Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents

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ABSTRACT

BACKGROUND

The incidence of coronavirus disease 2019 (Covid-19) among adolescents between 12 and 17 years of age was approximately 900 per 100,000 population from April 1 through June 11, 2021. The safety, immunogenicity, and efficacy of the mRNA-1273 vaccine in adolescents are unknown.

METHODS

In this ongoing phase 2–3, placebo-controlled trial, we randomly assigned healthy adolescents (12 to 17 years of age) in a 2:1 ratio to receive two injections of the mRNA-1273 vaccine (100 μg in each) or placebo, administered 28 days apart. The primary objectives were evaluation of the safety of mRNA-1273 in adolescents and the noninferiority of the immune response in adolescents as compared with that in young adults (18 to 25 years of age) in a phase 3 trial. Secondary objectives included the efficacy of mRNA-1273 in preventing Covid-19 or asymptomatic severe acute respiratory syndrome coronavirus 2 infection.

RESULTS

A total of 3732 participants were randomly assigned to receive mRNA-1273 (2489 participants) or placebo (1243 participants). In the mRNA-1273 group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 93.1% and 92.4%, respectively), headache (in 44.6% and 70.2%, respectively), and fatigue (in 47.9% and 67.8%, respectively); in the placebo group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 34.8% or 30.3%, respectively), headache (in 38.5% and 30.2%, respectively), and fatigue (in 36.6% and 28.9%, respectively). No serious adverse events related to mRNA-1273 or placebo were noted. The geometric mean titer ratio of pseudovirus neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, −1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group.

CONCLUSIONS

The mRNA-1273 vaccine had an acceptable safety profile in adolescents. The immune response was similar to that in young adults, and the vaccine was efficacious in preventing Covid-19. (Funded by Moderna and the Biomedical Advanced Research and Development Authority; Teen COVE ClinicalTrials.gov number, NCT04649151.)

DURING THE GLOBAL CORONAVIRUS DIS-ease 2019 (Covid-19) pandemic, which has resulted in considerable illness and death around the world,[1] the incidence of Covid-19 among adolescents between 12 and 17 years of age was approximately 900 per 100,000 population from April 1 through June 11, 2021.[2] Although Covid-19 illness is generally milder in children than adults, children can have severe disease leading to hospitalization.[3,4] Approximately one third of adolescents hospitalized because of Covid-19 were admitted to an intensive care unit, and 4.9% received invasive mechanical ventilation.[4] Multisystem inflammatory syndrome in children (MIS-C) is a serious but rare condition associated with Covid-19 that occurs in children who present with fever, rash, conjunctival injection, and gastrointestinal symptoms.[5] The opening of schools may indirectly be associated with a 26% increase in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission from children and teenagers.[6] Children continue to be disproportionately affected by the Covid-19 pandemic in social costs (stressors, school closures, loss of social support, and child maltreatment).[7-10]

The mRNA-1273 vaccine (Moderna) is a lipid nanoparticle dispersion containing an mRNA that encodes the SARS-CoV-2 S glycoprotein stabilized in the prefusion conformation. The safety, immunogenicity, and efficacy of mRNA-1273 have been evaluated in several ongoing clinical trials involving adults.[11-15] In the Coronavirus Efficacy (COVE) trial, a large phase 3, observer-blinded, placebo-controlled trial involving adults (≥18 years of age), the mRNA-1273 vaccine was safe and highly effective in preventing Covid-19.[15] On the basis of these findings, mRNA-1273 received emergency use authorization from the Food and Drug Administration (FDA) in December 2020 for use in adults 18 years of age or older.[16] The COVE trial is currently in an open-label follow-up phase implemented after the emergency use authorization was granted. We conducted a phase 2–3 trial to evaluate the use of mRNA-1273 in adolescents between the ages of 12 and 17 years of age. Here, we report the interim results of the Teen COVE trial, an observer-blinded, placebo-controlled evaluation of the safety, immunogenicity, and efficacy of the vaccine.

METHODS

TRIAL OVERSIGHT

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, and the protocol (available with the full text of this article at NEJM.org) was approved by regulatory and institutional committees. All the participants provided written informed consent.

The trial sponsor, Moderna, was responsible for the overall trial design (with input from the Biomedical Advanced Research and Development Authority), site selection and monitoring, and data analysis. Investigators were responsible for data collection. Two medical writers funded by Moderna assisted in drafting the manuscript for submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS, RANDOMIZATION, AND BLINDING

Male and female adolescents between the ages of 12 and 17 years were eligible for enrollment if they were considered to be in good general health by the 26 U.S. investigators (listed in the Supplementary Appendix, available at NEJM.org). Exclusion criteria included travel outside of the United States in the 28 days before screening, pregnancy or breast-feeding, acute illness or fever 24 hours before or at screening, previous administration of an investigational vaccine against SARS-CoV-2, or current treatment with investigational agents for prophylaxis against Covid-19. The trial did not exclude participants with previous anaphylaxis or serious allergic reactions to foods, medications, or both other than to a vaccine. Full inclusion and exclusion criteria are provided in the protocol.

