Safety, Immunogenicity and Antibody Persistence of a Bivalent Beta-Containing Booster Vaccine

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Research Article

Keywords: SARS-CoV-2, variants, bivalent, vaccine, antibodies

Posted Date: April 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1555201/v1

Safety, Immunogenicity and Antibody Persistence of a Bivalent Beta-Containing Booster Vaccine

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants have caused multiple waves of infection globally. This phase 2/3 study evaluated the safety and immunogenicity of the bivalent vaccine candidate mRNA-1273.211 (equal mRNA amounts of ancestral SARS-CoV-2 and Beta variant spike proteins) as 50-µg (n=300) and 100-µg (n=595) first booster doses approximately 8.8-9.8 months after the mRNA-1273 primary series. The mRNA-1273.211 booster (50 and 100-µg) elicited higher neutralizing antibody responses against the ancestral SARS-CoV-2 and the Beta variant than that after the second mRNA-1273 dose. Antibody responses after the 50-µg mRNA-1273.211 booster dose were also higher than that after a 50-µg mRNA-1273 booster dose for the ancestral SARS-CoV-2, Beta, Omicron and Delta variants (28 days after the booster dose) and for the ancestral SARS-CoV-2, Beta and Omicron (180 days after the booster dose), and the immunogenicity objectives were met. The safety and reactogenicity profile of the mRNA-1273.211 booster (50-µg) was comparable to mRNA-1273 (50-µg). These results indicate that bivalent booster vaccines can induce potent and durable antibody responses providing a new tool in response to emerging variants.

Trial registration: https://www.clinicaltrials.gov NCT04927065

Introduction

The development and global deployment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines has been important for reducing the burden of coronavirus disease 2019 (COVID-19). The mRNA-1273 vaccine encodes the spike protein of the ancestral SARS-CoV-2 (Wuhan-HU-1 isolate) and was well-tolerated and demonstrated 93.2% efficacy against COVID-19 after a median follow-up of 5.3 months following a 2-dose 100-µg primary series in the phase 3 Coronavirus Vaccine Efficacy and safety (COVE) trial.[1,2]

SARS-CoV-2, similar to other pathogenic coronaviruses, has the propensity to rapidly mutate and several SARS-CoV-2 variants have emerged.[3,4] SARS-CoV-2 variants such as Beta (B.1.351) have key antibody escape mutations in the spike protein and others, such as the Delta variant (B.1.617.2), carry mutations which render enhanced transmissibility.[4] The potential of Beta to circumvent immunity, associated with increased morbidity and mortality, was not accompanied by a growth advantage, whereas the highly-transmissible Delta variant became the dominant SARS-CoV-2 variant in multiple geographies. In November of 2021, the Omicron variant (B.1.1.529) emerged as the most antigenically divergent variant to date with >30 mutations in the spike protein, 15 of which are clustered in the receptor binding domain.[5] Omicron shares key antibody escape site mutations with the Beta variant and it also exhibits substantial transmissibility advantages.[6-8]

During the placebo-controlled part of the COVE trial, the predominant circulating variants were the ancestral SARS-CoV-2 with the D614G mutation and the Alpha (B.1.1.7) variant; subsequent infection waves caused by other SARS-CoV-2 variants (Delta, Omicron) led to the need for booster doses.[9-14] Following a 50-µg booster dose of mRNA-1273, antibodies against variants such as Delta and Omicron were detectable at higher titers than after the mRNA-

1273 primary series.[10,15] However, antibody titers, especially against antigenically divergent variants such as Omicron appear to be lower than that against the ancestral SARS-CoV-2 and wane over time after a 50-µg dose of the prototype booster. In addition, emerging vaccine effectiveness data suggest decreased long-term booster vaccine effectiveness against infection from Omicron, although protection against hospitalization and severe disease is maintained.[10,16,17]

When Beta first emerged in late 2020, Beta-specific antibody titers after primary series vaccination were found to be lower than the antibody titers against the ancestral virus.[18] It was hypothesized that a bivalent booster vaccine that would contain mRNAs for the ancestral SARS-CoV-2 and the Beta spike protein could enhance the immune response by increasing antibody diversity[19]. mRNA-1273.211 contains equal amounts of two spike protein mRNA sequences: one for the ancestral SARS-CoV-2 and another for the Beta variant and it was the first modified, bivalent booster candidate to be evaluated in the clinic in a phase 2/3 booster vaccine study in adults. The study was designed to evaluate the safety, immunogenicity, and durability of the antibody response to variant-matched booster vaccines. Herein, we summarize the safety and immunogenicity results of an interim analysis of two dose levels (50 and 100 µg) of the booster vaccine candidate mRNA-1273.211 to provide key safety and immunogenicity insights for bivalent booster vaccines. Evaluation of an Omicron-matched bivalent booster vaccine is ongoing.

Methods

Study design and participants

This is part A of an open-label, Phase 2/3 study (NCT04927065) to evaluate the safety, reactogenicity and immunogenicity of a single booster dose of the bivalent mRNA candidate vaccine mRNA-1273.211 (see "Trial Vaccine") in adults who had previously received the primary series of two doses of 100 µg mRNA-1273 in the phase 3 COVE trial at least 6 months earlier (Supplementary Figure 1).[1,2] Study participants are being followed for approximately 12 months after administration of the booster dose.

896 participants ≥18 years of age who were enrolled and compliant in the phase 3 COVE trial and who had completed a two-dose primary series of mRNA-1273 at least 6 months prior were enrolled across 9 clinical sites in the United States (NCT04927065). A total of 300 participants were enrolled in the 50-µg mRNA-1273.211 booster group and 596 participants in the 100-µg mRNA-1273.211 booster group (first booster doses, Supplementary Figure 1). Participants who had a history of SARS-CoV-2 infection in the COVE trial or who were found to have evidence of SARS-CoV-2 infection at study screening were excluded (see inclusion and exclusion criteria in the supplement and online protocol).

In addition, 584 participants who received the 2-dose primary series of mRNA-1273 (100-µg) were randomly selected from the random sub-cohort for Immunogenicity of the phase 3 COVE trial. This COVE group serves as a historical control group when comparing the antibody responses after the mRNA-1273.211 booster doses (50- and 100-µg) with that after the mRNA-1273 series (see Statistical Analysis).

Lastly, 171 participants ≥18 years of age enrolled in a separate phase 2 study (NCT04405076) and received the authorized mRNA-1273 booster (50-µg, first booster dose), at

least 6 months after completing the mRNA-1273 primary series and serve as the external comparator group when comparing the antibody responses between the mRNA-1273.211 (50-µg) and mRNA-1273 (50-µg) boosters (Supplementary Figure 1).

The trials have been conducted in accordance with the International Council for Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice Guidance, and applicable government regulations. The central Institutional Review Board approved the protocol and consent forms. All participants provided written informed consent.

Trial vaccine

The mRNA-1273 vaccine contains an mRNA that encodes the spike glycoprotein of the Wuhan-Hu-1 isolate of SARS-CoV-2 encapsulated in a lipid nanoparticle (LNP). The booster doses of mRNA-1273 were administered at a dose level of 50 µg mRNA-1273 in a 0.5 mL volume. The bivalent mRNA-1273.211 vaccine is the same LNP containing equal amounts of mRNA that encode for the spike glycoproteins of Wuhan-Hu-1 and the Beta (B.1.351) variant. The booster doses of mRNA-1273.211 were administered at a dose level of 50 µg or 100 µg mRNA-1273.211.

Study outcomes

The primary safety objective was to evaluate the safety and reactogenicity of a 50-µg or 100-µg mRNA-1273.211 administered as a single booster dose. Reactogenicity included solicited local and systemic adverse reactions (ARs) that occurred ≤7 days after the booster injection as recorded daily by participants. Unsolicited adverse events (AEs) were recorded by

study sites for 28 days post-booster administration. Serious adverse events (SAEs), medically-attended AEs (MAAEs) and AEs of special interest (AESIs) are recorded by the study sites for the entire study period (~12 months).

There were two pre-specified immunogenicity objectives in the study. The primary objective was to demonstrate a non-inferior antibody response against the ancestral SARS-CoV-2 and the Beta variant 28 days after the booster dose of 50 or 100 µg mRNA-1273.211 candidate vaccine compared with the antibody response 28 days after the second dose of the 100-µg mRNA-1273 primary series in the historical control group based on endpoints of the antibody geometric mean titer ratio and group difference in seroresponse rates (see statistical analysis).

The second pre-specified immunogenicity objective was to perform a non-inferiority and superiority comparison of the antibody response of the 50-µg mRNA-1273.211 booster candidate with the antibody response of the 50-µg mRNA-1273 booster dose for the ancestral SARS-CoV-2 and for the Beta, Delta and Omicron variants based on the endpoint of the antibody geometric mean titer ratio 28 and 180 days after the booster doses (see statistical analysis).

Immunogenicity assays

Neutralizing antibody geometric mean titers (GMT) at inhibitory dilutions 50% (ID50) were assessed in validated SARS-CoV-2 spike-pseudotyped lentivirus neutralization assays. Titers were generated against pseudoviruses containing the SARS-CoV-2 full-length spike proteins for the ancestral virus with the D614G mutation and the Beta, Delta and Omicron variants. GMTs were also assessed in an anti-spike protein binding IgG antibody assay (Meso

Scale Discovery [MSD]) against the ancestral SARS-CoV-2 with D614G, Gamma (P.1), Alpha (B.1.1.7) and Beta (B.1.351) variants. Immunogenicity assays are further described in the supplement.

Statistical analysis

Safety was evaluated in the safety set with participants who received the 50-µg or 100-µg mRNA-1273.211 booster doses and solicited adverse reactions were assessed in the solicited safety set (see further information on analysis sets in Supplementary Methods). The numbers and percentages of participants with any solicited local and systemic adverse reactions occurring within 7 days post-boost are provided. Unsolicited AEs, SAEs, severe AEs, MAAEs, AESIs and AEs leading to study discontinuation are also summarized.

The primary immunogenicity objective for 50-µg and 100-µg mRNA-1273.211 booster doses was assessed in the immunogenicity set consisting of all participants who received the booster dose and had antibody data available at the pre-booster and the day 29 visit with no major protocol deviations. The primary immunogenicity objective was to demonstrate non-inferior antibody responses, against the ancestral SARS-CoV-2 and the Beta variant 28 days after the booster dose, compared to that of the mRNA-1273 primary series (historical control group). The primary immunogenicity objective also included a heterologous comparison to demonstrate a non-inferior antibody response against the Beta variant, 28 days after the booster dose, compared to the antibody response against the ancestral SARS-CoV-2 after the mRNA-1273 primary series (historical control group). The clinical endpoints assessed to demonstrate non-inferiority included the geometric mean titer ratio (GMR) and the group difference in

seroresponse rates (SRR) (see Supplementary Methods). Non-inferiority was considered met if the lower bound of the 95% CI of the GMR was ≥ 0.67 (1/1.5, non-inferiority margin of 1.5). Non-inferiority of the difference in SRR was considered met if the lower bound of the 95% CI of the SRR difference was >-10%. Seroresponse was defined as a 4-fold titer rise for participants with a pre-vaccination baseline titer (=titer before receiving the mRNA-1273 primary series) ≥lower limit of quantification (LLOQ) of the neutralizing antibody assay or ≥ 4 times the LLOQ of the assay for those participants with a pre-vaccination baseline <LLOQ.

