	0
Leading to discontinuation from participation in the study	0	0	0
Severe	0	0	0
Special interest of MIS-C	0	0	0

Abbreviations: MIS-C = Multisystem Inflammatory Syndrome in Children
Note: Percentages are based on the number of safety subjects. A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Source: Study P203, Table 3.2.1.1.

2.5.5.2.2 Most Common Unsolicited Adverse Events

Unsolicited TEAE up to 28 days after any dose were more common in participants in the mRNA-1273 group (20.5%) compared to participants in the placebo group (15.9%) (Table 12).

Overall, the most commonly reported (≥2%) unsolicited TEAEs in all participants in the 28 days after any dose by preferred term (PT) were injection site lymphadenopathy (3.0%) and headache (2.4%). Imbalances in unsolicited TEAEs up to 28 days after any dose observed in the mRNA-1273 group were primarily attributable to events related to local injection site reactions in the general disorders and administration site conditions system organ class (SOC), which included events of injection site lymphadenopathy (4.3%), injection site erythema (1.9%), injection site induration (1.1%), injection site pain (1.1%), injection site pruritis (0.5%), injection site hypersensitivity (0.3%), and urticaria (0.2%) (Table 16). All of the reports of injection site lymphadenopathy were identified as axillary (underarm) swelling or tenderness ipsilateral to the side of the injection. The incidence of TEAEs of lymphadenopathy within 28 days of any dose was higher in the mRNA-1273 group (0.7%) than the placebo group (< 0.1%). The majority of these events were localized to the axilla, supraclavicular, or cervical regions. The imbalance in events of lymphadenopathy and injection site lymphadenopathy is consistent with the imbalance observed for solicited local ARs of axillary swelling/tenderness. An imbalance of unsolicitied TEAEs within 28 days of any dose in the skin and subcutaneous tissue disorders SOC was also observed (28 [1.1%] participants in the mRNA-1273 group and 7 [0.6%] in the placebo group) (Table 16). The most commonly reported unsolicited TEAEs within 28 days of any dose in this SOC in the mRNA-1273 group were urticaria (0.2%) followed by ptyriasis rosea (0.1%) and rash (0.1%) (Study P203, Table 3.2.2.1). Unsolicited TEAEs of COVID-19 within 28 days of any dose were more frequently reported in the placebo group (13 participants [1.0%]) than those in the mRNA-1273 group (5 participants [0.2%]) (Table 16).

Table 16: Incidence of Unsolicited TEAEs With Occurrence in ≥ 1% of Participants in Any Treatment Group up to 28 Days After Any Dose Classified by MedDRA Primary System Organ Class and Preferred Term, All Participants Aged ≥ 12 to < 18 Years (Safety Set)

Primary System Organ Class Preferred Term	mRNA-1273 (N = 2,486)		Placebo (N = 1,240)	
	Any n (%)	Severe n (%)	Any n (%)	Severe n (%)
Infections and infestations				
Adverse events in any PT[a]	76 (3.1)	1 (<0.1)	51 (4.1)	0
COVID-19	5 (0.2)	0	13 (1.0)	
Nervous system disorders				
Adverse events in any PT[a]	68 (2.7)	0	31 (2.5)	0
Headache	60 (2.4)		28 (2.3)	
Respiratory, thoracic, and mediastinal disorders				
Adverse events in any PT[a]	34 (1.4)	0	12 (1.0)	0
Gastrointestinal disorders				
Adverse events in any PT[a]	28 (1.1)	1 (<0.1)	20 (1.6)	0
Skin and subcutaneous tissue disorders				
Adverse events in any PT[a]	28 (1.1)	0	7 (0.6)	0

Primary System Organ Class Preferred Term	mRNA-1273 (N = 2,486)		Placebo (N = 1,240)	
	Any n (%)	Severe n (%)	Any n (%)	Severe n (%)
Musculoskeletal and connective tissue disorders				
Adverse events in any PT[a]	58 (2.3)		32 (2.6)	
Myalgia	29 (1.2)	0	14 (1.1)	0
General disorders and administration site conditions				
Adverse events in any PT[a]	250 (10.1)	0	50 (4.0)	0
Injection site lymphadenopathy	108 (4.3)		5 (0.4)	
Injection site erythema	48 (1.9)		3 (0.2)	
Fatigue	46 (1.9)		23 (1.9)	
Injection site induration	28 (1.1)		3 (0.2)	
Injection site pain	28 (1.1)		8 (0.6)	
Injury, poisoning, and procedural complications				
Adverse events in any PT[a]	55 (2.2)	1 (<0.1)	31 (2.5)	0

Abbreviations: COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Percentages are based on the number of safety participants. The Safety Set consists of all randomized participants who received any study injection. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.

[a] Participant experienced at least 1 TEAE within the SOC regardless of the MedDRA PT.

Source: Study P203 Table 3.2.2.1 and Table 3.2.8.