Participants were randomly assigned in a 2:1 ratio to receive two injections of either mRNA-1273 vaccine (each injection containing 100 μg, for a total dose of 200 μg) or placebo (saline), 28 days apart (Fig. 1). Randomization was performed with the use of a centralized interactive response technology system. The investigators and trial staff, participants, site monitors, and sponsor personnel (or its designees) were unaware of the trial vaccine administered until unblinding of the trial data as specified in the protocol; how-
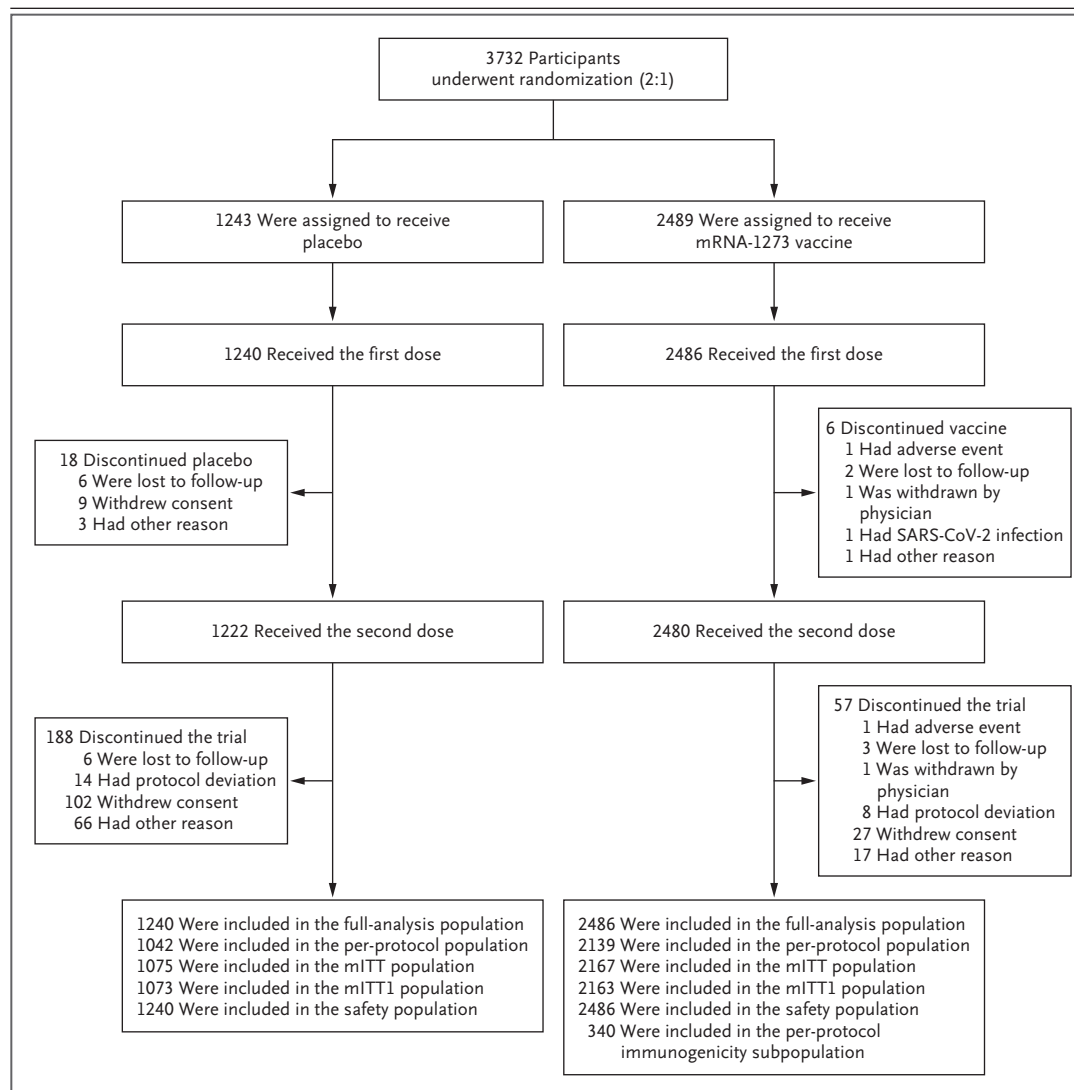
Figure 1. Randomization and Analysis Populations.

The full analysis population consisted of all participants who had undergone randomization and received at least one injection of mRNA-1273 or placebo; the per-protocol population consisted of all participants in the full analysis population who had received planned injections of mRNA-1273 or placebo, complied with the timing of the second injection, had no immunologic and virologic evidence of previous Covid-19 at baseline, and had no major protocol deviations; the modified intention-to-treat (mITT) population consisted of all participants in the full analysis population who had no serologic or virologic evidence of previous SARS-CoV-2 infection before the first injection (both a negative reverse-transcriptase–polymerase-chain-reaction [RT-PCR] test for SARS-CoV-2 and a negative serologic test based on binding antibodies specific to SARS-CoV-2 nucleocapsid) at baseline; the mITT1 population consisted of all participants in the mITT population with the exclusion of those who received the incorrect injection; and the safety population consisted of all participants who received at least one injection. The per-protocol immunogenicity subpopulation consisted of randomly selected participants who had received the planned injections of mRNA-1273 or placebo according to schedule, complied with the timing of the second injection, had no immunologic and virologic evidence of previous Covid-19 at baseline, complied with the immunogenicity testing schedule, and had no major protocol deviations that affected the key or critical data; participants who were seropositive at baseline were excluded from the per-protocol immunogenicity subpopulation. Two participants who received placebo did not receive the second injection and then discontinued the trial later for a reason listed as "other." One participant who received mRNA-1273 did not receive the second injection and continued in the trial.

ever, pharmacists and vaccine administrators who were involved in injection preparation and administration and who had no other role in trial conduct were aware of these assignments.