For the immunogenicity objective of the booster-to-booster comparison, the antibody responses elicited by the 50-µg mRNA-1273.211 booster dose were compared to that elicited by 50-µg mRNA-1273 booster dose (external comparator group) at 28 and 180 days post-boost. The booster-to-booster comparison was assessed using the immunogenicity set (excluding participants with evidence of infection pre-booster). The clinical endpoint assessed to demonstrate non-inferiority and superiority was based on GMR; non-inferiority (antibody response of mRNA-1273.211 50 µg over mRNA-1273 50 µg) was considered met if the lower bound of GMR 95% CI was ≥ 0.67, and superiority was considered met if the lower bound of 95% CI was >1. All tests were performed at nominal alpha level of 0.05 (2-sided) (see Supplementary Methods).

For the immunogenicity endpoints, geometric mean titers were analyzed using: 1) an analysis of covariance (ANCOVA) model for the antibody response non-inferiority assessment to the mRNA-1273 primary series, and 2) a mixed effect model of repeated measure (MMRM, given multiple time-points) for the booster-to-booster non-inferiority and superiority comparison. In addition, between group comparisons for SRR differences were based on the Miettinen-Nurminen (score) method (see supplement for additional information).

All analyses were conducted using SAS Version 9.4 or higher.

Results

Trial population

From May 28 to June 4, 2021, and June 30 to July 15, 2021, a total of 895 participants from the Phase 3 COVE trial received a single booster dose of 50 µg (n=300) or 100 µg (n=595) mRNA-1273.211 respectively (one enrolled participant was removed from all analyses given that the participant received multiple COVID-19 vaccines outside the study, Supplementary Figure 1). Participant demographic and baseline characteristics are shown in Table 1 for the two mRNA-1273.211 groups, for the historical control group (mRNA-1273 primary series) from the COVE trial, and for the external comparator (mRNA-1273 booster dose, 50 µg) from the separate phase 2 study[1,15,20-22]. Demographics and baseline characteristics were overall comparable in the 50 and 100-µg mRNA-1273.211 groups and the historical control and external comparator groups. The mean age of the participants was 50.7 years (50 µg mRNA-1273.211), 53.0 years (100 µg mRNA-1273.211), 52.1 years (historical control group) and 52.0 years (external comparator). In terms of gender, 56% were female in the 50 and 100 µg mRNA-1273.211 groups, 47% in the historical control and 61% in the external comparator. Most participants were White (86% in 50 µg mRNA-1273.211, 87% in 100 µg mRNA-1273.211, 72% in historical control and 96% in the external comparator), and 13%, 9%, 31% and 6% were Hispanic or Latinx in these groups, respectively. There was a higher percentage of participants who were Black or African American in the historical control group (19%) compared to the groups that received 50 or 100 µg of mRNA-1273.211 (6%) or 50 µg of mRNA-1273 (3%). The percentages of participants with evidence of prior SARS-CoV-2 infection at baseline (day of the booster dose) were 1% (4/300) in the 50µg mRNA-1273.211, 2% (13/595) in the 100 µg mRNA-1273.211 groups, and 4% (6/171) in the 50 µg mRNA-1273. The median (Q1, Q3) durations

between the second dose of mRNA-1273 and the booster dose were 264 (246, 276) days (50 µg mRNA-1273.211), 294 (286, 303) days (100 µg mRNA-1273.211) and 219 (199, 231) days (50 µg mRNA-1273).

Safety

The incidences of solicited local and systemic adverse reactions within seven days after the mRNA-1273.211 booster injection (50 and 100 µg dose levels) are shown in Figure 1 and in Supplementary Table 1. The incidences of adverse reactions after the second dose of the mRNA-1273 primary series and after the 50-µg dose of the prototype mRNA-1273 have been previously published[1,15,21].

The most common solicited local adverse reactions within 7 days after administration of the 50-µg dose of mRNA-1273.211 was injection site pain (85%; 253/298). The most common solicited systemic adverse reactions after administration of the 50-µg dose of mRNA-1273.211 were fatigue (64%; 192/298), headache (51%; 151/298), and myalgia (49%; 146/298). The most common solicited local adverse reactions of the 100-µg dose of mRNA-1273.211 was injection site pain (91%; 542/593) and the most common systemic adverse reactions were fatigue (70%; 413/593), headache (56%; 333/593), and myalgia (56%; 335/593). Most solicited adverse reactions in participants who received the 50-µg booster dose of mRNA-1273.211 were mild (local adverse reactions, Grade 1 [69%; 205/298], Grade 2 [14%; 41/298], Grade 3 [3%; 8/298]; systemic adverse reactions, Grade 1 [35%; 105/298], Grade 2 32%; 96/298] Grade 3 [8%; 25/298]), Figure 1; Supplementary Table 1). Most solicited adverse reactions in participants who received the 100-µg mRNA-1273.211 booster dose were Grade 1 or Grade 2 (local adverse

reactions, Grade 1 [64%; 377/593], Grade 2 [22%; 128/593], Grade 3 [7%; 39/593]; systemic adverse reactions, Grade 1 [29%; 173/593], Grade 2 [41%; 240/593] Grade 3 [11%; 66/593]), Figure 1; Supplementary Table 1). Overall, the 50-µg dose of mRNA-1273.211 had a comparable reactogenicity profile to the 50-µg dose of the prototype mRNA-1273 and the second dose of the mRNA-1273 primary series whereas the incidence of local and systemic adverse reactions was higher with the 100-µg dose of mRNA-1273.211.[1,15,21]

Unsolicited adverse events regardless of the relationship to the vaccination up to 28 days after the 50 and 100 µg 1273.211 booster dose were reported in 63 (21.0%) and 129 (21.7%) of participants in these groups, respectively (Supplementary Table 2). No participants in the 50-µg and 5 (0.8%) participants in the 100-µg group had serious adverse events (SAEs). These SAEs included hip pain, urinary tract infection, transient ischemic attack, and bradycardia in a participant with history of cardiac disease; one of the five participants had multiple SAEs (cholelithiasis, urinary tract infection, urosepsis and nocturnal hypoxia). There were no fatal events, no SAEs related to vaccination, as assessed by investigators, or adverse events leading to study discontinuations in either mRNA-1273.211 group. Overall, the frequency and types of unsolicited adverse events were comparable to those after the second dose of the mRNA-1273 primary series and the 50-µg mRNA-1273 booster dose.[15,21]

Efficacy

Although the study was not designed to evaluate booster vaccine effectiveness, routine surveillance for SARS-CoV-2 infections with polymerase chain reaction (PCR) and anti-nucleocapsid antibody testing was performed at the clinic visits 28 and 180 days after the mRNA-1273.211 booster doses. There were 10 (10/296, 3.4%) and 70 (70/582, 12.0%) SARS-

CoV-2 infections following the 50 and 100-µg mRNA-1273.211 booster doses, respectively. Routine surveillance at the day 181 clinic visits for some participants in the 100-µg mRNA-1273.211 group occurred during the Omicron wave in the United States, likely accounting for the higher frequency of infections in this group. From these SARS-CoV-2 infections, 1 (1/296, 0.3%) and 27 (27/582, 4.6%) in the 50 and 100-µg mRNA-1273.211 groups, respectively, were symptomatic and hence counted as COVID-19 events. There were no hospitalizations due to COVID-19. Lastly, there were 27 (27/171, 15.8%) participants with SARS-CoV-2 infections after the mRNA-1273 50-µg booster dose in the external comparator group and 16 (16/149, 10.7%) with SARS-CoV-2 infections in the immunogenicity set (excluding participants with evidence of infection pre-booster) of the external comparator group. Four of the 171 (2.3%) participants with a SARS-CoV-2 infection also had symptoms (COVID-19 events) in the external comparator group.

Immunogenicity

For the primary immunogenicity objective of assessing non-inferiority of the antibody response after the mRNA-1273.211 doses to that of the mRNA-1273 primary series (historical control group), the GMTs (ANCOVA model) against the ancestral SARS-CoV-2 with the D614G mutation at 28 days after the 50-µg booster dose of mRNA-1273.211 (1996.2 [1777.9-2241.4]) were higher than those at 28 days after the second 100 µg mRNA-1273 dose of the primary series in the historical control group (1053.4 [967.2-1147.2]) (Supplementary Table 3) with a geometric mean titer ratio (GMR; 95% CI) of 1.9 (1.7-2.2) meeting the non-inferiority criterion (GMR lower bound of 95% CI ≥0.67). The GMTs against the ancestral SARS-CoV-2 with the D614G mutation at 28 days after the 100-µg booster dose of mRNA-1273.211 (4324.7

[3974.6-4705.6]) were higher than those at 28 days after the second 100-µg mRNA-1273 dose of the primary series in the historical control group (1087.3 [999.7-1182.6]) with a GMR of 4.0 (3.6-4.4), also meeting the non-inferiority criterion (GMR lower bound of 95% CI ≥0.67) (Supplementary Table 3). The seroresponse (SRR) against the ancestral SARS-CoV-2 with D614G at 28 days after the 50-µg booster dose of mRNA-1273.211 was 98.7% (96.6-99.6), compared with 98.1% (96.7-99.1) in the historical control group with a difference of 0.5% (-1.6%-2.2%), which met the non-inferiority criterion (SRR difference lower bound of 95% CI>-10%) (Supplementary Table 3). The seroresponse (SRR) against the ancestral SARS-CoV-2 with D614G at 28 days after the 100-µg booster dose of mRNA-1273.211 was 99.8% (99.0-100.0), compared with 98.1% (96.7-99.1) in the historical control group with a difference of 1.7% (0.7%-3.2%), which also met the non-inferiority criterion (SRR difference lower bound of 95% CI>-10%) (Supplementary Table 3).

The Beta-specific GMTs at 28 days after the 50-µg booster dose of mRNA-1273.211 were 953.9 (844.1-1078.0) and the GMTs against the ancestral SARS-CoV-2 with D614G at 28 days after the second dose of 100 µg mRNA-1273 of the primary series were 1058.0 (966.9-1157.7) with a GMR of 0.9 (0.8-1.0), meeting the non-inferiority criterion (Supplementary Table 3). The Beta-specific GMTs at 28 days after the 100-µg booster dose of mRNA-1273.211 were 1574.6 (1439.4-1722.5) and the GMTs against the ancestral SARS-CoV-2 with D614G 28 days after the second dose of 100 µg mRNA-1273 of the primary series were 1085.7 (992.9-1187.2) with a GMR of 1.5 (1.3-1.6), also meeting the non-inferiority criterion (Supplementary Table 3). The SRR for the Beta variant at 28 days after the 50-µg booster dose of mRNA-1273.211 was 98.0% (95.6-99.3) and the SRR against the ancestral SARS-CoV-2 with D614G was 98.1% (96.7-99.1) in the historical control group with a difference of -0.1% (-2.6-1.7) which met the

noninferiority criterion (Supplementary Table 3). Lastly, the SRR against the Beta variant at 28 days after the 100-µg booster dose of mRNA-1273.211 was 99.1% (98.0-99.7) and the SRR against the ancestral SARS-CoV-2 with D516G in the historical control group was 98.1% (96.7-99.1) with a SRR difference of 1.0% (-0.4,2.6) which also met the noninferiority criteria (Supplementary Table 3).

For the immunogenicity objective of assessing non-inferiority and superiority of the antibody response after the mRNA-1273.211 booster dose (50-µg) to the mRNA-1273 booster (50-µg, external comparator), the GMTs (MMRM model, Table 2) against the ancestral SARS-CoV-2 with the D614G mutation at 28 days after the 50-µg booster dose of mRNA-1273.211 (2278.0 [2074.0-2502.1]) were higher than those at 28 days after 50-µg booster dose of mRNA-1273 (1782.7 [1561.3, 2035.6]) with a GMT ratio (95% CIs) of 1.28 (1.08, 1.51). The GMTs against the ancestral SARS-CoV-2 with D614G mutation were also higher at 180 days after the 50-µg booster dose of mRNA-1273.211 (1040.0 [926.4-1167.3]) than that after the 50-µg mRNA-1273 dose (617.2 [525.1, 725.5]) with a GMT ratio of 1.68 (1.38, 2.06). The superiority criterion was met (GMR lower bound of the 95% CI >1) at both timepoints, 28 days and 180 days after the booster dose, with nominal alpha of 0.05.