2.5.5.2.3 Treatment-Related Unsolicited Adverse Events

More unsolicited TEAEs were assessed by the Investigator as related to study treatment in the mRNA-1273 group than the placebo group. Treatment-related TEAEs up to 28 days after any injection were reported by 312 (12.6%) participants who received mRNA-1273 and 72 (5.8%) participants who received placebo (Table 12). In the mRNA-1273 group, treatment-related TEAEs reported in ≥ 2% of participants in the 28 days after any dose by PT included injection site lymphadenopathy (108 [4.3%] participants) and headache (55 [2.2%] participants) (Study P203, Table 3.2.3).

2.5.5.2.4 Unsolicited Severe Adverse Events

Severe AEs were defined as AEs that prevented the participant's daily activity and required intensive therapeutic intervention.

The incidence of unsolicited severe TEAEs in the 28 days after any dose was low (5 [0.1%] participants overall), and generally similar in the mRNA-1273 group (4 [0.2%]) compared with the placebo group (1 [<0.1%] participant) (Study P203, Table 3.2.1.1 and Table 3.2.8). All unsolicited severe TEAEs up to 28 days after any dose were reported in a single participant each and included one event of obstructive nephropathy in a participant receiving placebo and one event each of appendicitis, diarrhea, vomiting, drug-induced liver injury, testicular torsion, and

concussion in a total of 4 participants receiving mRNA-1273. No unsolicited severe TEAEs within 28 days of any dose were assessed by the Investigator as related to the IP (Study P203, Table 3.2.9). All unsolicited severe TEAEs were also MAAEs (Study P203, Table 3.2.10.3).

2.5.5.2.5 Unsolicited Medically-Attended Adverse Events

An MAAE was an AE that led to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (including unscheduled visits to the study site).

The incidence of MAAEs within 28 days of any dose was generally similar between participants who received mRNA-1273 (156 [6.3%] participants) and those who received placebo (81 [6.5%] participants; Table 12). The incidence of MAAEs within 28 days of any dose assessed by the Investigator as related to study treatment was higher in participants that received mRNA-1273 (19 [0.8%] participants) compared with placebo (5 [0.4%] participants) (Table 12 and Study P203, Table 3.2.11). The imbalance in treatment-related MAAEs within 28 days of injection is driven primarily by events in participants in the mRNA-1273 group of local injection site reactions of a variety of PTs within the general disorders and administrative site conditions SOC (5[0.2%] participants), events of lymphadenopathy (3 [0.1%] participants), and potential hypersensitivity reactions. The potential hypersensitivity reactions included events by PT of type IV hypersensitivity reaction, wheezing, photosensitivity reaction, pruritus, and urticaria reported in a single participant each in the mRNA-1273 group.

As of the data snapshot, the incidence of unsolicited MAAEs in the overall observation period, was generally similar in the mRNA-1273 and placebo groups (203 [8.2%] and 104 [8.4%] participants, respectively) (Study P203, Table 3.2.10.2). MAAEs of COVID-19 and Asymptomatic COVID-19 were reported more frequently in participants receiving placebo (20 [1.6%] and 11 [0.9%] participants respectively) than in participants receiving mRNA-1273 (6 [0.2%] and 9 [0.4%] participants respectively).

Severe unsolicited MAAEs within 28 days of any injection were the same events as those discussed in Section 2.5.5.2.4.

2.5.5.2.6 Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

2.5.5.2.6.1 Deaths

There were no SAEs with a fatal outcome in the placebo or mRNA-1273 groups. At the time of the data snapshot (08 May 2021), no deaths were reported in Study P203 (Study P203, Table 1.1 and Listing 4).

2.5.5.2.6.2 Other Serious Adverse Events

The incidence of any SAE in the 28 days after any dose was similar between the mRNA-1273 group (2 [<0.1%] participants) and placebo group (1 [<0.1%] participant) (Study P203, Table 3.2.1.1). The SAEs within 28 days after any injection reported in mRNA-1273 participants included one event of drug-induced liver injury in one participant and one event each of appendicitis, diarrhea, vomiting, and post-procedural fever in a second participant. The event of drug-induced liver injury was likely associated with sulfamethoxazole-trimethoprim and led to study discontinuation per physician decision and discussion with the Sponsor.

As of the data snapshot, the incidence of SAEs was similar in the mRNA-1273 (0.2%) and placebo groups (0.2%) during the overall study period (Table 17).

There were no SAEs assessed by the Investigator as related to study vaccine (Study P203, Listing 3.4).

Details for each participant with an SAE are available in Study P203 Listing 3.4 and narratives are provided in Module 5.3.5.1 for Study P203.