SAFETY ASSESSMENTS

The primary safety objective was the safety and reactogenicity of a total dose of 200 μg of mRNA-1273 administered in two injections 28 days apart (Table S1 in the Supplementary Appendix). Participants recorded solicited local and systemic adverse reactions daily through 7 days after each injection by completing an electronic diary. Unsolicited adverse events from days 1 through 28 after each injection and medically attended adverse events, adverse events leading to withdrawal, serious adverse events, and data on MIS-C were collected until end of the trial. A data and safety monitoring board conducted periodic unblinded data reviews.

EFFICACY ASSESSMENTS

The primary immunogenicity objective was to infer the efficacy of mRNA-1273 in adolescents by comparing serum antibody responses, as measured for both primary objectives: the geometric mean titer ratio of pseudovirus neutralizing antibody titers and serologic response in adolescents 28 days after receipt of the second injection of mRNA-1273 (day 57) in phase 2 with those of young adult recipients in the efficacy phase 3 trial. Neutralizing antibody titers were measured with the use of a validated lentivirus pseudovirus (D614G) assay with a 50% inhibitory concentration as the primary objective, as described in the Supplementary Methods section in the Supplementary Appendix. Binding antibodies specific to the SARS-CoV-2 spike protein that were measured with the use of a Meso Scale Discovery assay and an enzyme-linked immunosorbent assay were used as supportive analyses.

The secondary objectives included the incidence of SARS-CoV-2 infection, asymptomatic SARS-CoV-2 infection, and Covid-19 (defined as clinical symptoms consistent with SARS-CoV-2 infection and a positive reverse-transcriptase–polymerase-chain-reaction [RT-PCR] test for SARS-CoV-2) with an onset of 14 days after the second injection of mRNA-1273 or placebo. Vaccine efficacy was calculated as 1 minus the ratio of the incidence of cases per 1000 person-years in the mRNA-1273 group as compared with the placebo group.

We defined a diagnosis of Covid-19 in two ways. In the first method, we used the primary case definition used in the phase 3 COVE trial of at least two systemic symptoms or at least one respiratory symptom plus at least one nasopharyngeal swab, nasal swab, or saliva sample positive for SARS-CoV-2 by RT-PCR. Because of a lower incidence and milder symptoms of Covid-19 among adolescents, we also used a secondary case definition of Covid-19 based on the Centers for Disease Control and Prevention (CDC) criteria, which required one systemic or respiratory symptom and a positive RT-PCR for SARS-CoV-2.[17]

The assessment of vaccine efficacy in the per-protocol population and starting 2 weeks after the second dose was consistent with the analysis population used in the phase 3 trial of mRNA-1273 in adults. The assessment of vaccine efficacy in adolescents in the modified intention-to-treat-1 population that excluded those who received the incorrect injection (hereafter called the mITT1 population) and starting 2 weeks after the first dose was more aligned with the epidemiologic and pathophysiological characteristics of Covid-19 in adolescents and allowed a longer observation period for case occurrence. Asymptomatic infection was a composite objective determined by positive serologic findings against the nucleocapsid antigen (indicating the presence of anti-nucleocapsid antibodies as markers of previous immunologic exposure) or positive RT-PCR for SARS-CoV-2 at scheduled or unscheduled post-baseline visits without any Covid-19 symptoms in participants with negative SARS-CoV-2 serologic findings and negative RT-PCR test results at baseline.

STATISTICAL ANALYSIS

Approximately 3000 participants were expected to be randomly assigned in a 2:1 ratio to receive mRNA-1273 or placebo. With 2000 participants who received mRNA-1273, the trial had at least 90% probability to observe at least one adverse event at a true 0.25% adverse event rate. The safety analysis was performed in the safety population, which included all the participants who had received any trial injection.

We performed an analysis in a per-protocol immunogenicity subpopulation consisting of participants who received planned injections of mRNA-1273 and were selected from adolescents in the phase 2 trial and young adults in the

phase 3 trial. In March 2021, for a comparison immunogenicity analysis involving adolescents who were 12 to 17 years of age, we used a random number generator to select a sample of 340 young adults (18 to 25 years of age) from the immunogenicity subgroup of the phase 3 COVE trial. Those participants had been randomly assigned to receive mRNA-1273 (the full analysis population), and their baseline SARS-CoV-2 status was available. This primary analysis in the COVE trial (with data based on a November 25, 2020, snapshot) provided support for the emergency use authorization in the United States for the mRNA-1273 vaccine in adults. The per-protocol immunogenicity subpopulation included participants who received planned injections of trial vaccination and immunogenicity blood sampling according to schedule, with negative SARS-CoV-2 status at baseline, and had no major protocol deviations. For the primary immunogenicity objective, with approximately 289 adolescents and 289 young adults expected to receive mRNA-1273, the trial had greater than 90% power to show noninferiority of the immune response for adolescents over young adults.