The Beta-specific GMTs at 28 days after the 50-µg mRNA-1273.211 booster dose (1095.3 [981.1-1222.7]) were higher than that after the 50-µg mRNA-1273 booster dose (825.6 (706.6, 964.7) with a GMR of 1.33 (1.09, 1.61) (Table 2). The Beta-specific GMTs were also higher 180 days after the 50-µg booster dose of mRNA-1273.211 (343.5 [303.7-388.5]) than that after the 50-µg mRNA-1273 dose (125.2 [105.4, 148.8]) with a GMR of 2.74 (2.22, 3.40). The

superiority criterion was met (GMR lower bound of the 95% CI >1) at both timepoints, 28 days and 180 days after the booster dose, with nominal alpha of 0.05.

The Omicron-specific GMTs 28 days after the 50-µg mRNA-1273.211 booster dose (1389.8 [1212.1-1593.4]) were higher than that 28 days after 50-µg booster dose of mRNA-1273 (630.5 [520.0, 764.9]) with GMR of 2.20 (1.74, 2.79) (Table 2). The Omicron-specific GMTs 180 days after the 50-µg booster dose of mRNA-1273.211 (312.9 [269.5-363.4]) were higher than that after the 50-µg mRNA-1273 booster dose (145.6 [118.1, 179.5]) with GMR of 2.15 (1.66, 2.78). The superiority criterion was met (GMR lower bound of the 95% CI >1) at both timepoints, 28 days and 180 days after the booster dose, with nominal alpha of 0.05.

The Delta-specific GMTs 28 days after the 50-µg booster dose of mRNA-1273.211 (1481.2 [1335.8-1642.3]) were higher than that after the 50-µg booster dose of mRNA-1273 (844.1 [730.2, 975.8]) with a GMR of 1.75 (1.47, 2.10) (Table 2). The Delta-specific GMTs at 180 days after the 50-µg mRNA-1273.211 booster dose were 491.3 (437.8-551.5) and were higher than that after the 50-µg booster dose of mRNA-1273, [408.0 (347.5, 479.1] with a GMR of 1.20 (0.99, 1.47). The superiority criterion was met (GMR lower bound of the 95% CI >1) 28 days after the booster dose and non-inferiority was met at the 180 days post-boost timepoint (GMR lower bound of the 95% CI >0.67) with nominal alpha of 0.05.

The observed neutralizing antibody GMTs against the ancestral SARS-CoV-2 with D614G and Beta, after the mRNA-1273 primary series and after the mRNA-1273.211 booster doses are shown in Figure 2. In addition, the observed neutralizing antibody GMTs after the 50-µg mRNA-1273 booster dose and after the mRNA-1273.211 booster doses against the ancestral

SARS-CoV-2 with D614G, Beta, Delta and Omicron variants are shown in Figure 3 (also see Supplementary Results and Supplementary Figure 2).

The observed binding antibody titer (AU/mL) for the ancestral SARS-CoV-2 with D614G was 592,403 (541,404-648,206) 28 days after the administration of the 50-µg booster dose of mRNA-1273.211, 480,711 (387,143-596,895) after the 50-µg dose of mRNA-1273 booster dose, and 803,379 (755,724-854,040) after the 100-µg booster dose of mRNA-1273.211 (Figure 4 and Supplementary Table 5). The Beta-specific binding antibody titers at 28 days after the administration of the 50-µg booster dose of mRNA-1273.211 were 299,241 (272,631-328,450), 199,067 (161,716-245,044) after the 50-µg dose of mRNA-1273, and 393,776 (369,877-419,220) after the 100-µg booster dose of mRNA-1273.211. The Gamma-specific binding antibody titers at 28 days after the administration of the 50-µg booster dose of mRNA-1273.211 were 313,177 (285,485-343,556), 231,094 (198,010-269,706) after the 50-µg dose of mRNA-1273, and 406,226 (381,449-432,613) after the 100-µg booster dose of mRNA-1273.211. The Alpha-specific binding antibody titers at 28 days after the administration of the 50-µg booster dose of mRNA-1273.211 were 454,210 (412,515-500,118), 368,165 (311,720-434,829) after the 50-µg dose of mRNA-1273, and 603,467 (566,823-642,479) after the 100-µg dose of mRNA-1273.211.

Discussion

The results of this study indicate that the bivalent mRNA-1273.211 booster vaccine given to individuals who previously received a 2-dose regimen of 100-µg of the mRNA-1273 primary series has a clinically acceptable safety and reactogenicity profile for both dose levels of mRNA-1273.211 (50 and 100 µg). The 50-µg mRNA-1273.211 booster dose has a safety and reactogenicity profile similar to that of the standard-of-care 50-µg booster dose of mRNA-1273 and to the second dose of the mRNA-1273 primary series.[1,15,21] The incidence of adverse reactions was higher with the 100-µg dose of mRNA-1273.211 compared to that after the 50-µg dose of mRNA-1273.211. This higher incidence of adverse reactions has also been observed with the prototype mRNA-1273 booster when administered at the 100-µg dose level.[23]

Neutralizing antibody titers against SARS-CoV-2 variants remain detectable (GMT<100) 7.0-9.8 months after immunization with the mRNA-1273 primary series at lower levels than the titers against the ancestral SARS-CoV-2. Approximately one month after a first booster dose with mRNA-1273.211 (50 and 100 µg) neutralizing antibodies rose to levels that exceeded the titers after immunization with the primary series (1.9-fold higher for ancestral SARS-CoV-2 and 7.1-fold higher for Beta with 50-µg dose of mRNA-1273.211) and the primary immunogenicity objective of non-inferiority to the primary series vaccination was met. Therefore, immunization with the primary series does not set a ceiling to the neutralizing antibody response and a booster dose of the bivalent vaccine elicits a robust response with titers that are likely to be protective against COVID-19.[1,21,24,25] The neutralizing antibody titers following the 100-µg mRNA-1273.211 dose exceeded the titers after the 50-µg dose. However, the 50-µg mRNA-1273.211 booster dose titers were observed to be at least equivalent to those of the 50-µg dose of mRNA-

1273, and the higher incidence of adverse reactions with the 100-µg booster doses has previously led to the wide use of the 50-µg booster dose in adults[23,26].

A first booster dose with the standard-of-care booster (50-µg mRNA-1273) elicited a potent neutralizing response against the ancestral SARS-CoV-2 and the Beta, Delta and Omicron variants, however the antibody titers, especially for Beta and Omicron, waned 6 months after the booster dose. To evaluate whether a bivalent booster can enhance the breadth and the durability of the neutralizing antibody response, we compared these responses with the mRNA-1273.211 booster (50-µg). The neutralizing antibody titers against ancestral SARS-CoV-2 and all three variants significantly increased 1 and 6-months post-boost with mRNA-1273.211 compared to mRNA-1273 and the superiority immunogenicity objective was met (except for Delta at 6-months, nominal alpha of 0.05). Given that 3.4% and 10.7% of the mRNA-1273.211 (50-µg) and mRNA-1273 booster (50-µg) vaccinees, respectively, had evidence of a SARS-CoV-2 infection, it is unlikely that natural infection led to increased antibody titers in the mRNA-1273.211 group (50-µg) or influenced the booster-to-booster comparison in favor of the mRNA-1273.211 group. In addition, the binding antibody responses (ancestral SARS-CoV-2, Beta, Alpha and Gamma) were consistently higher with the bivalent booster vaccine than the mRNA-1273 booster at approximately one month after the booster dose. Although it is conceivable that the presentation of multiple antigens following the bivalent booster vaccine induces further maturation and evolution of the humoral response, evaluation of antigen-reactive B-cells in the B-cell compartment is needed to further elucidate the mechanisms of enhancing the immune response[27,28].

There are several limitations of this study. The study was not designed and randomized to compare different booster candidates or dose levels head-to-head and the evaluation of booster

candidates was sequential and open-label. Neutralization results from different groups were not generated in the laboratory at the same time and the study was not designed to evaluate vaccine effectiveness or multiple intervals between the primary immunization series and the booster dose. We adjusted for the pre-booster titer levels when comparing the antibody responses between mRNA-1273.211 and mRNA-1273 booster groups to help address this limitation.

Overall, the bivalent mRNA-1273.211 booster vaccine had a clinically acceptable safety profile, comparable to the standard-of-care booster mRNA-1273 when administered at the 50-µg dose level. In addition, the mRNA-1273.211 vaccine (50-µg) elicited robust and persistent antibody responses against multiple variants of concern, even when some of these variants were not contained in the vaccine. Cross-neutralization of multiple variants and the potency and durability of the antibody response appear to be advantages of bivalent booster vaccines that contain both the ancestral SARS-CoV-2 and variant spike sequences, and such vaccines may represent an important strategy as we respond to emerging SARS-CoV-2 variants.

Author Contributions: SC, BN, JF, JMM and HZ contributed to the design of the study and oversight. SC, FE, BE, SK, RP and DCM contributed to data collection. RP and DCM were responsible for immunogenicity assays. SC, HZ, JF, RP, RD and BN contributed to data analysis and/or interpretation of the data. SC, BN and JF contributed to drafting the manuscript. All authors critically reviewed and provided input to manuscript drafts and approved the final version for submission to the journal.

Declaration of Interest: DM reports funding from Moderna, Inc. to perform the pseudovirus neutralization assays; SRW reports funding from Moderna, Inc., Janssen/Johnson and Johnson, and Sanofi for clinical trials; LRB is a co-primary principal investigator of the COVE trial funded by NIAID and conducted in conjunction with Moderna, Inc; and SC, BN, JF, XC, YC, HZ, DKE, RP, BL, JMM, and RD are employees of Moderna Inc. and may hold stock/stock options in the company; BE and FE report no conflicts of interest.

Acknowledgements: Frank J. Dutko and Joanne E. Tomassini (Moderna consultants) for writing and editorial support.

Funding: This study was funded by Moderna Inc., Cambridge, MA.

Data Sharing Statement: As the trial is ongoing, access to patient-level data and supporting clinical documents with qualified external researchers may be available upon request and subject to review once the trial is complete.

Table 1. Demographics and study participant characteristics.

