CORRESPONDENCE

Phase 3 Trial of mRNA-1273 during the Delta-Variant Surge

TO THE EDITOR: After emergency use of the mRNA-1273 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine was authorized, the observer-blinded, pivotal Coronavirus Efficacy (COVE) trial was amended on December 23, 2020, to include an open-label phase in which participants were offered the option to have their group assignment unblinded, and those who had received placebo were offered vaccination.[1,2] Coronavirus disease 2019 (Covid-19) surveillance during the open-label phase followed the same procedures as those used in the blinded phase. The emergence of the B.1.617.2 (delta) variant of SARS-CoV-2 in the United States was associated with an increased incidence of Covid-19 in the community beginning in July 2021.[3-5]

Here we report the incidence of Covid-19 from July 1 to August 27, 2021, during the open-label phase of the COVE trial, among participants who had initially been assigned to receive the mRNA-1273 vaccine (the mRNA-1273e group; vaccinated during the period from July through December 2020) and among those who had initially been assigned to placebo and elected to receive the vaccine in the open-label phase (the mRNA-1273p group; vaccinated during the period from December 2020 through April 2021). This analysis included participants who underwent randomization, received at least one dose of the mRNA-1273 vaccine or placebo, and were negative for SARS-CoV-2 at the time of trial entry in the blinded phase and excluded participants who had had Covid-19 or SARS-CoV-2 infection during the blinded phase, did not enter the open-label phase or received a nontrial Covid-19 vaccine, or had Covid-19 occur after the blinded phase but before the first dose of vaccine in the open-label phase. There were 14,746 participants in the mRNA-1273e group and 11,431 in the mRNA-1273p group.

The baseline characteristics of the participants were similar in the two groups, except that more participants in the mRNA-1273p group than in the mRNA-1273e group were 65 years of age or older, and more participants in the mRNA-1273e group were health care workers (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The median follow-up time, beginning at the time of receipt of the first vaccine dose, was 13.0 months in the mRNA-1273e group (including the blinded phase and the open-label phase) and 7.9 months in the mRNA-1273p group (including only the open-label phase).

The number of Covid-19 cases that occurred among all participants through June 2021 (during the open-label phase) was low, with an increase observed in July and August 2021 (Fig. S1). The incidence rate of Covid-19 was the same in the two groups (9.4 cases per 1000 person-years) through June 30, 2021. During the earlier, blinded phase, the incidence rate had been much lower in the mRNA-1273 group than in the placebo group (11.8 cases per 1000 person-years vs. 148.8 cases per 1000 person-years) (Table S3).

During July and August 2021, a total of 162 cases of Covid-19, with onset starting 14 days after receipt of the second dose, occurred in the mRNA-1273e group, and 88 occurred in the mRNA-1273p group (Table 1 and Table S2). Of the isolates sequenced, 144 of 149 (97%) in the mRNA-1273e group and 86 of 87 (99%) in the mRNA-1273p group were identified as the delta variant (Table S4). During these 2 months, the incidence rate of Covid-19 was lower in the mRNA-1273p group (49.0 cases per 1000 person-years) than in the mRNA-1273e group (77.1 cases per 1000 person-years), with a 36.4% (95% confidence interval [CI], 17.1 to 51.5) relative difference in the observed incidence rates (Table 1). These findings indicate an incidence of approximately 4 cases per 1000 person-months in the mRNA-1273p group and 6 cases per 1000 person-months in the mRNA-1273e group during July and August 2021. Similar between-group differences in Covid-19 cases were seen with the use of a Cox proportional-hazards model that was adjusted for age, status as a health care worker, and risk factors for severe Covid-19 (Table S5). Between-group differences in incidence rates

Table 1. Covid-19 Cases and Incidence Rates after Receipt of the Second Dose of mRNA-1273 Vaccine, from July 1 to August 27, 2021.*