The success criteria for both primary objectives were a lower boundary of the 95% confidence interval for the geometric mean titer ratio of more than 0.67 with the use of a noninferiority margin of 1.5, a point estimate greater than 0.80; and a lower boundary of the 95% confidence interval for the difference in serologic response of −10% or more with the use of a noninferiority margin of 10%, and a point estimate of more than −5%. The minimum point-estimate threshold criteria were prespecified in addition to the noninferiority margins for the two primary objectives to exclude the possibility that the margins for the geometric mean titer ratio of adolescents relative to young adults may be met for noninferiority, even though the geometric mean titer ratio may be substantially less than 1.0. Details regarding the immunogenicity analysis are provided in the Supplementary Methods section in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

Between December 9, 2020, and February 28, 2021, a total of 3732 adolescents were randomly assigned in a 2:1 ratio to receive mRNA-1273 (2489 participants) or placebo (1243 participants) at 26 sites in the United States (Fig. 1 and Fig. S1). More than 98% of the participants received a second injection. The most common reasons for not receiving a second injection were withdrawal of consent (10 participants) and loss to follow-up (8 participants).

The baseline characteristics were generally balanced in the mRNA-1273 and placebo groups. The mean age of the participants was 14.3 years (74% were 12 to 15 years of age), half of the participants were male (51%), most were White (84%) and most were not Hispanic or Latinx (88%), and 93% had a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 30 (Table 1). The median duration of follow-up from randomization to the data snapshot was 83 days, and the median duration from the second injection to the database lock was 53 days.

The demographic characteristics of the adolescents were generally similar to those of the young adults in the phase 3 trial (Table S12). A total of 2% of the adults in the phase 3 trial had a positive SARS-CoV-2 status at baseline as compared with 6% of the adolescents. The demographic characteristics of the per-protocol immunogenicity subpopulations are shown in Table S10. The percentages of adolescents as compared with the young adults years were 8% and 27% for Hispanic or Latinx, 1% and 11% for Black, and 79% and 48% for White non-Hispanic participants, respectively (Table S10).

SAFETY

Solicited local reactions occurred more frequently in the mRNA-1273 group after the first injection (94.2%) and after the second injection (93.4%) than in the placebo group (36.8% and 32.6%, respectively). In the mRNA-1273 group, the most common solicited local reaction was injection-site pain after the first injection (93.1%; grade 3, 5.4%) and second injection (92.4%; grade 3, 5.1%); in the placebo group, injection-site pain was reported in 34.8% of the participants after the first injection and in 30.3% after the second injection. Grade 3 local adverse reactions in the mRNA-1273 group occurred in 6.8% of the participants after the first injection and in 8.9% after the second injection (Fig. 2 and Table S2).

In the mRNA-1273 group, systemic adverse reactions were reported in 68.5% of the partici-