Characteristics n (%)*	50 µg mRNA-1273.211 Booster Dose	100 µg mRNA-1273.211 Booster Dose	Historical Control Group; 100 µg mRNA-1273 Primary Series	External comparator; 50 µg mRNA-1273 Booster Dose
	N=300	N=595	N=584	N=171
Age at Screening (yr)				
Mean (range)	50.7 (19, 85)	53.0 (19, 85)	52.1 (18-87)	52.0 (18, 87)
Age subgroup				
≥18 and <65 years	238 (79)	449 (75)	438 (75)	133 (78)
≥65 years	62 (21)	146 (25)	146 (25)	38 (22)
Gender				
Male	133 (44)	264 (44)	308 (53)	67 (39)
Female	167 (56)	331 (56)	276 (47)	104 (61)
Ethnicity				
Hispanic or Latino	38 (13)	52 (9)	183 (31)	10 (6)
Not Hispanic or Latino	262 (87)	539 (91)	398 (68)	161 (94)
Not reported or unknown	0	4 (1)	3 (1)	0
Race				
White	257 (86)	520 (87)	419 (72)	164 (96)
Black or African American	19 (6)	34 (6)	109 (19)	5 (3)
Asian	9 (3)	18 (3)	13 (2)	1 (1)
American Indian or Alaska Native	1 (<1)	5 (1)	8 (1)	1 (1)
Native Hawaiian or Other Pacific Islander	0	1 (<1)	3 (1)	0
Multiracial	7 (2)	7 (1)	11 (2)	0
Other	4 (1)	6 (1)	16 (3)	0
Not reported or unknown	3 (1)	4 (1)	5 (1)	0
Body Mass Index, (kg/m^2)				
n	300	593	581	168
Mean (SD)	30.7 (7.6)	30.0 (7.1)	31.1 (7.9)	25.5 (3.2)
Duration between second injection of mRNA-1273 and the booster (days)				
n	300	595	NA	170

Median	264	294		219
Q1, Q3	246-276	286-303		199-231
Pre-booster RT-PCR SARS-CoV-2				
Negative	300 (100)	590 (99)	584 (100)	149 (100)
Positive	0	5 (1)	0	3 (2)
Missing	0	0	0	19 (98)
Pre-booster antibody to SARS-CoV-2 nucleocapsid§				
Negative	296 (99)	587 (99)	584 (100)	155 (100)
Positive	4 (1)	8 (1)	0	3 (2)
Missing	0	0	0	13 (98)
Pre-booster SARS-CoV-2 status†				
Negative	296 (99)	582 (98)	584 (100)	140 (82)
Positive	4 (1)	13 (2)	0	6 (4)
Missing	0	0	0	25 (15)

Table 1 Legend: RT-PCR = reverse transcription polymerase chain reaction. Percentages based on the number of participants in the safety set for study P205 or the total number of participants in the historical control and external comparator groups. †Pre-booster (baseline). SARS-CoV-2 status was positive if there was evidence of prior Covid-19, defined as positive binding antibody against the SARS-CoV-2 nucleocapsid or positive RT-PCR at day 1; Negative SARS-CoV-2 status was defined as negative binding antibody against the SARS-CoV-2 nucleocapsid and a negative RT-PCR at day 1. §Elecsys assay for binding antibody to SARS-CoV-2 nucleocapsid.

Table 2: Neutralizing antibody estimated geometric mean titers after the 50-µg mRNA-1273.211 and the 50-µg mRNA-1273 booster doses.

	Day after booster dose	mRNA-1273.211 50 µg booster dose GMT* (95% CI)	mRNA-1273 50 µg booster dose GMT*(95% CI)	**Geometric Mean Ratio**
Ancestral SARS-CoV-2 with D614G	Day 29	2278.0 (2074.0, 2502.1)	1782.7 (1561.3, 2035.6)	**1.28 (1.08, 1.51)**
	Day 181	1040.0 (926.4, 1167.3)	617.2 (525.1, 725.5)	**1.68 (1.38, 2.06)**
Beta	Day 29	1095.3 (981.1, 1222.7)	825.6 (706.6, 964.7)	**1.33 (1.09, 1.61)**
	Day 181	343.5 (303.7, 388.5)	125.2 (105.4, 148.8)	**2.74 (2.22, 3.40)**
Omicron	Day 29	1389.8 (1212.1, 1593.4)	630.5 (520.0, 764.9)	**2.20 (1.74, 2.79)**
	Day 181	312.9 (269.5, 363.4)	145.6 (118.1, 179.5)	**2.15 (1.66, 2.78)**
Delta	Day 29	1481.2 (1335.8, 1642.3)	844.1 (730.2, 975.8)	**1.75 (1.47, 2.10)**
	Day 181	491.3 (437.8, 551.5)	408.0 (347.5, 479.1)	**1.20 (0.99, 1.47)**

Legend: The number of participants was 282-295 for the mRNA-1273.211 group, and 146-149 for the mRNA-1273 group; *Geometric Mean titers (GMTs) are estimated Geometric Least Squares Mean titers with a Mixed Model for Repeated Measures (MMRM) adjusting for age groups and pre-booster titer levels.

Figure 1: Solicited Local and systemic adverse reactions

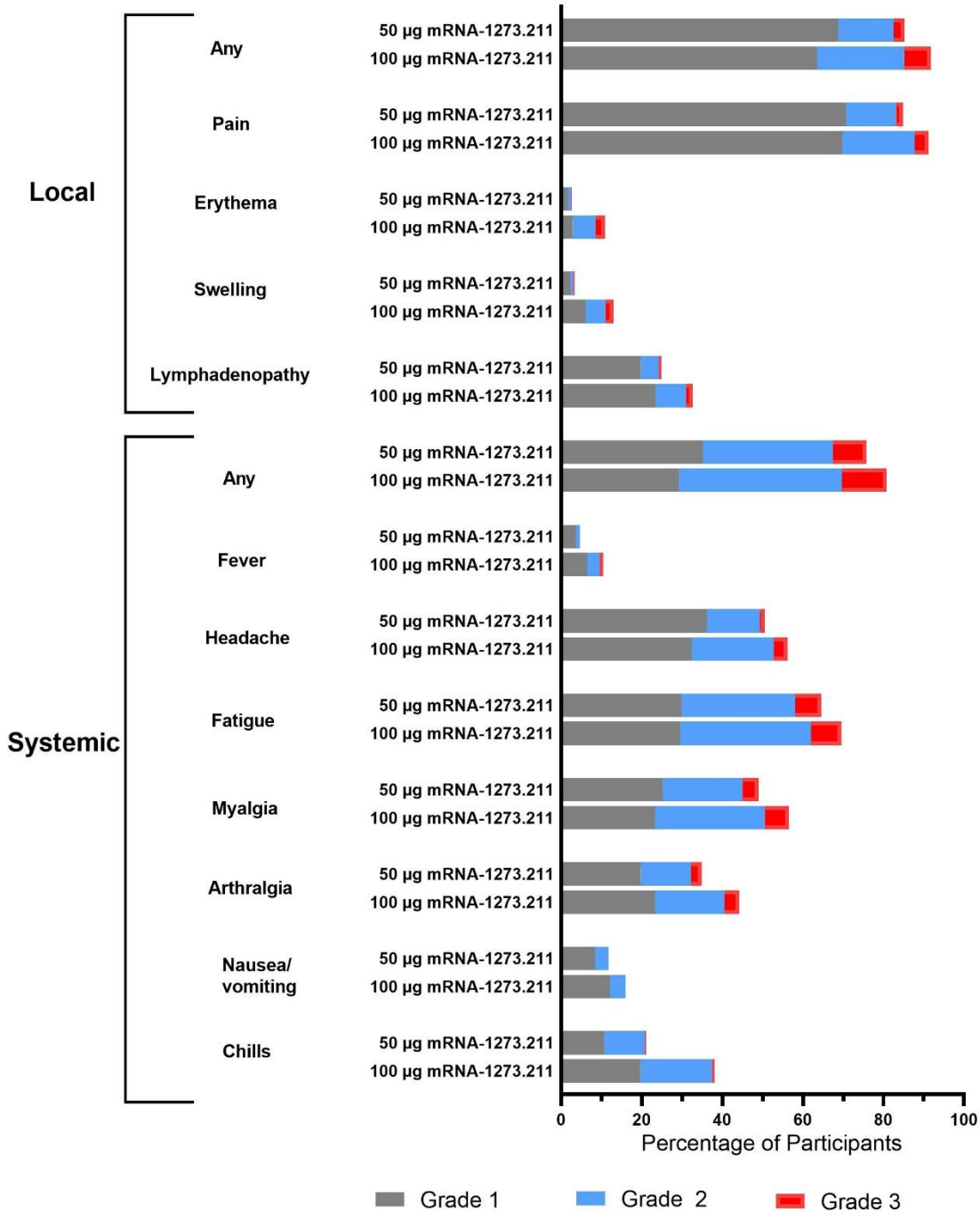


Figure 1: Solicited Local and systemic adverse reactions. Percentages of participants who had a solicited local or systemic reaction within 7 days following 50- and 100-µg doses of the mRNA-1273.211 booster.

Figure 2: Observed neutralizing antibody geometric mean titers against the ancestral SARS-CoV-2 and the Beta variant after the mRNA-1273 primary series and after the booster doses of 50 and 100 µg of mRNA-1273.211.

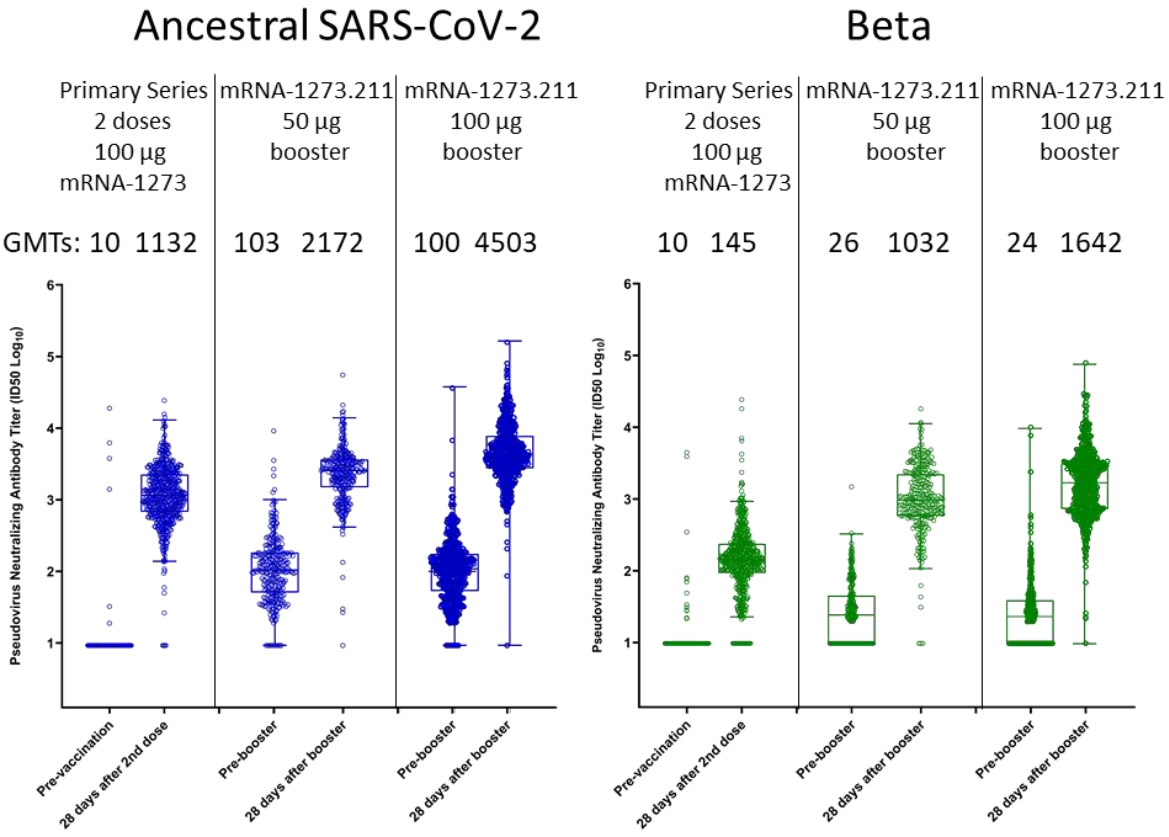
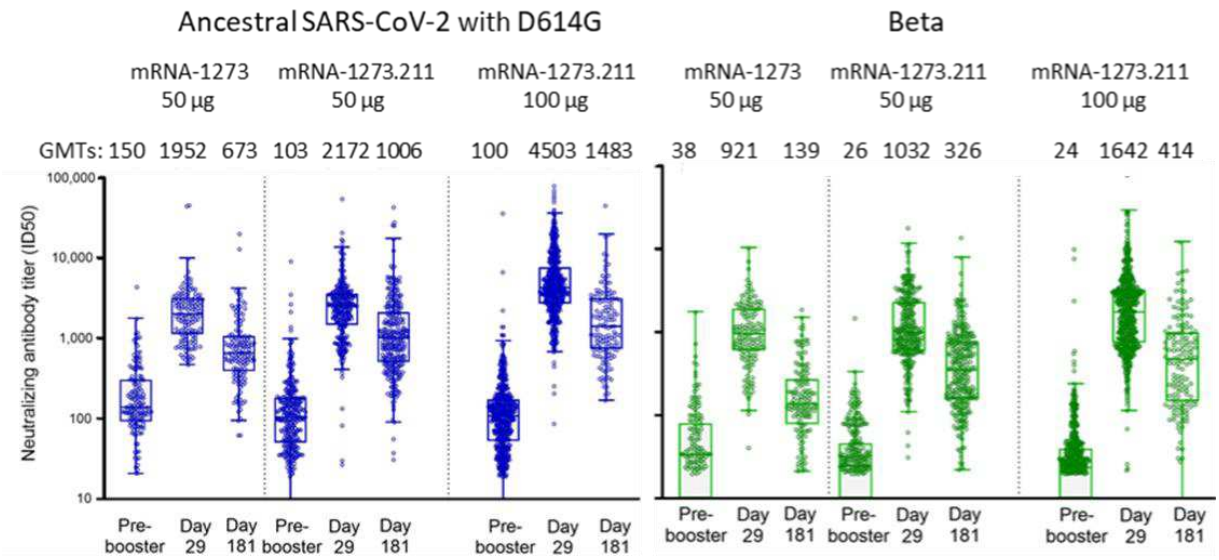