Table 17: Participant Incidence of Serious TEAE by SOC and PT in Overall Stage, All Participants Aged ≥ 12 to < 18 Years (Safety Set)

System Organ Class Preferred Term	Placebo (N = 1,240) n (%)	mRNA-1273 (N = 2,486) n (%)	Total (N = 3,726) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	2 (0.2)	6 (0.2)	8 (0.2)
Number of Unsolicited Adverse Events	2	9	11
Infections and infestations	0	1 (< 0.1)	1 (< 0.1)
Appendicitis	0	1 (< 0.1)	1 (< 0.1)
Psychiatric disorders	1 (< 0.1)	3 (0.1)	4 (0.1)
Suicidal ideation	0	2 (< 0.1)	2 (< 0.1)
Depression suicidal	0	1 (< 0.1)	1 (< 0.1)
Suicide attempt	1 (< 0.1)	0	1 (< 0.1)

System Organ Class Preferred Term	Placebo (N = 1,240) n (%)	mRNA-1273 (N = 2,486) n (%)	Total (N = 3,726) n (%)
Gastrointestinal disorders	0	1 (< 0.1)	1 (< 0.1)
Diarrhoea	0	1 (< 0.1)	1 (< 0.1)
Vomiting	0	1 (< 0.1)	1 (< 0.1)
Hepatobiliary disorders	0	1 (< 0.1)	1 (< 0.1)
Drug-induced liver injury	0	1 (< 0.1)	1 (< 0.1)
Renal and urinary disorders	1 (< 0.1)	0	1 (< 0.1)
Obstructive nephropathy	1 (< 0.1)	0	1 (< 0.1)
Congenital, familial and genetic disorders	0	1 (< 0.1)	1 (< 0.1)
Pectus excavatum	0	1 (< 0.1)	1 (< 0.1)

Abbreviations: PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event
Note: Percentages are based on the number of safety subjects. A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
MedDRA version 23.0.
Source: Study P203, Table 3.2.4.2.

2.5.5.2.6.3 Other Clinically Meaningful Unsolicited Adverse Events

2.5.5.2.6.3.1 Discontinuation From Investigational Product or Study Participation

One (< 0.1%) participant in the mRNA-1273 group discontinued from study vaccine due to a grade 1 MAAE of COVID-19 that began on Day 10 day after dose 1 of mRNA-1273 and was assessed by the Investigator as not related to IP (Study P203, Listing 1 and Listing 3.1). This participant is included in the disposition summary table and listing (Study P203, Table 1.1 and Listing 1) as discontinuing dosing due to an AE as the participant's "mother did not want the subject to receive the second dose of vaccine within 90 days of [participant's] COVID-19 diagnosis". There is a discrepancy between the disposition analysis and the analysis for unsolicited AEs leading to discontinuation from study vaccine because the "action taken" field in EDC for the AE of COVID-19 in this participant was "dose not changed" at the time of the data snapshot (Study P203, Listing 3.1 and Listing 3.5). One (< 0.1%) participant in the mRNA-1273 group discontinued the study 4 days after dose 2 due to a MAAE of grade 2 right eye swelling, which was assessed as not related to IP (Table 12 and Study P203, Listing 3.6). In addition, one participant did not receive dose 2 of mRNA-1273 and was discontinued from the study vaccine per physician decision and discussion with the Sponsor, following a grade 3 serious MAAE of drug-induced liver injury, likely secondary to sulfamethoxazole-trimethoprim, that was assessed by the Investigator as not related to IP. The participant was also discontinued from the study per physician decision. A narrative for this event is provided in Module 5.3.5.1 for Study P203.

2.5.5.2.6.3.2 Hypersensitivity

All unsolicited treatment-emergent adverse events (TEAEs) within the narrow and the narrow and broad hypersensitivity standard Medical Dictionary for Regulatory Activities queries (SMQs) were summarized. There were no reports of anaphylactic reaction assessed as related to IP in participants receiving mRNA-1273.

The number of participants reporting events within the narrow hypersensitivity SMQ and the combined narrow and broad hypersensitivity SMQ in the overall stage was higher in the mRNA-1273 group (1.6% and 1.9%) than the placebo group (0.5% and 0.8%), respectively (Study P203, Table 3.3.2 and Table 3.3.2.1). Within the mRNA-1273 group, 46 participants experienced a total of 49 events of potential hypersensitivity reactions. Of these 49 events within the narrow and broad hypersensitivity SMQ reported in the mRNA-1273 group, 27 TEAEs (55.1%) were assessed by the Investigator as related to IP (Study P203, Listing 3.10 and Table 3.3.2.2).

The most commonly reported events within the narrow and broad hypersensitivity SMQ in the mRNA-1273 group by PT were injection site hypersensitivity (0.3%), injection site urticaria (0.2%), rash (0.2%) and urticaria (0.2%).

Six participants (4 [0.2%] participant in the mRNA-1273 group and 2 [0.2%] participants in the placebo group) reported a hypersensitivity-related event < 24 hours after any injection. One (< 0.1%) participant in the mRNA-1273 reported a MAAE of grade 2 contact dermatitis on the right eye < 24 hours after the second injection, which was assessed as not related to IP. One (<0.1%) participant in the mRNA-1273 group reported a grade 1 unsolicited TEAE of rash vesicular with minimal additional details provided that was assessed by the Investigator as related to IP. The remaining 2 participants in the mRNA-1273 group reported events of urticaria (2 [< 0.1%] participants), one event localized in the groin region was assessed as related to IP and one event in a second participant which was assessed by the Investigator as not related to IP (Study P203, Table 3.3.2.2 and Listing 3.10).