Table 1. Demographic and Clinical Characteristics in the Safety Population at Baseline.*
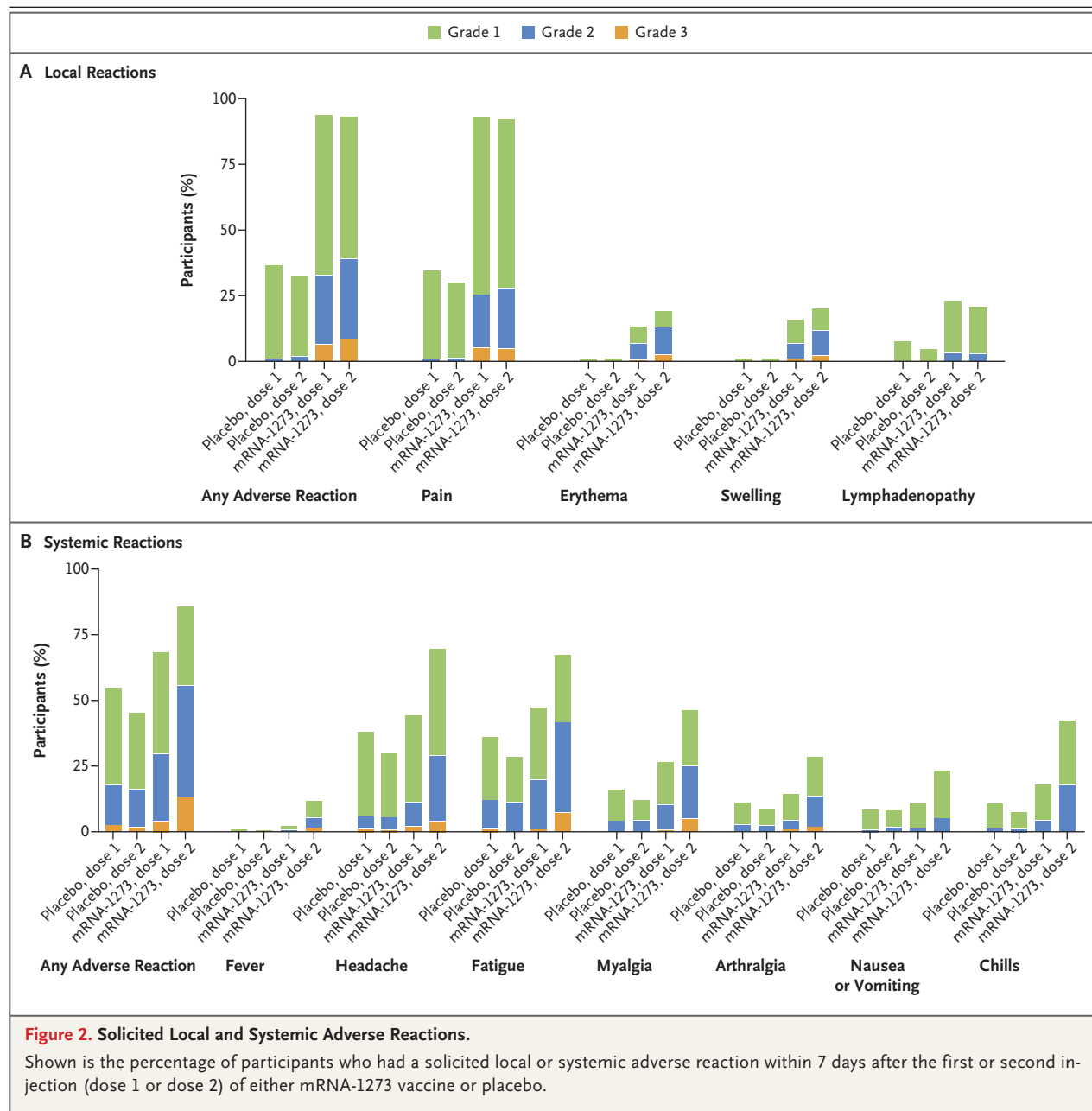
Characteristic	Placebo (N = 1240)	mRNA-1273 (N = 2486)	Total (N = 3726)
Age — yr	14.2±1.6	14.3±1.6	14.3±1.6
Age category — no. (%)			
16–17 yr	311 (25)	648 (26)	959 (26)
12–15 yr	929 (75)	1838 (74)	2767 (74)
Sex — no. (%)			
Male	632 (51)	1283 (52)	1915 (51)
Female	608 (49)	1203 (48)	1811 (49)
Body-mass index — no. (%)†			
<30	1146 (92)	2316 (93)	3462 (93)
≥30	94 (8)	170 (7)	264 (7)
Race or ethnic group — no. (%)‡			
White race	1041 (84)	2085 (84)	3126 (84)
Black race	42 (3)	83 (3)	125 (3)
Asian race	79 (6)	142 (6)	221 (6)
Native Hawaiian or Other Pacific Islander ethnic group	0	2 (<1)	2 (<1)
American Indian or Alaska Native ethnic group	7 (1)	12 (<1)	19 (1)
Multiple races or ethnic groups	50 (4)	118 (5)	168 (5)
Other ethnic group	9 (1)	27 (1)	36 (1)
Not reported	11 (1)	11 (<1)	22 (1)
Unknown	1 (<1)	6 (<1)	7 (<1)
Hispanic or Latinx ethnic group — no. (%)‡			
Yes	152 (12)	280 (11)	432 (12)
No	1076 (87)	2188 (88)	3264 (88)
Not reported or unknown	12 (1)	18 (1)	30 (1)
Race and ethnic group — no. (%)‡			
White non-Hispanic	912 (74)	1857 (75)	2769 (74)
Communities of color	325 (26)	625 (25)	950 (26)
Missing	3 (<1)	4 (<1)	7 (<1)
RT-PCR test — no. (%)			
Positive	9 (1)	13 (1)	22 (1)
Negative	1139 (92)	2308 (93)	3447 (93)
Missing data	92 (7)	165 (7)	257 (7)
Anti–SARS-CoV-2 nucleocapsid assay result — no. (%)			
Positive	63 (5)	139 (6)	202 (5)
Negative	1153 (93)	2299 (92)	3452 (93)
Missing	24 (2)	48 (2)	72 (2)
SARS-CoV-2 status — no. (%)§			
Positive	69 (6)	147 (6)	216 (6)
Negative	1075 (87)	2167 (87)	3242 (87)
Missing data	96 (8)	172 (7)	268 (7)
Median trial duration (range) — days			
From randomization to database lock	82 (9–151)	84 (30–151)	83 (9–151)
From second injection to database lock	51 (0–121)	53 (0–121)	53 (0–121)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. RT-PCR denotes reverse-transcriptase polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was reported by the participant. Participants could be included in more than one category.
§ Baseline SARS-CoV-2 status was positive if there was immunologic or virologic evidence of previous illness with Covid-19, as defined by a positive RT-PCR test or a positive immunoassay result (i.e., detection of binding antibodies against the SARS-CoV-2 nucleocapsid [Elecsys, Roche] above the limit of detection or the lower limit of quantification at day 1). Baseline SARS-CoV-2 status was negative if there was a negative RT-PCR test and a negative immunoassay result (i.e., no detection of binding antibodies against the SARS-CoV-2 nucleocapsid [Elecsys, Roche] below the limit of detection and the lower limit of quantification at day 1).