Figure 2 Legend: The neutralizing antibody titers in the pseudovirus assay against the ancestral SARS-CoV-2 with D614G (blue) or the Beta variant (green) are shown for serum samples collected before the first dose of 100 µg of mRNA-1273 in the primary series (pre-vaccination), before the booster dose of 50 or 100 µg of mRNA-1273.211 (pre-booster), at 28 days after the second dose of mRNA-1273 in the primary series (28 days after 2nd dose), and at 28 days after the booster dose (28 days after booster). The circles show the results from individual serum samples. The horizontal lines in the middle of the boxes are the median titers. The boxes extend from the 25th percentile to the 75th percentile. The whiskers were determined using the Tukey method. The tops of the whiskers show the 75th percentile plus 1.5 times the IQR (the difference between the 25th and 75th percentiles). The bottoms of the whiskers show the 25th percentile minus 1.5 times the IQR.

Figure 3: Observed neutralizing antibody geometric mean titers against the ancestral SARS-CoV-2 and against the Beta, Omicron and Delta variants pre-booster, 28 and 180 days after the mRNA-1273 and mRNA-1273.211 booster doses

A. Ancestral SARS-CoV-2 with D614G; Beta



B. Omicron; Delta

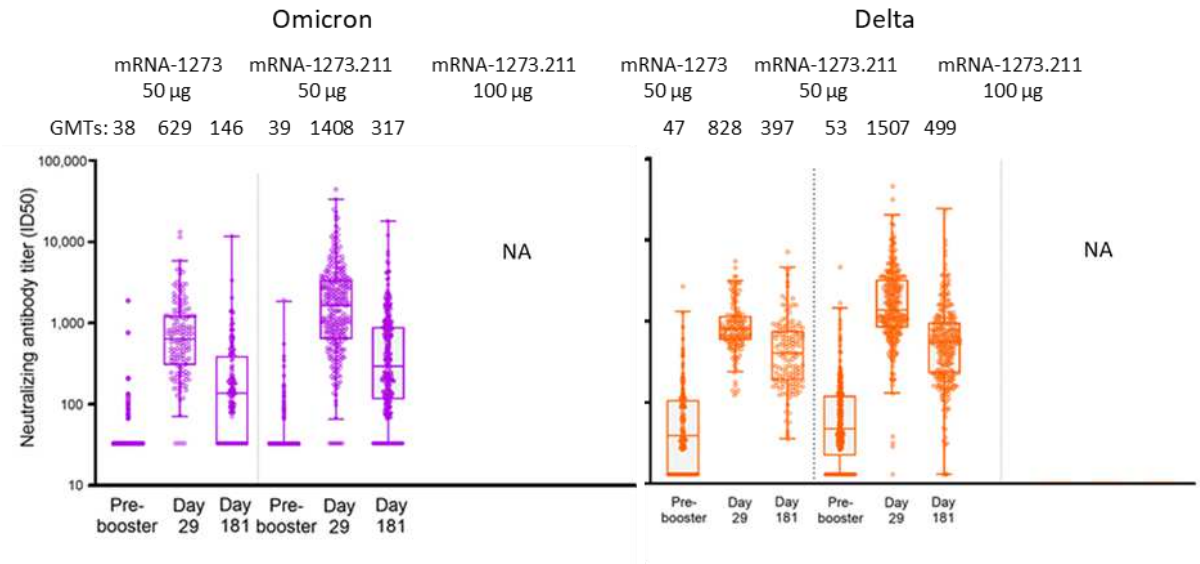


Figure 3 Legend: The neutralizing antibody titers in the pseudovirus assay against the ancestral SARS-CoV-2 with D614G (blue), the Beta variant (green), the Omicron variant (purple) and the Delta variant (orange) are shown for serum samples collected before the booster dose of 50 µg of mRNA-1273, 50 µg of mRNA-1273.211 or 100 µg of mRNA-1273.211 (pre-booster), at 28 days after the booster dose (Day 29), or at 180 days after the booster injection (Day 181). The dots show the results from individual serum samples. The horizontal lines in the middle of the boxes

show the median titers. The boxes extend from the 25th percentile to the 75th percentile. The whiskers were determined using the Tukey method. The tops of the whiskers show the 75th percentile plus 1.5 times the IQR (the difference between the 25th and 75th percentiles). The bottoms of the whiskers show the 25th percentile minus 1.5 times the IQR.

Figure 4: Binding antibody geometric mean titers after the 50 or 100 µg mRNA-1273.211, or 50 µg mRNA-1273 booster doses.

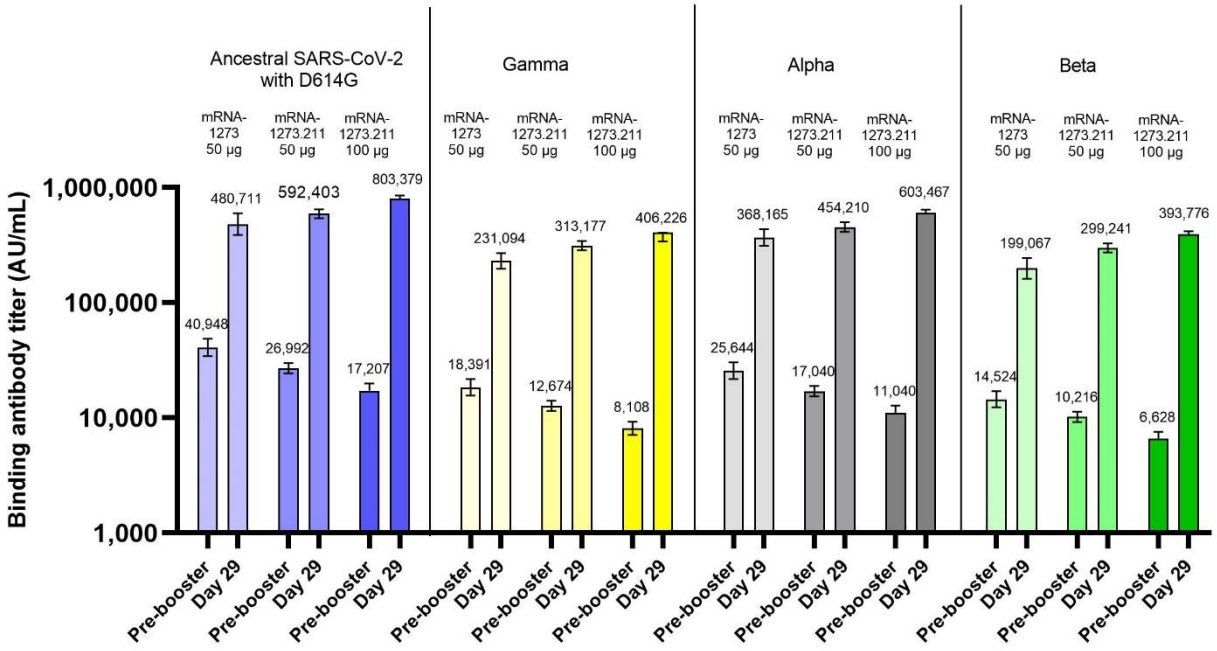


Figure 4 Legend: GM=geometric mean. The titers (AU/mL) of IgG antibodies that specifically bind to the SARS-CoV-2 (blue), Gamma (yellow), Alpha (gray) or Beta (green) spike proteins were measured with the Meso Scale Discovery (MSD) Multi-plex assay. Serum samples were collected before the booster dose of 50 µg of mRNA-1273, 50 µg of mRNA-1273.211 or 100 µg of mRNA-1273.211 (pre-booster), and at 28 days after the booster injection (Day 29). Antibody values reported as below the lower limit of quantification (LLOQ) were replaced by 0.5 times the LLOQ. Antibody values reported as greater than the upper limit of quantification (ULOQ) were converted to the ULOQ if the actual values were not available. The 95% confidence intervals shown by whiskers were calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for the GM value then back transformed to the original scale for presentation.

Supplementary Information

Supplementary Methods

Study Eligibility Criteria

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:

- Male or female, at least 18 years of age at the time of consent (screening visit).
- Investigator's assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
- Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
- Female participants of nonchildbearing potential may be enrolled in the study.
- Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥12 consecutive months prior to Screening [Day 0] without an alternative medical cause). A follicle-stimulating hormone level may be measured at the discretion of the investigator to confirm postmenopausal status.
- Female participants of childbearing potential may be enrolled in the study if the participant fulfills all of the following criteria:
- Has a negative pregnancy test on the day of vaccination (day 1).
- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to day 1.
- Has agreed to continue adequate contraception through 3 months following vaccination.
- Is not currently breastfeeding.
- Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration approved contraceptive method in accordance with the product label.
- Participant must have been previously enrolled in the mRNA-1273 COVE study, must have received 2 doses of mRNA-1273 in Part A of that study (ie, is already unblinded and aware of their actual treatment), with their second dose at least 6 months prior to enrollment in this mRNA-1273 study, and must be currently enrolled and compliant in that study (ie, has not withdrawn or discontinued early).

Exclusion Criteria:

Participants meeting any of the following criteria at the Screening Visit, unless noted otherwise, will be excluded from the study:

- Had significant exposure to someone with SARS CoV 2 infection or coronavirus disease 2019 (COVID-19) in the past 14 days, as defined by the CDC as a close contact of someone who has COVID-19).
- Has known history of SARS CoV-2 infection including during the mRNA-1273 COVE study.
- Is acutely ill or febrile (temperature ≥ 38.0°C [100.4°F]) less than 72 hours prior to or at the screening visit or day 1. Participants meeting this criterion may be rescheduled and will retain their initially assigned participant number.

- Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care, to include significant change in therapy or hospitalization for worsening disease, at the discretion of the investigator.
- Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
- Has a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus, immune-mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
- Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to screening (for corticosteroids ≥ 10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.
- Has known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients.
- Has a medical history consistent with an adverse event of special interest (AESI) (as described in the Appendix).
- Coagulopathy or bleeding disorder considered a contraindication to intramuscular (IM) injection or phlebotomy.
- Has received or plans to receive any licensed vaccine ≤ 28 days prior to the injection (Day 1) or a licensed vaccine within 28 days before or after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.
- Has received systemic immunoglobulins or blood products within 3 months prior to the screening visit (day 0) or plans for receipt during the study.
- Has donated ≥ 450 mL of blood products within 28 days prior to the screening visit or plans to donate blood products during the study.
- Plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.
- Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.
- Is currently experiencing an SAE in Study mRNA-1273 COVE at the time of screening for this study.