The incidence of potential hypersensitivity events in the mRNA-1273 group (0.4%) was higher than the placebo group (<0.1%) with onset between Day 2 to Day 7. These events were primarily non-specific rashes assessed as not related to IP or local injection site reactions. One (<0.1%) participant in the mRNA-1273 group, who had experienced an event of angioedema not related to IP after the first injection, had a Grade 1 non-serious TEAE of eyelid edema (verbatim: left eyelid edema). The event of eyelid edema was reported with onset on Day 3 after the second injection after tree nut exposure at school, resolved the same day (after Benadryl and methylprednisolone had been administered) and was also assessed as not related to IP. One

(<0.1%) participant in the mRNA-1273 group had a Grade 2 non-serious MAAE of eye swelling (verbatim: swollen right eye and vision was obstructed) with onset on Day 4 after the second injection that was assessed as not related to IP and led to discontinuation from participation in the study. Additional single events each of rash pruritic and urticaria were reported in 2 different participants receiving mRNA-1273 which were assessed as related to IP (Study P203, Table 3.3.2.2 and Listing 3.10).

The incidence of potential hypersensitivity events in the mRNA-1273 group (0.8%) was higher than the placebo group (<0.1%) with onset between Day 8 and Day 14, which was primarily due to delayed local injection site reactions. One (<0.1%) participant in the mRNA-1273 group experienced a grade 1 non-serious MAAE of angioedema with facial swelling after eating a nut on Day 10 after the first injection that was assessed by the Investigator as not related to IP. The participant reportedly received one dose of oral steroids, had no other symptoms and the event resolved by the following day.

Potential hypersensitivity reactions were observed ≥ 15 days after any injection and were reported by 10 (0.3%) participants aged ≥ 12 to ≤ 18 years (7 [0.3%] participants in the mRNA-1273 group and 3 [0.2%] participants in the placebo group) (Study P203, Table 3.3.2.2). One participant in the mRNA-1273 group experienced an anaphylactic reaction that occurred on Day 21 after the second injection of mRNA-1273 due to a MAAE of grade 2 anaphylaxis to tree nuts that was assessed as not related to IP (Study P203, Listing 3.10). There were no reports of anaphylactic reaction assessed as related to IP in participants receiving mRNA-1273. The other events ≥ 15 days after any injection were primarily non-specific rashes. These events were generally not assessed as related to IP (Study P203, Listing 3.10).

In general, while events of potential hypersensitivity reactions were reported more frequently in participants receiving mRNA-1273 than placebo, the majority of these events reflected local injection site reactions, including delayed injection site reactions, or were non-specific rashes or assessed as not related to IP.

2.5.5.2.6.3.3 Analysis of Adverse Events of Special Interest

2.5.5.2.6.3.3.1 Multisystem Inflammatory Syndrome in Children

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. In Study P203, MIS-C was considered an AESI. As such, any case had to be reported to the Sponsor or designee immediately and in all circumstances

within 24 hours of becoming aware of the event via the EDC system throughout the entire study period.

There were no cases of MIS-C reported in Study P203 (Study P203, Table 3.2.12.2).

2.5.5.2.7 Subgroup Analyses of Unsolicited Adverse Reactions

2.5.5.2.7.1 Age Group

There were no notable differences in unsolicited AEs observed between participants aged 12 to < 16 years and participants aged 16 to < 18 years (Study P203, Table 3.2.1.1, Table 3.2.1.1.4, Table 3.2.1.3, Table 3.2.2.1, Table 3.2.2.1.4, Table 3.2.3, Table 3.2.4.1, Table 3.2.4.2, Table 3.2.5, Table 3.2.6, Table 3.2.7.1, Table 3.2.8, Table 3.2.10.1, Table 3.2.10.2, Table 3.2.10.3, Table 3.2.11, Table 3.2.12.1, Table 3.2.12.2, Table 3.3.1).

2.5.5.2.7.2 Baseline SARS-CoV-2 Status

The incidence of unsolicited TEAEs up to 28 days after any dose among participants with positive baseline status for SARS-CoV-2 was 15.0% in the mRNA-1273 group and 10.1% in the placebo group. Among participants with negative baseline status for SARS-CoV-2, the incidence of unsolicited TEAEs up to 28 days after any dose was 20.8% in the mRNA group and 16.1% in the placebo group (Study P203, Table 3.2.1.1.3, Table 3.2.1.1.5, and Table 3.2.2.1.3).

The incidence of treatment-related unsolicited TEAEs and MAAEs in participants with negative baseline status for SARS-CoV-2 was higher than in participants with positive baseline status for SARS-CoV-2 in the mRNA-1273 group (13% and 0.8% vs 6.1% and 0%, respectively) (Study P203, Table 3.2.1.1.3). The small number of baseline positive participants limits definitive conclusions.