Figure 2. Solicited Local and Systemic Adverse Reactions.

Shown is the percentage of participants who had a solicited local or systemic adverse reaction within 7 days after the first or second injection (dose 1 or dose 2) of either mRNA-1273 vaccine or placebo.

pants after the first injection and in 86.1% after the second injection; grade 3 events were reported in 4.4% and 13.7%, respectively. The most common systemic reactions were fatigue, headache, myalgia, and chills. Headache was reported in 44.6% of the participants in the mRNA-1273 group after the first injection and in 70.2% after the second injection, as compared with 38.5% and 30.2%, respectively, in the placebo group. Fatigue was reported in 47.9% of the participants in the mRNA-1273 group after the first injection and

in 67.8% after the second injection, as compared with 36.6% and 28.9%, respectively, in the placebo group. After the second injection, among the mRNA-1273 recipients with available data, grade 3 fever occurred in 46 of 2477 participants (1.9%) and grade 4 fever occurred in 1 of 2477 participants (<0.1%) (Fig. 2).

Solicited local or systemic reactions generally persisted for a mean of approximately 4 days (Table S4). Incidences of local reactions that persisted beyond 7 days were numerically higher in

the mRNA-1273 group than in the placebo group and were also higher after the first injection (6.4%) than after the second injection (1.6%) in the mRNA-1273 group (Table S5); these results were primarily attributed to axillary swelling or tenderness. The local reactions with onset after day 7 after any injection occurred in 1.3% of mRNA-1273 recipients (erythema in 0.7%, swelling in 0.4%, and axillary swelling or tenderness in 0.4%) (Table S13). The incidences of solicited systemic reactions that persisted beyond 7 days were similar in the mRNA-1273 group (3.1%) and the placebo group (2.6%); those with onset after day 7 after any injection occurred in 0.7% and 0.3%, respectively.

Overall, the incidence of solicited adverse reactions was generally similar among participants 12 to 15 years of age and those 16 to 17 years of age (Fig. S4). In the mRNA-1273 group, the incidence of solicited local or systemic adverse reactions was generally similar among adolescent participants and young adults, but the incidence of erythema was higher among adolescents than among young adults (Table S8).

Unsolicited adverse events up to 28 days after any injection were more frequent in the mRNA-1273 group (20.5%) than in the placebo group (15.9%) (Table S3); the most common events in the mRNA-1273 group were injection-site lymphadenopathy (in 4.3%) and headache (in 2.4%). Adverse events that were considered by the investigators to be related to the vaccine or placebo within 28 days were reported by 12.6% participants in the mRNA-1273 group and 5.8% in the placebo group. One participant had a medically attended adverse event of grade 2 anaphylaxis to tree nuts on day 21 after the second injection of mRNA-1273 that was considered by the investigators to be unrelated to the vaccine. No deaths, MIS-C, or adverse events of special interest occurred. No cases of myocarditis or pericarditis have been reported at the time of this report.

IMMUNOGENICITY

The primary analysis was based on noninferiority of neutralizing antibody titers in adolescents in the phase 2 trial as compared with young adults in the phase 3 trial. The geometric mean titer ratio for neutralizing antibodies in adolescents relative to young adults was 1.08 (95% CI, 0.94 to 1.24) (Table 2). The levels of antibodies specific for the spike protein are shown in Table

S6. In addition, the serologic response was 98.8% among adolescents and 98.6% among young adults, and the absolute difference in serologic response between the adolescents and young adults was 0.2 percentage points (95% CI, −1.8 to 2.4). Therefore, the criteria for noninferiority were met for both primary objectives.

EFFICACY

The vaccine efficacy of mRNA-1273 14 days after the second injection was difficult to assess precisely because of the low incidence of Covid-19 in the trial population (four cases in the placebo group and no cases in the mRNA-1273 group) (Fig. 3 and Table S7). The vaccine efficacy of mRNA-1273 according to the less stringent CDC definition of Covid-19 with an onset of 14 days after the second injection was 93.3% (95% CI, 47.9 to 99.9) in the per-protocol population and 92.7% (95% CI, 67.8 to 99.2) for cases with an onset of 14 days after the first injection in the mITT1 population (Fig. 3 and Fig. S2). For the secondary objectives of prevention of SARS-CoV-2 infection with an onset of 14 days after the second injection (in the per-protocol population) and 14 days after the first injection (in the mITT1 population), the vaccine efficacy estimates for mRNA-1273 were 55.7% (95% CI, 16.8 to 76.4) and 69.8% (95% CI, 49.9 to 82.1), respectively (Fig. 3).

The vaccine efficacy of mRNA-1273 was 39.2% (95% CI, −24.7 to 69.7) for asymptomatic infection with an onset of 14 days after the second injection (per-protocol population) and 59.5% (95% CI, 28.4 to 77.3) with an onset of 14 days after the first injection (mITT1 population) (Fig. 3). The breakdown of asymptomatic cases starting 14 days after the first dose (mITT1 population) were 14 cases in the mRNA-1273 group and 20 in the placebo group according to RT-PCR results and 15 cases in each group according to serologic results against nucleocapsid (Table S11). The person-years of follow-up were 513 to 522 (6156 to 6264 person-months) in the mRNA-1273 group and 238 to 248 (2856 to 2976 person-months) in the placebo group.

