9 BENEFITS AND RISKS CONCLUSIONS

9.1 Benefit-Risk Analysis Evaluation

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

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

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

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

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

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

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

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

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

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

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

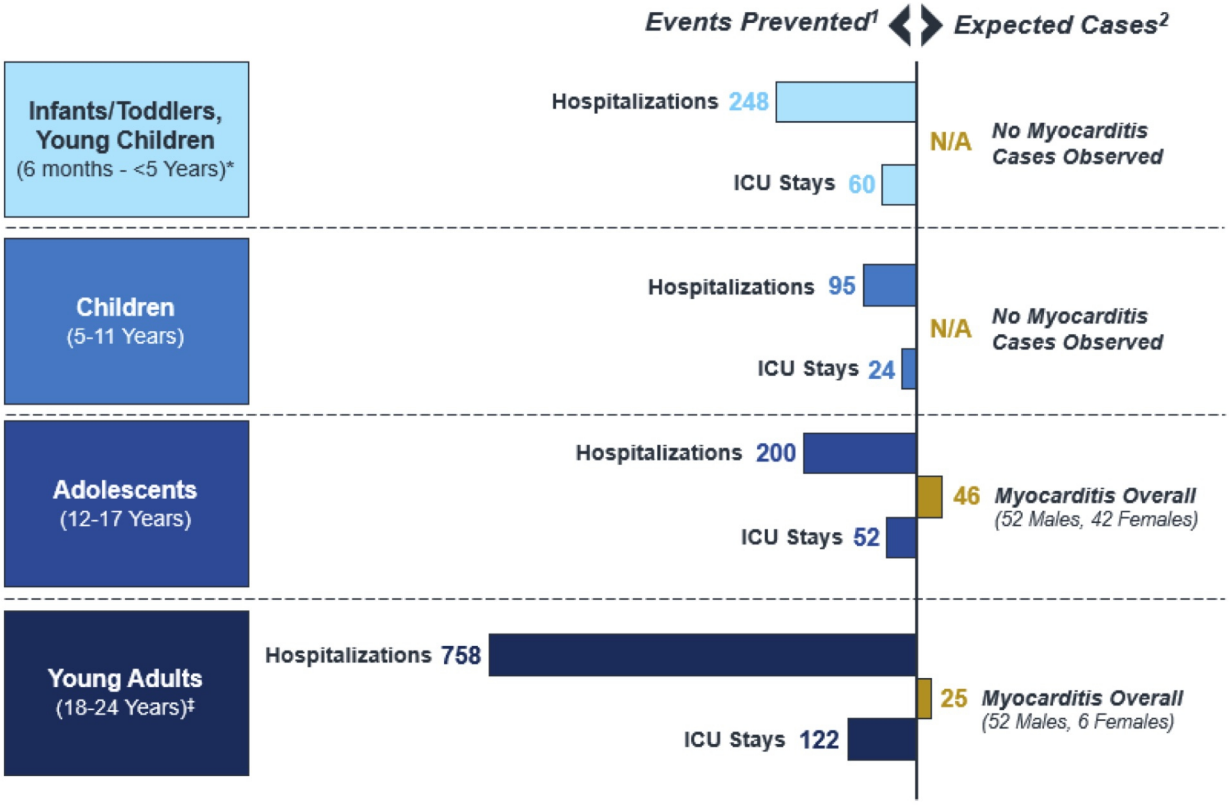
the safety profile of the mRNA-1273 vaccine is closely monitored on a continuous basis through post-market surveillance and a range of post-approval studies. The post-authorization safety data show that mRNA-1273 vaccine is well tolerated.

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

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

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

Figure 30: mRNA-1273 Benefit-Risk Assessment



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

9.2 Conclusions

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

11.2 Appendix: Benefit-Risk Assessment Methodology

The benefit-risk assessment methodology was as follows:

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

a. the projected 2021 US population (CDC Wonder)

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

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

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

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

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

   iv. All data sources were accessed 22 May 2022.

2. Benefit model assumptions and parameters tested:

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

   b. The following parameters were tested in the model:

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

      ii. Doses: set at 1 million

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

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

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