2.5.5.2.8 Other Safety Data

2.5.5.2.8.1 Pregnancies

There have been no pregnancies reported during Study P203 through the data snapshot date (Study P203, Table 1.1 and Listing 5.1).

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 Benefits

Vaccine effectiveness in adolescents aged ≥ 12 to <18 years was inferred by demonstrating noninferiority of both GM serum nAb and seroresponse rate from adolescents compared with those from young adults enrolled in Study P301 (aged ≥ 18 to ≤ 25 years). The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the 1.5-fold noninferiority criterion (ie, lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb seroresponse rates at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the 10% noninferiority criterion (lower bound of the 95% of the seroresponse rate difference is > -10%). The analyses by age group and baseline SARS-CoV-2 status yielded similar results.

In addition, direct clinical benefit in the reduction in COVID-19 cases was demonstrated. COVID-19, defined using either of 2 case definitions (including the definition utilized in the adult efficacy study), prevented disease starting 14 days after dose 1. Applying the same case definition and interval (starting 14 days after dose 2) as that used in the adult efficacy study, VE was 100% (lower bound, 95%CI 28.9%), with 4 cases in the placebo group and 0 cases in the vaccine group.

The CDC case definition of COVID-19, requiring only one symptom and laboratory confirmation, allowed assessment of VE against a higher number of cases as expected, and using a definition well-suited to adolescence for whom COVID-19 is typically less symptomatic. Applying this case definition, VE of 93.3% (95% CI: 47.9%, 99.9%) was demonstrated 14 days after dose 2. This benefit was also evident starting as soon as 14 days after dose 1, with a VE of 92.7% (95% CI: 67.8, 99.2), based on accrual of a total of 15 cases (2 cases [3.828 per 1,000 person-years] in mRNA-1273 group and 13 cases [52.47 per 1,000 person-years] in the placebo group.

Accordingly, VE in adolescents against COVID-19 cases was consistent with efficacy of mRNA-1273 demonstrated in adults, whether assessed using more or less symptomatic case definitions and following 1 or 2 doses. Across both definitions and assessment intervals, the lowest boundary of the 95% CI for VE exceeded 28%.

An additional benefit, while less direct, is the VE against asymptomatic SARS-CoV-2 infection. While this adolescent study was not designed to systematically and comprehensively evaluate VE against asymptomatic infection, collection of periodic mucosal samples and serology allowed an assessment of VE against this parameter. VE against asymptomatic infection occurring at least

14 days after dose 2 was 39.2% (95% CI: -0.247, 0.697) and starting 14 days after dose 1 was 59.5% (95% CI: 0.284, 0.773). VE against all SARS-CoV-2 infection (regardless of symptoms) based on confirmatory testing starting 14 days after dose 2 was 55.7% (95% CI: 0.168, 0.7464) and starting 14 days after dose 1 was 69.8% (0.499, 0.821).

In summary, vaccine effectiveness was successfully inferred in adolescents by immunobridging to young adults shown to be protected from COVID-19, and direct benefit was demonstrated by VE measured against COVID-19 and against SARS-CoV-2 infections. As COVID-19 has been associated with severe sequelae in children and adolescents, including MIS-C, the reduction in disease and infection achieved by mRNA-1273 would be expected to lead to reduced rates of disease sequelae as well.

2.5.6.2 Risks

COVID-19 Vaccine Moderna is an investigational vaccine and is not FDA-approved for prevention of COVID-19 in any age group.

The safety of mRNA-1273 in adolescents aged ≥ 12 through <18 years is based on data from Phase 2/3 Study P203 using a 08 May 2021 data snapshot. The safety analysis set of 3,726 participants, included 2,486 study mRNA-1273 participants with a median study follow-up duration of 53 days after dose 2. In the mRNA-1273 group, the median follow-up time after dose 1 was 83.5 days and the median follow-up time after dose 2 was 53 days.

Solicited local ARs occurred more frequently in the mRNA-1273 group after dose 1 and dose 2. Pain was the most common local solicited AR. The majority of the solicited local ARs in the mRNA-1273 group occurred within the first 1 to 2 days after each dose and generally persisted for a median of 3 days. Solicited systemic ARs were also more common in the mRNA-1273 group and were more common after dose 2. The most common solicited systemic ARs were headache, fatigue, myalgia and chills. The majority of solicited systemic ARs were grade 1 to grade 2 in severity; however, there was a higher occurrence of grade 3 or higher solicited reactions in the mRNA-1273 group. Fever occurred more often in the mRNA-1273 group after any dose. The majority of the solicited local and systemic ARs in the mRNA-1273 group occurred within the first 1 to 2 days after each dose and generally persisted for a median duration of 1 to 3 days. Solicited local ARs that persisted beyond 7 days were more frequently reported in the mRNA-1273 group after the first dose; while solicited systemic ARs that persisted beyond 7 days were similarly reported in the mRNA-1273 and placebo groups.