Covid-19 Cases and Age Group	mRNA-1273e Group (N=14,746)			mRNA-1273p Group (N=11,431)			Difference in Incidence Rates (95% CI)
	no. of cases	*no. of person-yr*	*incidence rate per 1000 person-yr*	*no. of cases*	*no. of person-yr*	*incidence rate per 1000 person-yr*	%
All cases	162	2102	77.1	88	1796	49.0	36.4 (17.1 to 51.5)
Age 18 to <65 yr	136	1558	87.3	68	1289	52.8	39.6 (18.6 to 55.5)
Age ≥65 yr	26	544	47.8	20	507	39.5	17.4 (–53.9 to 56.3)
Severe cases	13	2102	6.2	6	1796	3.3	46.0 (–52.4 to 83.2)
Age 18 to <65 yr	7	1558	4.5	4	1289	3.1	30.9 (–171.7 to 85.2)
Age ≥65 yr	6	544	11.0	2	507	3.9	64.2 (–100.2 to 96.5)

* The current analysis included participants who underwent randomization, received at least one dose of the mRNA-1273 vaccine or placebo, and were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the time of trial entry in the blinded phase and excluded participants who had had coronavirus disease 2019 (Covid-19) or SARS-CoV-2 infection during the blinded phase, did not enter the open-label phase or received a nontrial Covid-19 vaccine, or had Covid-19 occur after the blinded phase but before the first dose of vaccine in the open-label phase. Person-years were calculated for the analysis period, from July 1 to August 27, 2021. The mRNA-1273e group included participants who had been assigned to receive the mRNA-1273 vaccine in the blinded phase of the trial (these participants were vaccinated during the period from July 27 to December 16, 2020). The mRNA-1273p group included participants who had been assigned to receive placebo in the blinded phase and elected to receive the mRNA-1273 vaccine in the open-label phase (these participants were vaccinated during the period from December 29, 2020, to April 30, 2021 [after emergency use had been authorized]). Shown are Covid-19 cases that occurred at least 14 days after receipt of the second dose of the mRNA-1273 vaccine during the analysis period. The incidence rate was calculated as the number of Covid-19 cases divided by the number of participants at risk at the beginning of the analysis period and was adjusted according to person-years in each group. The between-group differences in the incidence rates were calculated as 1 minus the ratio of incidence rates; 95% confidence intervals were calculated with the use of the exact method (Poisson distribution) with adjustment for person-years.

were greater in younger age groups than in older age groups (Table 1).

There were 13 protocol-specified severe cases of Covid-19 in the mRNA-1273e group (6.2 cases per 1000 person-years) and 6 (3.3 cases per 1000 person-years) in the mRNA-1273p group, with an estimated relative difference of 46.0% (95% CI, –52.4 to 83.2) (Table 1). There were three Covid-19–related hospitalizations, all in the mRNA-1273e group. Two of the hospitalized patients, who had been vaccinated more than 10 months earlier, died; both participants were men 70 years of age or older who had coexisting medical conditions (Table S6).

Overall, incidence rates of Covid-19 were lower among participants in the mRNA-1273p group (who had been vaccinated more recently) than among those in the mRNA-1273e group during July and August 2021, when the delta variant was dominant. The difference appears to have been driven by disease in younger participants, which indicates the presence of potential confounding behavioral factors in these participants that may have led to a higher exposure to the virus.

Limitations of this analysis include a difference in the number of participants in each group who did not continue to the open-label phase and a lack of randomization. Although a potential bias can be attributed to differences in the risks among the participants remaining in the trial, we observed consistent findings in a proportional-hazards analysis that was adjusted according to the original risk stratification factors in the trial. In addition, the current analysis evaluated Covid-19 cases during a 2-month period. With longer follow-up, the results and the differences between the two groups may change.

Analysis of the open-label phase of the ongoing COVE trial continues. Longer-term data may provide a better understanding of the efficacy of the mRNA-1273 vaccine over time.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

The trial is ongoing; access to patient-level data and supporting clinical documents with qualified external researchers may be available on request and subject to review once the trial is complete.

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