Study Objectives: 50 µg mRNA 1273.211 and 100 µg mRNA 1273.211 booster dose, comparison with mRNA-1273 primary series.

Objectives	Endpoints
Primary	
To be assessed for each dose level of mRNA-1273.211 • To demonstrate non-inferior immune response of a single booster dose of mRNA-1273.211 compared with 2 priming doses of mRNA-1273 in the pivotal Phase 3 efficacy trial (Study mRNA-1273-P301 [COVE]): – To demonstrate non-inferiority based on geometric mean titer (GMT) ratio (mRNA-1273.211 vs. mRNA-1273) against the ancestral SARS-CoV-2 with a non-inferiority margin of 1.5 – To demonstrate non-inferiority based on the seroresponse rate (SRR) (mRNA-1273.211 - mRNA-1273) against ancestral SARS-CoV-2 with a non-inferiority margin of 10%	**To be assessed for each dose level of mRNA-1273.211** • GMT ratio of GMT of mRNA-1273.211 against the ancestral SARS-CoV-2 at Day 29 after the booster dose over GMT of mRNA-1273 against the ancestral SARS-CoV-2 at Day 57 (historical control). • SRR difference between mRNA-1273.211 against the ancestral SARS-CoV-2 at Day 29 after the booster dose and mRNA-1273 against the ancestral SARS-CoV-2 at Day 57 (historical control).
To be assessed for each dose level of mRNA-1273.211 • To demonstrate non-inferior immune response based on GMT ratio of mRNA-1273.211 as a single booster dose against Beta variant, compared to mRNA-1273 after 2 priming doses against the ancestral SARS-CoV-2 with a non-inferiority margin of 1.5 • To demonstrate non-inferior immune response based on the SRR of a single booster dose of mRNA-1273.211 against the Beta variant compared to 2 priming doses of mRNA-1273 against the prototype strain with a non-inferiority margin of 10%	**To be assessed for each dose level of mRNA-1273.211** • GMT ratio of GMT of mRNA-1273.211 against the Beta variant at Day 29 after the booster dose over GMT of mRNA-1273 against ancestral SARS-CoV-2 at Day 57 (historical control). • SRR difference between mRNA-1273.211 against the Beta variant at Day 29 after the booster dose and mRNA-1273 against the ancestral SARS-CoV-2 at Day 57 (historical control).
• To evaluate the safety and reactogenicity of mRNA-1273.211	• Solicited local and systemic reactogenicity adverse reactions (ARs) during a 7-day follow-up period after vaccination • Unsolicited adverse events (AEs) during the 28-day follow-up period after vaccination • Serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal and AEs of special interest (AESIs) from Day 1 to end of study

Study Objectives: Comparison of 50 µg mRNA 1273.211 and 500 µg mRNA 1273 booster doses.

Objectives	Immunogenicity endpoints
• To compare the immune response 28 days after the booster dose of 50 µg mRNA-1273.211 to the immune response 28 days after the booster dose of 50 µg mRNA-1273 (external comparator group) • To compare the immune response 180 days after the booster dose of 50 µg mRNA-1273.211 to the immune response 180 days after the booster dose of 50 µg mRNA-1273 in a Phase 2 study (external comparator group)	• Geometric mean titers (GMTs) of the booster doses against the ancestral SARS-CoV-2 and against variants (Beta, Omicron, Delta) • Geometric mean titer ratios (GMR) of the GMT for mRNA-1273.211 / GMT for mRNA-1273, and the 95% confidence intervals (95% CI) o Non-inferiority is not demonstrated if the lower bound of the 95% CI of the GMR is < 0.67 o Non-inferiority without superiority is demonstrated if 0.67 ≤ lower bound of the 95% CI of the GMR ≤ 1 o Superiority is demonstrated if the lower bound of the 95% CI of the GMR is >1

Analysis Sets

Set	Description
Full Analysis Set (FAS)	The FAS consists of all participants who receive investigational product (IP).
Modified Intent-to-Treat (mITT) Set	The mITT Set consists of all participants in the FAS who have no serologic or virologic evidence of prior SARSCoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) pre-booster, ie, all FAS participants with baseline SARS-CoV-2 negative status at pre-booster.
Per-Protocol (PP) Set for Immunogenicity	The PP Set for Immunogenicity consists of all participants in the FAS who received the planned dose of study vaccination and no major protocol deviations that impact key or critical data. The PP Set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified.
Solicited Safety Set	The Solicited Safety Set consists of all participants who receive IP and contribute any solicited adverse reaction (AR) data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the study arm corresponding to the dose of IP that they actually received.
Safety Set	The Safety Set consists of all participants who receive IP. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the study arm corresponding to the dose of IP that they actually received.
Per-Protocol Set for Efficacy	The PP Set for Efficacy consists of all participants in the FAS who receive the planned dose of study vaccination, who are SARS-CoV-2 negative at baseline (ie, have a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at baseline), and have no major protocol deviations that impact key or critical data.

Immunogenicity Assays

SARS-CoV-2 Spike-Pseudotyped Virus Neutralization Assay

SARS-CoV-2 neutralizing antibodies (nAb) in samples were assessed using the validated SARS-CoV-2 Spike (S)-Pseudotyped Virus Neutralization Assay (PsVNA) in 293/ACE2 cells. The PsVNA quantifies nAb using lentivirus particles that express SARS-CoV-2 Wuhan-Hu-1 full-length spike proteins with the following amino acid substitutions (prototype [D614G]; Beta (B.1.351 [501Y-V2]; L18F, D80A, D215G, Δ242-244, R246I, K417N, E484K, N501Y, D614G, and A701V); and Delta ([B.1.617.2; AY.3]; T19R, G142D, Δ156- 157, R158G, L452R, T478K, D614G, P681R, D950N)] on their surface, and contain a firefly luciferase reporter gene for quantitative measurements of infection in transduced 293T cells expressing high levels of ACE2 (293T/ACE2 cells) by relative luminescence units (RLU). Serial dilution of antibodies was used to produce a dose-response curve. Neutralization was measured as the serum dilution at which RLU was reduced by 50% (ID50) relative to mean RLU in virus control wells (cells + virus but no sample) after subtraction of mean RLU in cell control wells (cells only). Positive controls were included on each assay plate in order to follow stability over time. The[10]

SARS-CoV-2 Meso Scale Discovery (MSD) assay

The validated Meso Scale Discovery (MSD, Rockville, MD) assay (SARSCOV2S2P [VAC83]; https://www.mesoscale.com/products/sars-cov-2-panel-2-igg-k15383u/) uses an indirect, quantitative, electrochemiluminescence method to detect SARS-CoV-2 binding IgG antibodies to the SARS-CoV-2 full-length spike protein (Wuhan-Hu-1 ancestral SARS-CoV-2 including D614G; Beta [B.1.351; [501Y-V2] with the following amino acid changes in the spike protein [L18F, D80A, D215G, Δ242-244, R246I, K417N, E484K, N501Y, D614G, and A701V]; Alpha [B.1.1.7; V1] with the following amino acid changes in the spike protein [ΔH69-V70, ΔY144Y, N501Y, A570D, D614G, P681H, T761I, S982A, and D1118H]; Gamma [P.1; V3] with the following amino acid changes in the spike protein [L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F]) in human serum. The assay was performed by PPD, Wilmington, NC. The assay is based on the MSD technology which employs capture molecule MULTI-SPOT® microtiter plates fitted with a series of electrodes.

Supplementary Statistical Analysis

There were four pre-specified immunogenicity endpoints for the primary immunogenicity objective:

(1) Two non-inferiority endpoints based on the Day 29 post-boost GMR (GMT against ancestral SARS-CoV-2 post-boost/GMT against ancestral SARS-CoV-2 after the second dose of the primary series; GMT against the Beta variant /GMT against the ancestral SARS-CoV-2 after the second dose of the primary series) with a non-inferiority margin of 1.5; the GMR-based endpoint was considered met if the lower bound of the 95% CI of each GMR $\geq$ 0.67 (1/1.5).

(2) two non-inferiority endpoints based on the day 29 post-boost difference in the seroresponse rate (SRR); SRR difference between the SRR against the ancestral SARS-CoV-2 post-boost and the SRR against ancestral SARS-CoV-2 after the second dose of the primary series; SRR against the Beta variant post-boost and the SRR against ancestral SARS-CoV-2 after the second dose of the primary series. The SRR difference-based endpoint was considered met if the lower bound of the 95% CI >-10%.

An analysis of covariance (ANCOVA) model was used to assess non-inferiority for the primary immunogenicity objectives. The model included log-transformed antibody titers Day 29 post-boost and 28 days post-second dose of primary series as the dependent variables, treatment groups (50 µg mRNA-1273.211 booster dose vs. 100 µg primary series; or 100 µg mRNA-1273.211 booster dose vs. 100 µg primary series) as explanatory variables and adjustment for age groups (< 65 years; $\geq$ 65 years). The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the antibody titers for each treatment group were calculated. The GLSM, and the corresponding 95% CI results in log-transformed scale estimated from the model were back-transformed to obtain estimates in the original scale. GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI were used to assess the treatment difference.

To assess non-inferiority of the antibody response based on SRR, the number and percentage (rate) of participants achieving seroresponse 28 days after the booster dose or after the second dose in the historical control group were summarized with 95% CI calculated using the Clopper-Pearson method for each group. The difference of SRRs between 50 µg or 100 µg mRNA-1273.211 28 days after the booster dose and 100 µg mRNA-1273 primary 28 days after the second dose were calculated with 95% CI using the Miettinen-Nurminen (score) method.

For the pre-specified booster-to-booster comparisons (antibody responses after the 50 µg mRNA-1273.211 vs. 50 µg mRNA-1273 at 28 and 180 days after the booster doses) the mixed effect model of repeated measure (MMRM) was used to analyze the post-boost observations. For the antibody response against the ancestral SARS-CoV-2 and variants (Beta, Omicron, Delta), the model included treatment groups, clinic visits, treatment by visit interaction, and adjustment for age groups and pre-booster titer levels. An unstructured covariance structure was used to model the within-participant covariance. The geometric least squares means and the corresponding 95% CI for each treatment group were estimated from the model at each post-

boost time-point. The GMR (geometric least squares mean titer after the mRNA-1273.211 booster dose over the mRNA-1273 booster dose) was estimated from the model and the corresponding 95% CI was provided for treatment comparisons at each timepoint.

Supplementary Results

The observed GMTs (95% CIs) against the ancestral SARS-CoV-2 with D614G, were 2171.7 (1952.3-2415.7) at 29 days after the administration of the 50-µg booster dose of mRNA-1273.211, 1951.7 (1729.6-2202.4) after the 50-µg dose of mRNA-1273 booster dose, and 4503.0 (4165.0-4868.5] after the 100-µg booster dose of mRNA-1273.211 (Figure 3; Supplementary Table 4). In addition, the GMTs against the ancestral SARS-CoV-2 with D614G were 1006.1 (880.0-1150.3) at 181 days after the 50-µg booster dose of mRNA-1273.211, 673.3 (578.2-784.0) after the 50-µg booster dose of mRNA-1273, and 1482.6 (1254.7-1752.0) after the 100-µg booster dose of mRNA-1273.211 (Figure 3; Supplementary Table 4).