The most commonly reported unsolicited TEAE in all participants in the 28 days after dose by PT was injection site lymphadenopathy. Imbalances in unsolicited TEAEs up to 28 days after any

dose observed in the mRNA-1273 group were primarily attributable to events related to reactogenicity in the general disorders and administration site conditions SOC, which included events of injection site lymphadenopathy, injection site erythema, injection site induration, injection site pain, injection site pruritis, injection site hypersensitivity, and injection site urticaria. There were no reports of anaphylactic reaction assessed as related to IP in participants receiving mRNA-1273. Overall, imbalances in events of lymphadenopathy and injection site reactions were comparable to the TEAEs observed in adults (participants aged ≥ 18 years in Study P301).

More unsolicited TEAEs were assessed by the Investigator as related to study treatment in the mRNA-1273 group. The incidence of unsolicited severe TEAEs in the 28 days after any dose was low and no severe TEAEs were assessed by the Investigator as related to the IP. The incidence of MAAEs within 28 days of injection was generally similar between mRNA-1273 and placebo groups. The incidence of treatment-related MAAEs up to 28 days after any injection was higher in the mRNA-1273 group (0.8%) compared to placebo (0.4%).

There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, no pregnancies, and no cases of MIS-C reported as of the data snapshot.

There were also no notable differences in solicited ARs and unsolicited AEs observed between participants aged ≥ 12 to < 16 years and participants aged ≥ 16 to < 18 years.

2.5.6.3 Risk-Benefit Assessment

There is an urgent public health need for further use of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19, which has more recently increased in younger age groups as more adults have been vaccinated. In addition to the direct medical impact of COVID-19 upon adolescents, this group also likely contributes to sustained household and community transmission of SARS-CoV-2. Immunobridging analyses infer vaccine effectiveness in adolescents aged ≥ 12 to < 18 years compared to young adults aged ≥ 18 to ≤ 25 years (in whom efficacy has been demonstrated). Direct clinical benefit is supported by VE against COVID-19 defined by 2 case definitions and measured as early as 14 days after the first dose. mRNA-1273 also reduced SARS-CoV-2 infections (regardless of symptoms) as well as asymptomatic infections.

There have been no emergent safety concerns in adolescents (aged ≥ 12 to ≤ 18 years) and the AE profile of mRNA-1273 consists primarily of grade 1 to grade 2 reactogenicity lasting 1 to 3 days. Overall, local reactogenicity was slightly higher and systemic reactogenicity was slightly lower for mRNA-1273 in adolescents than compared with that observed in the adult

mRNA-1273 P301 study. Vaccination with mRNA-1273 generally resulted in transient local injection site and systemic reactions. The incidence of unsolicited TEAEs and MAAEs assessed by the Investigator as related to study treatment were more common in the mRNA-1273; however, no severe TEAEs within 28 days of any injection or SAEs during the study were assessed by the Investigator as related to mRNA-1273. There were no deaths reported in Study P203. The overall safety profile observed in the adolescent study (Study P203) was generally consistent with the findings to date in the Phase 3 Study P301 in adults aged ≥ 18 years.

The data presented in this submission include inferred effectiveness and direct benefit and support the extension of the use of COVID-19 Vaccine Moderna to adolescents aged ≥ 12 through < 18 years for the prevention of COVID-19. Results are generally consistent with the efficacy and safety profile observed in adults aged ≥ 18 years. The immunogenicity, safety, and efficacy data from Study P203, support administration of mRNA-1273 as two 100 µg doses 28 days apart in adolescents aged ≥ 12 through < 18 years. Considering the ongoing public health emergency due to SARS-CoV-2, the burden of disease in adolescents, and the effectiveness and safety data from clinical Study P203 presented herein, the Sponsor considers that the known and potential benefits of the COVID-19 Vaccine Moderna outweigh the known and potential risks for the COVID-19 Vaccine Moderna.

2.5.7 REFERENCES

American Academy of Pediatrics (AAP) and the Children's Hospital Association (CHA). Children and COVID-19: State Data Report (version February 18, 2021). Retrieved from: https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%202.18.21%20FINAL.pdf (accessed 21 May 2021).

Ayoub HH, Chemaitelly H, Seedat S, Mumtaz GR, Makhoul M, Abu-Raddad LJ () Age could be driving variable SARS-CoV-2 epidemic trajectories worldwide. PLoS ONE 2020 15(8): e0237959. Available from: https://doi.org/10.1371/journal.pone.0237959 (accessed 21 May 2021).

Baron JE, Goldstein EG, Wallace CT. Suffering in silence: How COVID-19 school closures inhibit the reporting of child maltreatment. J. Public Econ. Abailable at: https://doi.org/10.1016/j.jpubeco.2020.104258. (accessed 24 May 2021).

Boehmer TK, DeVies J, Caruso E, van Santen KL, Tang S, Black CL, et al. Changing age distribution of the COVID-19 pandemic — United States, May-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69(39):1404-1409.