DISCUSSION

The results from this trial involving adolescents extend the evidence of safety and efficacy of mRNA-1273 previously reported in adults.[14,15] The primary immunogenicity objective was met and

Table 2. Immunogenicity of mRNA-1273 in Adolescents and Young Adults.*

Age Group	Participants	Serologic Response†	Difference in Serologic Response, 12 to 17 Yr vs. 18 to 25 Yr‡	Geometric Mean 50% Pseudovirus Neutralizing Antibody Titer (95% CI)§	Geometric Mean Titer Ratio (95% CI), 12 to 17 Yr vs. 18 to 25 Yr
	no.	no. of participants/total no. (%; 95% CI)	percentage points (95% CI)		
12 to 17 yr	340	336/340 (98.8; 97.0 to 99.7)	0.2 (–1.8 to 2.4)	1401.7 (1276.3 to 1539.4)	1.08 (0.94 to 1.24)
18 to 25 yr	296	292/296 (98.6; 96.6 to 99.6)	—	1301.3 (1177.0 to 1438.8)	—

* The 50% inhibitory concentration titer of neutralizing antibodies was determined at day 57 (1 month after the second injection of mRNA-1273 vaccine) in a pseudovirus (Wuhan-Hu-1 isolate including D614G) assay.
† The serologic response for the 50% inhibitory dilution of pseudovirus neutralizing antibody was defined as a change from below the lower limit of quantitation at baseline to equal or above the lower limit of quantitation, or at least 3.3 times the baseline antibody titer if baseline was equal to or above the lower limit of quantitation. The results were the same according to an alternative definition of serologic response (i.e., at least 4 times the lower limit of quantitation if baseline was below the lower limit of quantitation, or at least 4 times baseline if baseline was equal to or above the lower limit of quantitation). The 95% confidence intervals for serologic response were calculated with the use of the Clopper–Pearson method.
‡ The absolute difference between the serologic response in the adolescents and young adults is shown. The 95% confidence limits for the difference were computed with the use of the Miettinen–Nurminen method.
§ For neutralizing antibody values reported as being below the lower limit of quantitation, 0.5 times the lower limit of quantitation was used in the analysis. For values greater than the upper limit of quantitation, the upper limit of quantitation was used in the analysis if actual values were not available. The log-transformed antibody levels were analyzed with the use of an analysis of covariance model with the group variable (adolescents in the current trial and young adults in the COVE trial) as a fixed effect. The resulting least-square means, the difference of least-square means, and 95% confidence intervals were back-transformed to the original scale for presentation.

showed the noninferiority of immune response based on both the geometric mean titer and serologic response in adolescents as compared with that in young adults. The safety and reactogenicity of mRNA-1273 in adolescents was similar to that observed in adults between the ages of 18 and 64 years in the phase 3 COVE trial.[14,15] In addition, the vaccine efficacy in these adolescents was 93% according to the less stringent CDC case definition.

Several studies that have examined the transmission of SARS-CoV-2 in children and adolescents have generally concluded that most infections in this age group result from household exposure rather than from exposure in a school setting.[18-21] Although the precise role of adolescents in the transmission of SARS-CoV-2 to adults is not known, it seems reasonable that widespread vaccination of this younger age group could further decrease community transmission and potentially contribute to herd immunity.[22] Therefore, a safe and effective vaccine in adolescents could reduce Covid-19–related morbidity and mortality. The availability of effective vaccines in adolescents is also important to further reduce the reservoir of SARS-CoV-2. The BNT162b2 vaccine has been authorized for emergency use in adolescents 12 to 15 years of age.[23,24]

No cases of myocarditis or pericarditis in this trial have been reported at the time of this report. The reported incidence of myocarditis and pericarditis associated with mRNA vaccination against SARS-CoV-2 in young men has been estimated to be in the range of 13 cases per million doses of vaccine; thus, it was expected that these events would not be detected in this trial.[25] Current postlicensure vaccine surveillance systems, including the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink, are designed to detect exceedingly rare events that cannot be identified in clinical trials.