The observed Beta-specific GMTs (95% CI) were 1032.4 (912.8-1167.8) at 29 days after the 50-µg dose of mRNA-1273.211, 920.5 (797.3-1062.8) after the 50-µg dose of mRNA-1273, and 1641.9 (1504.0-1792.6) after the 100-µg dose of mRNA-1273.211 (Figure 3; Supplementary Table 4). The Beta-specific GMTs were 326.4 (284.2-375.0) at 181 days after the 50-µg dose of mRNA-1273.211, 138.7 (115.6-166.5) after the 50-µg dose of mRNA-1273, and 413.8 (334.9-511.3) after the 100 µg 1273.211 booster (Figure 3; Supplementary Table 4).

The observed Omicron-specific GMTs (95% CI) were 1408.1 (1215.2-1631.6) at 29 days after the 50-µg dose of mRNA-1273.211, and 628.7 (526.0-751.4) after the 50-µg dose of mRNA-1273 (Figure 3; Supplementary Table 4). The Omicron-specific GMTs were 316.5 (269.9-371.3) at 181 days after the 50-µg dose of mRNA-1273.211, and 145.6 (119.3-177.6) after the 50-µg dose of mRNA-1273 (Figure 3; Supplementary Table 4).

The observed Delta-specific GMTs (95% CI) were 1507.4 (1334.2-1703.0) at 29 days after the 50-µg dose of mRNA-1273.211, and 827.8 (738.5-927.9) after the 50-µg dose of mRNA-1273 (Figure 3; Supplementary Table 4). The Delta-specific GMTs were 499.5 (438.6-568.9) at 181 days after the 50-µg dose of mRNA-1273.211, and 397.2 (338.9-465.6) after the 50-µg dose of mRNA-1273 (Figure 3; Supplementary Table 4).

Supplementary Table 1: Solicited local and systemic adverse reactions within 7 days following booster injections of mRNA-1273.211 50 µg or 100 µg, the second dose of mRNA-1273 100 µg primary series, or the booster injection of mRNA-1273 50 µg.

Adverse Reaction, N (%)	50 µg mRNA-1273.211 Booster Dose N=298	100 µg mRNA-1273.211 Booster Dose N=593
Solicited AR, N1	298	593
Any Solicited AR	270 (91)	556 (94)
Grade 1	140 (47)	217 (37)
Grade 2	98 (33)	250 (42)
Grade 3	32 (11)	88 (15)
Grade 4	0	1 (0.2)
Any Solicited Local AR, N1	298	593
Any Solicited Local AR	254 (85)	544 (92)
Grade 1	205 (69)	377 (64)
Grade 2	41 (14)	128 (22)
Grade 3	8 (3)	39 (7)
Local AR, Pain, N1	298	593
Pain	253 (85)	542 (91)
Grade 1	211 (71)	414 (70)
Grade 2	37 (12)	107 (18)
Grade 3	5 (2)	21 (4)
Erythema, N1	298	593
Erythema	8 (3)	64 (11)
Grade 1	5 (2)	17 (3)
Grade 2	2 (1)	33 (6)
Grade 3	1 (0.3)	14 (2)
Swelling, N1	298	593
Swelling	10 (3)	77 (13)
Grade 1	7 (2)	36 (6)
Grade 2	2 (1)	29 (5)
Grade 3	1 (0.3)	12 (2)
Axillary Swelling or Tenderness, N1	298	593
Axillary Swelling	74 (25)	194 (33)
Grade 1	59 (20)	139 (23)

Grade 2	13 (4)	45 (8)
Grade 3	2 (0.7)	10 (2)
Any Systemic AR, N1	298	593
Any Systemic AR	226 (76)	480 (81)
Grade 1	105 (35)	173 (29)
Grade 2	96 (32)	240 (40)
Grade 3	25 (8)	66 (11)
Grade 4	0	1 (0.2)
Fever, N1	298	593
Fever	14 (5)	63 (11)
Grade 1	11 (4)	38 (6)
Grade 2	3 (1)	19 (3)
Grade 3	0	5 (1)
Grade 4	0	1 (0.2)
Headache, N1	298	593
Headache	151 (51)	333 (56)
Grade 1	108 (36)	192 (32)
Grade 2	39 (13)	121 (20)
Grade 3	4 (1)	20 (3)
Grade 4	0	0
Fatigue, N1	298	593
Fatigue	192 (64)	413 (70)
Grade 1	89 (30)	175 (30)
Grade 2	84 (28)	193 (33)
Grade 3	19 (6)	45 (8)
Grade 4	0	0
Myalgia, N1	298	593
Myalgia	146 (49)	335 (56)
Grade 1	75 (25)	138 (23)
Grade 2	59 (20)	162 (27)
Grade 3	12 (4)	35 (6)
Grade 4	0	0
Arthralgia, N1	298	593
Arthralgia	104 (35)	262 (44)

Grade 1	59 (20)	138 (23)
Grade 2	37 (12)	102 (17)
Grade 3	8 (3)	22 (4)
Grade 4	0	0
Nausea/ vomiting, N1	298	593
Nausea / vomiting	35 (12)	95 (16)
Grade 1	25 (8)	72 (12)
Grade 2	10 (3)	23 (4)
Grade 3	0	0
Grade 4	0	0
Chills, N1	298	593
Chills	63 (21)	226 (38)
Grade 1	32 (11)	117 (20)
Grade 2	30 (10)	105 (18)
Grade 3	1 (0.3)	4 (1)
Grade 4	0	0

AR=adverse reaction. Any=Grade 1 or higher. N1=Number of exposed participants with any information about the adverse event.

Supplementary Table 2. Summary of Unsolicited Adverse Events ≤28 Days Post-injection

n (%)	mRNA-1273.211 50 µg (N=300)	mRNA-1273.211 100 µg (N=595)
Unsolicited AEs Regardless of Relationship to Study Vaccination		
All	63 (21.0)	129 (21.7)
Serious	0	5 (0.8)
Fatal	0	0
Medically attended	21 (7.0)	74 (12.4)
Leading to discontinuation from study	0	0
Severe	1 (0.3)	12 (2.0)
AESI	0	0
Unsolicited AEs related to study vaccination		
All	27 (9.0)	54 (9.1)
Serious	0	0
Fatal	0	0
Medically attended	1 (0.3)	1 (0.2)
Leading to discontinuation from study	0	0
Severe	1 (0.3)	7 (1.2)
AESI	0	0

Legend: AE, adverse event; AESI, adverse event of special interest.
An adverse event was defined as any event not present prior to study vaccination or any event already present that worsened in intensity or frequency after vaccination. Percentages are based on the number of participants in the safety set.

Supplementary Table 3: Estimated neutralizing antibody titers after the mRNA-1273 primary series and after the 50-µg and 100-µg booster dose of mRNA-1273.211

	Ancestral SARS-CoV-2 (D614G)		Beta (B.1.351)	Ancestral SARS-CoV-2 (D614G)
	50 µg mRNA-1273.211 Booster Dose	Historical Control 100 µg mRNA-1273 Primary Series	50 µg mRNA-1273.211 Booster Dose	Historical Control 100 µg mRNA-1273 Primary Series
	N=299	N=584	N=299	N=584
Pre-vaccination Baseline n†	299	584	297	584
GMT (95% CI)§	9.4 (9.1-9.7)	9.7 (9.3-10.1)	9.8 (NE-NE)	9.7 (9.3-10.1)
28 days post-booster or 2nd dose, n	299	584	299	584
Estimated GMT (95% CI)¶	1996.2 (1777.9-2241.4)	1053.4 (967.2-1147.2)	953.9 (844.1-1078.0)	1058.0 (966.9-1157.7)
GMR (mRNA-1273.211-50 µg vs 100 µg mRNA-1273) (95% CI)	1.9 (1.7-2.2)		0.9 (0.8-1.0)	
Seroresponse rates n/N1 (%) (vs. pre-vaccination)‖	295/299 (98.7)	573/584 (98.1)	291/297 (98.0)	576/572 (98.1)
(95% CI)‡	96.6-99.6	96.7-99.1	95.7-99.3	96.7-99.1
Difference % (95% CI)††	0.5 (-1.6-2.2)		-0.1 (-2.6-1.7)	
	100 µg mRNA-1273.211 Booster Dose	Historical Control 100 µg mRNA-1273 Primary Series	100 µg mRNA-1273.211 Booster Dose	Historical Control 100 µg mRNA-1273 Primary Series
	N=578	N=584	N=584	N=584
Pre-vaccination Baseline n†	578	584	571	584
GMT (95% CI)§	9.4 (9.2-9.5)	9.7 (9.3-10.1)	9.8 (9.7-9.9)	9.7 (9.3-10.1)
28 days post-booster or 2nd dose, n	578	584	578	584
Estimated GMT (95% CI)¶	4324.7 (3974.6-4705.6)	1087.3 (999.7-1182.6)	1574.6 (1439.4-1722.5)	1085.7 (992.9-1187.2)
GMR (mRNA-1273.211-100 µg vs 100 µg mRNA-1273) (95% CI)	4.0 (3.6, 4.4)		1.5 (1.3, 1.6)	
Seroresponse rates n/N1 (%) (vs. pre-vaccination)‖	577/578 (99.8)	573/584 (98.1)	566/571 (99.1)	573/584 (98.1)
(95% CI)‡	(99.0-100.0)	(96.7-99.1)	(98.0-99.7)	(96.7-99.1)
Difference % (95% CI)††	1.7 (0.7-3.2)		1.0 (-0.4-2.6)	

Legend: ANCOVA=analysis of covariance, CI = Confidence interval, GMT=geometric mean titer. GMR = Geometric mean ratio. ID50, 50% inhibitory dose; LLOQ, lower limit of quantification; LS, least squares; NE=Not Estimated; ULOQ, upper limit of quantification.
Antibody values assessed by pseudovirus neutralizing antibody assay reported as below the LLOQ are replaced by 0.5 × LLOQ and values greater than ULOQ are replaced by the ULOQ if actual values are not available.
* Betas-specific antibody data is shown for the mRNA-1273.211 booster and for the ancestral SARS-Cov-2 with D614G for the historical control.
†Number of subjects with non-missing data at the timepoint (baseline or post-baseline).
§95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.
¶The log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years). The treatment variable corresponds to the historical control group and each individual study group (mRNA-1273.211) dose levels. The resulting least squares means, difference of the least squares means, and 95% CI are back transformed to the original scale for presentation.
‖Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline (=titer before receiving the mRNA-1273 primary series) is equal to or above the LLOQ. Percentages were based on the number of participants with non-missing data at baseline and the corresponding time point (N1). For study participants with negative SARS-CoV-2 status prior to the primary series, antibody titers are imputed as <LLOQ at pre-dose 1 of the primary series. For participants without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at pre-dose 1 of the primary series.
‡95% CI calculated using the Clopper-Pearson method.
††95% CI calculated using the Miettinen-Nurminen (score) confidence limits.