Centers for Disease Control and Prevention (CDC). 2021a. Coronavirus Disease 2019 (COVID-19). Retrieved from: https://covid.cdc.gov/covid-data-tracker/#demographics. (accessed 2021 June 01).

Centers for Disease Control and Prevention (CDC). 2021b. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Retrieved from: https://www.cdc.gov/mis-c/hcp/. (accessed 2021 May 31).

Centers for Disease Control and Prevention (CDC). 2020a. Coronavirus Disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/. (accessed 20 Nov 2020).

Centers for Disease Control and Prevention (CDC). 2020b. Coronavirus Disease 2019 (COVID-19). Retrieved from: https://www.cdc.gov/coronavirus/2019-ncov/symptomstesting/symptoms.html (accessed 2021 Apr 26).

Chen Y, Lu S, Jia H, Deng Y, Zhou J, Huang B, et al. A novel neutralizing monoclonal antibody targeting the N-terminal domain of the MERS-CoV spike protein. Emerg Microbes Infect. 2017 May 24;6(5):e37.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus in Wuhan, China: a descriptive study. The Lancet. 2020 Feb 15;395(10223):507-13.

Corti D, Zhao J, Pedotti M, Simonelli L, Agnihothram S, Fett C, et al. Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus. Proc Natl Acad Sci U S A. 2015 Aug 18;112(33):10473-8.

Davies N, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CAB, et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. London, United Kingdom: Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine; 2021. Available at: https://cmmid.github.io/topics/covid19/uk-novel-variant.html (accessed 21 May 2021).

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Development and licensure of vaccines to prevent COVID-19. June 2020 [cited 2020 Nov 16] [24 screens]. Available from: https://www.fda.gov/media/139638/download.

Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol. 2012 Jun 22;12(7):479-91.

European Centre for Disease Prevention and Control (ECDC). 2020. COVID-19 in children and the role of school settings in transmission - first update. Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/children-and-school-settings-covid-19-transmission (accessed 21 May 2021)

European Centre for Disease Prevention and Control (ECDC). 2021a. COVID-19 Surveillance Report. Available at: https://covid19-surveillance-report.ecdc.europa.eu/#Weekly_surveillance_summary (accessed 21 May 2021).

European Centre for Disease Prevention and Control (ECDC). 2021b. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission (accessed 23 May 2021).

Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. G. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/. Accessed on 17 May 2021.

Fechter P, Brownlee GG. Recognition of mRNA cap structures by viral and cellular proteins. J Gen Virol. 2005 May;86(Pt 5):1239-49.

Forbes H, Morton CE, Bacon S, McDonald HI, Minassian C, Brown JP, et al. Association between living with children and outcomes from covid-19: OpenSAFELY cohort study of 12 million adults in England. BMJ. 2021;372:n628. Available at: https://www.bmj.com/content/bmj/372/bmj.n628.full.pdf (accessed 21 May 2021).

Han MS, Choi EH, Chang SH, et al. Clinical characteristics and viral RNA detection in children with coronavirus disease 2019 in the Republic of Korea. JAMA Pediatr 2020. Available at: https://doi.org/10.1001/jamapediatrics.2020.3988 (accessed 23 May 2021).

Hay James A, Haw David J, Hanage William, Metcalf C Jessica E, Mina Michael. Implications of the age profile of the novel coronavirus. Harvard Library Office of Schloarly Communication (2020). Available from: http://nrs.harvard.edu/urn-3:HUL.InstRepos:42639493. (accessed 21 May 2021).

Hurst JH, Heston SM, Chambers HN, et al. SARS-CoV-2 infections among children in the biospecimens from respiratory virus-exposed kids (BRAVE kids) study [preprint]. medRxiv 2020; Available at: https://doi.org/10.1101/2020.08.18.20166835 (accessed 23 May 2021).

Hyde Z. COVID-19, children and schools: overlooked and at risk. Med J Aust. 2020 213(10:444-446.e1. Available at: https://doi.org/10.5694/mja2.50823 (accessed 23 May 2021).

Johnson RF, Bagci U, Keith L, Tang X, Mollura DJ, Zeitlin L, et al. 3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012. Virology. 2016 Mar;490:49-58.

Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity. 2005 Aug;23(2):165-75.

Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 1-July 25, 2020. MMWR. 2020;69(32):1081-1088.

Kim Y, Lee H, Park K, Park S, Lim JH, So MK, et al. Selection and characterization of monoclonal antibodies targeting middle east respiratory syndrome coronavirus through a human synthetic fab phage display library panning. Antibodies (Basel). 2019 Jul 31;8(3):42.

Kozak M. An analysis of vertebrate mRNA sequences: intimations of translational control. J Cell Biol. 1991 Nov;115(4):887-903.

Lee S, Kim T, Lee E, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. JAMA Intern Med 2020; Available at: https://doi.org/10.1001/jamainternmed.2020.3862 (accessed 23 May 2021).