This trial has several limitations. The efficacy analyses were secondary objectives of the trial because of milder Covid-19 disease and a lower disease incidence among adolescents than among adults in the phase 3 trial. However, the effectiveness of the mRNA-1273 vaccine in adolescents between the ages of 12 and 17 years is supported by both the noninferiority of the immunogenicity results for the vaccine and the preliminary estimate of vaccine efficacy. A relatively limited number of asymptomatic infections resulted in a negative lower boundary of the 95% confidence interval for efficacy starting 14 days after a second mRNA-1273 injection; however, the number of asymptomatic cases after the first injection was higher, with a vaccine efficacy of 59.5% (95% CI, 28.4 to 77.3). The efficacy of mRNA-1273 for the prevention of asymptomatic infection in adults also appears to be lower than
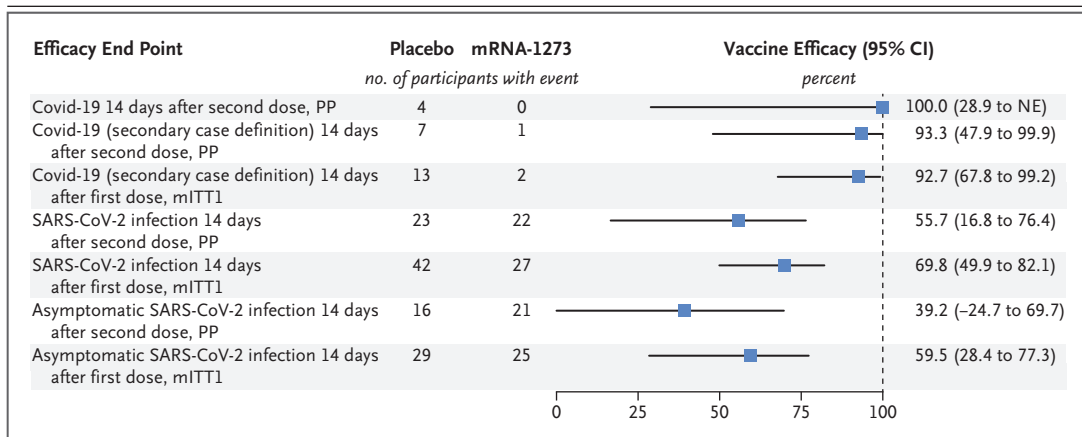
Efficacy End Point	Placebo	mRNA-1273	Vaccine Efficacy (95% CI)
	no. of participants with event		percent
Covid-19 14 days after second dose, PP	4	0	100.0 (28.9 to NE)
Covid-19 (secondary case definition) 14 days after second dose, PP	7	1	93.3 (47.9 to 99.9)
Covid-19 (secondary case definition) 14 days after first dose, mITT1	13	2	92.7 (67.8 to 99.2)
SARS-CoV-2 infection 14 days after second dose, PP	23	22	55.7 (16.8 to 76.4)
SARS-CoV-2 infection 14 days after first dose, mITT1	42	27	69.8 (49.9 to 82.1)
Asymptomatic SARS-CoV-2 infection 14 days after second dose, PP	16	21	39.2 (−24.7 to 69.7)
Asymptomatic SARS-CoV-2 infection 14 days after first dose, mITT1	29	25	59.5 (28.4 to 77.3)

Figure 3. Secondary Analyses of Efficacy.

Vaccine efficacy was calculated as 1 minus the ratio of the incidence of SARS-CoV-2 infection per 1000 person-years (mRNA-1273 vs. placebo). The primary definition of Covid-19 was at least two systemic symptoms or at least one respiratory symptom plus at least one nasopharyngeal swab, nasal swab, or saliva sample that was positive for SARS-CoV-2 by RT-PCR. The secondary case definition of Covid-19 was at least one systemic or respiratory symptom plus a swab that was positive for SARS-CoV-2 by RT-PCR. The category of SARS-CoV-2 infection (regardless of symptoms) was defined as a combination of postbaseline symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in participants with a negative SARS-CoV-2 status at baseline. Asymptomatic SARS-CoV-2 infection was defined as the absence of symptoms and infections detected by a postbaseline positive RT-PCR or serologic test in participants with a negative SARS-CoV-2 status at baseline. The per-protocol (PP) population consisted of all participants who had received at least one injection of mRNA-1273 or placebo and received planned injections of mRNA-1273 or placebo, complied with the timing of the second injection, had no immunologic and virologic evidence of previous Covid-19 at baseline, and had no major protocol deviations; this population included 1042 participants in the placebo group and 2139 participants in the mRNA-1273 group. The modified intention-to-treat population with the exclusion of those who had received the incorrect injection (mITT1) consisted of all participants who had no serologic or virologic evidence of previous SARS-CoV-2 infection before the first injection of mRNA-1273 or placebo (both a negative RT-PCR test for SARS-CoV-2 and a negative serologic test based on binding antibodies specific to SARS-CoV-2 nucleocapsid at baseline; this population included 1073 participants in the placebo group and 2163 participants in the mRNA-1273 group. NE denotes not estimated.

that for symptomatic disease in adults. However, the latter finding was based solely on detection with RT-PCR–positive swabs in the absence of symptoms.[15] The safety data presented here for mRNA-1273 in adolescents are based on an interim analysis of 83 median days of follow-up from randomization and may change over time. It is difficult to compare our results with those for the BNT162b2 vaccine (Pfizer–BioNTech) in which the neutralizing antibody titers in adolescents were higher than those in young adults because the neutralizing antibodies for mRNA-1273 were measured in a pseudovirus assay whereas those for BNT162b2 were measured in a live virus neutralization assay.[26] Finally, the trial population was less diverse than that in the phase 3 trial and, as such, is less representative of the U.S. population.

In this interim analysis of the ongoing trial, the overall benefit–risk profile of mRNA-1273

was favorable in adolescents. The immunogenicity of mRNA-1273 in adolescents was noninferior to that in young adults in the phase 3 trial, with a similar safety profile. The number of documented cases of Covid-19 is too small to generate robust assessments of vaccine efficacy. However, it appears that the mRNA-1273 vaccine safely induced levels of antiviral antibodies that should be protective against SARS-CoV-2 infection.

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