Supplementary Table 4: Observed neutralizing antibody geometric mean titers (ID50s) after the 50 or 100 µg mRNA-1273.211 and 50 µg mRNA-1273 booster doses

	Booster Dose		
	50 µg mRNA-1273	50 µg mRNA-1273.211	100 µg mRNA-1273.211
Pre-booster, Ancestral with D614G, n	149	299	578
GMT	150.2	103.0	99.9
95% CI	125.7, 179.5	91.4, 116.1	92.2, 108.3
Day 29,n	149	299	578
GMT	1951.7	2171.7	4503.0
95% CI	1729.6, 2202.4	1952.3, 2415.7	4165.0, 4868.5

Day 181, n	147	287	143
GMT	673.3	1006.1	1482.6
95% CI	578.2, 784.0	880.0, 1150.3	1254.7, 1752.0
Pre-booster, Beta (B.1.351), n	149	299	578
GMT	37.5	25.6	23.9
95% CI	31.4, 44.9	23.0, 28.5	22.1, 25.9
Day 29, n	149	299	578
GMT	920.5	1032.4	1641.9
95% CI	797.3, 1062.8	912.8, 1167.8	1503.9, 1792.6
Day 181, n	147	287	143
GMT	138.7	326.4	413.8
95% CI	115.6, 166.5	284.2, 375.0	334.9, 511.3
Pre-booster, Omicron (B.1.1.529), n	147	298	NA
GMT	38.3	38.6	
95% CI	35.1, 41.9	36.4, 40.9	
Day 29, n	147	298	NA
GMT	628.7	1408.1	
95% CI	526.0, 751.4	1215.2, 1631.6	
Day 181, n	146	287	NA
GMT	145.6	316.5	
95% CI	119.3, 177.6	269.9, 371.3	
Pre-booster, Delta (B.1.617.2), n	149	298	NA
GMT	47.4	52.8	
95% CI	39.3, 57.1	46.5, 59.9	
Day 29, n	149	298	NA

GMT	827.8	1507.4	
95% CI	738.5, 927.9	1334.2, 1703.0	
Day 181, n	147	286	NA
GMT	397.2	499.5	
95% CI	338.9, 465.6	438.6, 568.9	

Legend: GMT=geometric mean titer. NA=not available. The observed GMTs (ID50s) for neutralizing antibodies in the pseudovirus lentivirus assay are shown.

Supplementary Table 5: Binding antibody titers after the 50 or 100 µg mRNA-1273.211, or 50 µg mRNA-1273 booster doses

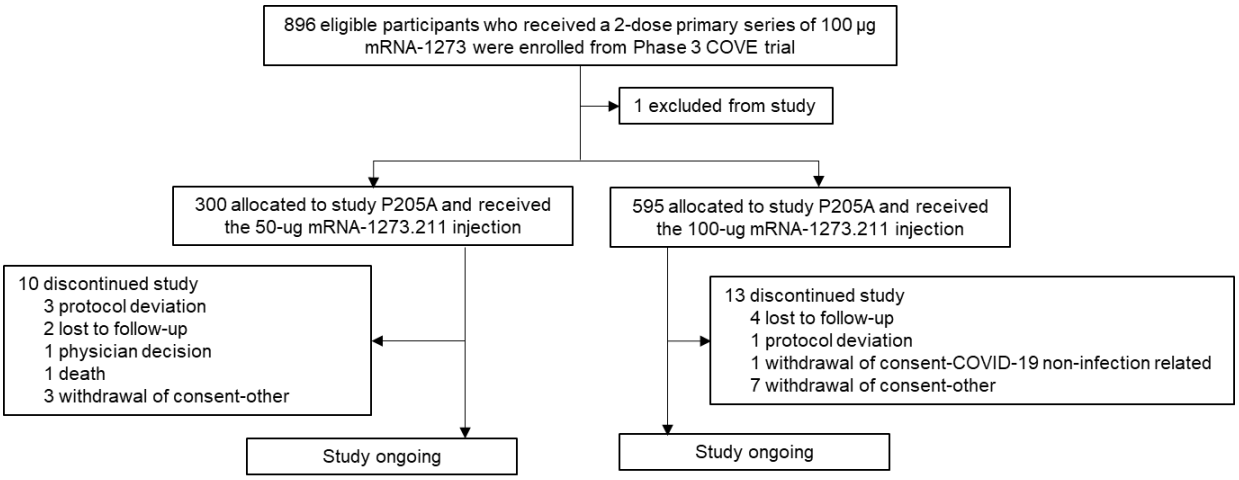
	50 µg mRNA-1273	50 µg mRNA-1273.211	100 µg mRNA-1273.211
Pre-booster, Ancestral with D614G, n	147	299	578
GMT (AU/mL)	40,948	26,992	17,207
95% CI	34,468-48,647	24,319-29,958	14,907-19,860
Day 29, n	148	299	577
GMT (AU/mL)	480,711	592,403	803,379
95% CI	387,143-596,895	541,404-648,206	755,724-854,040
Pre-booster, Gamma (P.1), n	147	299	578
GMT (AU/mL)	18,391	12,674	8,108
95% CI	15,618-21,656	11,418-14,068	7,105-9,252
Day 29, n	148	299	577
GMT (AU/mL)	231,094	313,177	406,226
95% CI	198,010-269,706	285,485-343,556	381,449-432,613
Pre-booster, Alpha (B.1.1.7), n	147	299	578
GMT (AU/mL)	25,644	17,040	11,040
95% CI	21,715-30,283	15,350-18,916	9,568-12,739
Day 29, n	148	299	577
GMT (AU/mL)	368,165	454,210	603,467
95% CI	311,720-434,829	412,515-500,118	566,823-642,479
Pre-booster, Beta (B.1.351), n	147	299	578

GMT (AU/mL)	14,524	10,216	6,628
95% CI	12,368-17,056	9,225-11,314	5,796-7,579
Day 29, n	148	299	577
GMT (AU/mL)	199,067	299,241	393,776
95% CI	161,716-245,044	272,631-328,450	369,877-419,220

Legend: GMT=geometric mean titer; CI=confidence interval. The titers (AU/mL) of IgG antibodies that specifically bind to the SARS-CoV-2, Gamma, Alpha or Beta spike proteins were determined by the Mesoscale Discovery (MSD) Multiplex (VAC83) assay. Serum samples were collected before the booster injection of 50 µg of mRNA-1273, 50 µg of mRNA-1273.211 or 100 µg of mRNA-1273.211 (pre-booster), and at 28 days after the booster injection (Day 29). Antibody values reported as below the lower limit of quantification (LLOQ) were replaced by 0.5 times the LLOQ. Antibody values reported as greater than the upper limit of quantification (ULLQ) were converted to the ULOQ if the actual values were not available. The 95% confidence intervals shown by whiskers were calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for the GM value then back transformed to the original scale for presentation.

Supplementary Figure 1. Trial profile.

A. **P205 Part A**



B. External comparator group

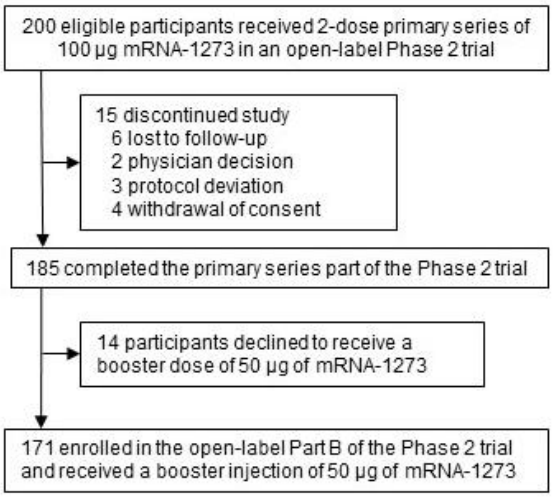
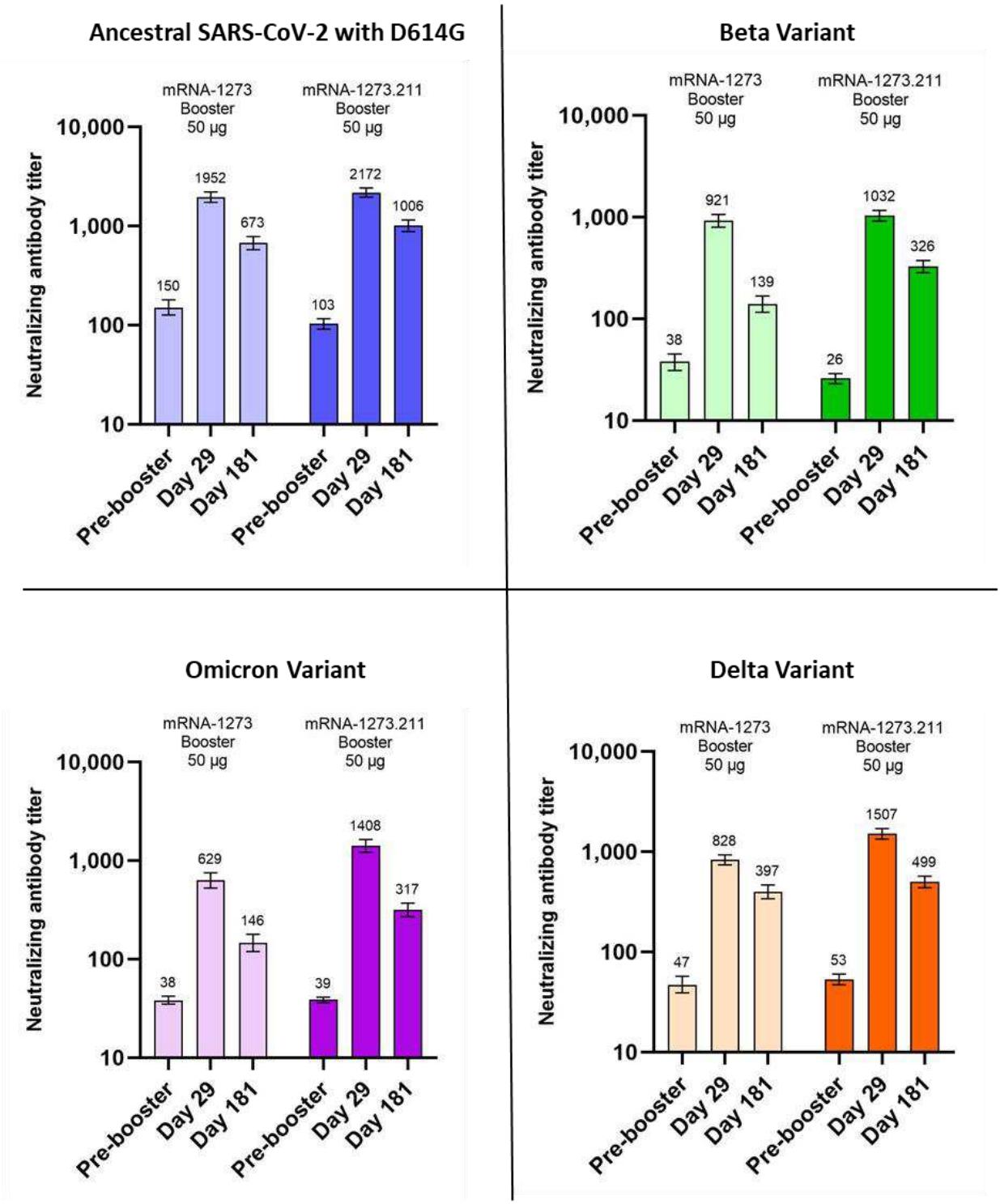


Figure 1. Trial profile. A. Study P205: Trial profile of participants in Study P205 Part A who received a booster dose of 50 µg mRNA-1273.211 or 100 µg mRNA-1273.211. **B.** Trial profile of participants who received 50 µg booster dose of mRNA-1273 in open-label Phase 2 trial.

Supplementary Figure 2: Observed neutralizing antibody titers after the 50 µg mRNA-1273.211 and 50 µg mRNA-1273 booster doses



Legend: The neutralizing antibody geometric mean titers in the pseudovirus assay against the ancestral SARS-CoV-2 with D614G (blue), Beta variant (green), Omicron variant (purple) and Delta variant (orange) are shown for serum samples collected before the booster injection of 50 µg of mRNA-1273 or

50 µg of mRNA-1273.211 (pre-booster), at 28 days after the booster injection (Day 29), and at 180 days after the booster injection (Day 181). The 95% confidence intervals shown by whiskers were calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for the GM value then back transformed to the original scale for presentation.

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