Leeb RT, Price S, Sliwa S, Kimball A, Szucs L, Caruso E, et al. COVID-19 trends among school aged children — United States, March 1-September 19 2020. MMWR Morb Mortal Wkly Rep.

Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. MMWR Morb Wkly Rep. 2021;70(3):88–942020;69(39):1410-15.

Licciardi F, Giani T, Baldini L, Favalli EG, Caporali R, Cimaz R. COVID-19 and what pediatric rheumatologists should know: a review from a highly affected country. Pediatr Rheumatol Online J. 2020 Apr 22;18(1):35.

Monod M, Blenkinsop A, Xi, X, Hebert D, Bershan, S, Tietze S, et al. Age groups that sustain resurging COVID-19 epidemics in the United States. Science 2021;371(6536), eabe8372. DOI: 10.1126/science.abe8372.

Oliver S. EtR framework: Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12-15 years. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/04-COVID-Oliver-508.pdf. Accessed on 31 May 2021.

Rothan HA, Byrareddy NS. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.

Rozenski J, Crain PF, McCloskey JA. The RNA Modification Database: 1999 update. Nucleic Acids Res. 1999;27(1):196-7.

Schwartz NG, Moorman AC, Makaretz A, Chang KT, Chu VT, Szablewski CM, et al. Adolescent with COVID-19 as the source of an outbreak at a 3-week family gathering — four states, June July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(40):1457–1459.

Sargent TH, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr. 2020; 174(9):902–3.

Scientific Advisory Group for Emergencies (SAGE). Children's Task and Finish Group: Update on Children, Schools and Transmission. London, United Kingdom. SAGE, 2020

Shen KL, Yang YH, Jiang RM, Wang TY, Zhao DC, Jiang Y, Lu XX, et al. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). World J Pediatr. 2020 Jun:16(3)232-39.

Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill 2020; 25:2001483.

Somekh I, Boker LK, Shohat T, Pettoello-Mantovani M, Simões EAF, Somekh E. Comparison of COVID-19 Incidence Rates Before and After School Reopening in Israel. JAMA Netw Open. 2021;4(4):e217105. doi:10.1001/jamanetworkopen.2021.7105.

Swedo E, Idaikkadar N, Leemis R, Dias T, Radhakrishnan L, Stein Z, et al. Trends in U.S. Emergency Department Visits Related to Suspected or Confirmed Child Abuse and Neglect Among Children and Adolescents Aged <18 Years Before and During the COVID-19 Pandemic — United States, January 2019–September 2020. MMWR Morb Mortal Wkly Rep. 2020 / 69(49);1841–1847. Int J Ment Health Nurs. 2020 May 7 : 10.1111/inm.12735. doi: 10.1111/inm.12735 [Epub ahead of print]

UNICEF COVID-19 and children. UNICEF data hub March 2020. Available at: https://data.unicef.org/covid-19-and-children/ (accessed 23 May 2021).

Usher K, Bhullar N, Durkin J, Gyamfi N, Jackson D. Family violence and COVID-19: Increased vulnerability and reduced options for support. Int J Ment Health Nurs. 2020 29(4):549–552. Available at: https://doi.org/10.1111/inm.12735 (accessed 24 May 2021).

Vlachos J, Hertegård E, B. Svaleryd H. The effects of school closures on SARS-CoV-2 among parents and teachers. Proceedings of the National Academy of Sciences. 2021;118(9):e2020834118. Available at: http://www.pnas.org/content/118/9/e2020834118.abstract (accessed 21 May 2021).

Wang L, Shi W, Joyce MG, Modjarrad K, Zhang Y, Leung K, et al. Evaluation of candidate vaccine approaches for MERS-CoV. Nat Commun. 2015 Jul 28;6:7712.

Wang L, Shi W, Chappell JD, Joyce MG, Zhang Y, Kanekiyo M, et al. Importance of neutralizing monoclonal antibodies targeting multiple antigenic sites on the middle east respiratory syndrome coronavirus spike glycoprotein to avoid neutralization escape. J Virol. 2018 Apr 27;92(10):e02002-17.

Widjaja I, Wang C, van Haperen R, Gutiérrez-Álvarez J, van Dieren B, Okba NMA, et al. Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. Emerg Microbes Infect. 2019;8(1):516-30.

World Health Organization (WHO) (2020a). (Data reported as of 13 Nov 2020). Weekly Operational Update on COVID-19. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---13-november-2020. (accessed 14 May 2021).

World Health Organization (WHO) (2020b). Dashboard. 16 Nov 2020. Available from: https://covid19.who.int/. (accessed 14 May 2021).

World Health Organization (WHO) (2020c). Scientific Brief. Transmission of SARS-CoV-2: implications for infection prevention precautions. 09 Jul 2020. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions. (accessed 15 Nov 2020).

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hseih CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367:1260-3.

Yu X, Zhang S, Jiang L, Cui Y, Li D, Wang D, et al. Structural basis for the neutralization of MERS-CoV by a human monoclonal antibody MERS-27. Sci Rep. 2015 Aug 18;5:13133.