Supplementary Appendix

Supplement to: Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2208343

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

TABLE OF CONTENTS

List of Investigators

Investigator	Institution	Location
Paul Bradley	Meridian Clinical Research	Savannah, Georgia
Adam Brosz	Meridian Clinical Research	Grand Island, Nebraska
Laurence Chu	Benchmark Research	Austin, Texas
Michael Cotugno	Benchmark Research	Metairie, Louisiana
Frank Eder	Meridian Clinical Research, LLC	Binghamton, New York
David Ensz	Meridian Clinical Research	Sioux City, Iowa
Brandon Essink	Meridian Clinical Research	Omaha, Nebraska
Carlos Fierro	Johnson County Clin-Trials	Lenexa, Kansas
Veronica Fragoso	DM Clinical Research - Texas Center for Drug Development	Houston, Texas
Carl Griffin	Lynn Health Science Institute	Oklahoma City, Oklahoma
Greg Hachigian	Benchmark Research	Sacramento, California
Shishir Khetan	Meridian Clinical Research	Rockville, Maryland
Michael Koren	Jacksonville Center for Clinical Research	Jacksonville, Florida
Vicki Miller	DM Clinical Research	Tomball, Texas
Paul Pickrell	Tekton Research Inc.	Austin, Texas
Rachel Presti	Infectious Disease Clinical Research	Saint Louis, Missouri
Howard Schwartz	Research Centers of America	Hollywood, Florida
William Seger	Benchmark Research	Fort Worth, Texas
Charles Harper. Keith Vrbicky,	Meridian Clinical Research	Norfolk, Nebraska
Larkin Wadsworth	Sundance Clinical Research	Saint Louis, Missouri
Stephen Walsh	Brigham and Womens Hospital	Boston, Massachusetts
Jordan Whatley	Meridian Clinical Research	Baton Rouge, Louisiana
Barton Williams	Trial Management Associates LLC	Wilmington, North Carolina
Marcus Zervos	Henry Ford Health System	Detroit, Michigan

SUPPLEMENTARY METHODS

Study Design

This is an open-label, ongoing, 6-part, phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of various modified mRNA-1273 vaccine candidates against Covid-19 administered as boosters (mRNA1273.211, mRNA1273, mRNA1273.617.2, mRNA-1273.213, mRNA1273.529, and mRNA-1273.214; clintrials.gov NCT04927065). Part G interim results are reported here. In part G, the bivalent mRNA-1273.214 vaccine which contains 25 ug each of two mRNAs encoding the ancestral SARS-CoV-2 and omicron variant (B.1.1.529) spike sequences is tested as a second booster dose at 50-µg in comparison to mRNA-1273 given as a second booster dose in part F, cohort 2) of the study. Study part F Cohort 2 will assess whether a single booster dose of the mRNA-1273.529 administered as a second booster dose elicits a similar or superior antibody response to the omicron (B.1.1.529) compared to a single booster dose of 50-µg mRNA-1273 as a second booster dose (part F, cohort 2, 50-µg mRNA-1273).

Enrollment of the mRNA-1273.214 50-µg second boost arm is initiated upon completion of enrollment of the mRNA-1273 50-µg arm in cohort 2 of part F. Part G evaluates the immunogenicity, safety, and reactogenicity of 50-µg of the mRNA1273.214 vaccine candidate when administered as a second booster dose to adults who have previously received 2 doses of 100 µg mRNA-1273 as a primary series and a first booster dose of mRNA-1273 (50 µg) in the Coronavirus Efficacy (COVE) trial[1,2] or under US emergency use authorization (EUA). The immunogenicity of mRNA-1273.214 50-µg is compared to that induced after the second booster dose of mRNA 1273 (Part F, cohort 2, 50-µg mRNA-1273).

Trial Registration

The study protocol was approved by the Institutional Review Board (IRB) on May 26th 2021, and enrollment in part A of the study was initiated on May 28, 2021, before the trial posting date of June 14, 2021 on the clintrials.gov registration website as we were emergently advancing Covid-19 booster vaccine candidates to combat the SARS-CoV-2 pandemic (the objective of this trial). Nonetheless, the trial was registered within 21 days after the first participant was enrolled, compliant per clintrials.gov guidance (https://clinicaltrials.gov/ct2/manage-recs/fdaaa). Additionally, in parts F and G of the study presented in this manuscript, the 819 participants were enrolled during February and March 2022. Moderna has received an emergency use authorization (EUA) of our booster vaccine mRNA-1273 by regulatory agencies, and we are also currently pursuing EUA for booster candidates evaluated in this trial.

Trial Oversight

The trial is being conducted across 23 US sites, in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice guidelines. The central IRB approved the protocol and consent forms. All participants provided written informed consent.

SC, JF, JMM, RD and HZ contributed to the design of the study and oversight. SC, CH, KV, SRW, BE, AB and NMcG contributed to data collection. BG and DCM were responsible for immunogenicity assays. SC, JF, HZ, RD, JMM, LRB and JET contributed to data analysis and/or interpretation of the data. SC, JF, LRB and JET 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.

Part G Study Eligibility Criteria
Inclusion Criteria:

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

1. Male or female, at least 18 years of age at the time of consent (Screening Visit).
2. Investigator's assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. 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.
5. 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)
6. Participant must have been either previously enrolled in the phase 3 mRNA 1273 COVE trial,[1,2] must have received 2 doses of mRNA 1273 in that study, with his/her second dose at least 6 months prior to enrollment in this study, and must be currently enrolled and compliant in that study (i.e., has not withdrawn or discontinued early); or participant must have received 2 doses of mRNA-1273 under the EUA with their second dose at least 6 months prior to enrollment in this study; or have received a 2 dose primary series of mRNA-1273 followed by a 50-µg booster dose of mRNA-1273 in the mRNA-1273 COVE trial or under EUA at least 3 months prior to enrollment this study; and able to provide proof of vaccination status at the time of screening (day 1).

Exclusion Criteria:

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

1. 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).
2. Has known history of SARS-CoV-2 infection within 3 months prior to enrollment.
3. 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.

4. 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.
5. 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.
6. Has a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus, immune-mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
7. 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.
8. Has known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients.
9. Has a documented history of myocarditis or pericarditis within 2 months prior to Screening Visit (day 0).
10. Coagulopathy or bleeding disorder considered a contraindication to intramuscular (IM) injection or phlebotomy.
11. 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.
12. Has received systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (day 0) or plans for receipt during the study.
13. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
14. Plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.
15. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.
16. Is currently experiencing an SAE in COVE trial at the time of screening for this study.

Trial Vaccine

The mRNA-1273.214 50-µg vaccine contains equal amounts of mRNAs (25-µg of each mRNA sequence) that encode the prefusion-stabilized spike glycoproteins of the ancestral SARS-CoV-2 (Wuhan-Hu-1) and the omicron variant (B.1.1.529 [BA.1]). The mRNA-1273 50-µg vaccine (Moderna Covid-19 Vaccine) contains only the mRNA sequence encoding the spike glycoprotein of the ancestral SARS-CoV-2. In both vaccines, mRNAs are encapsulated in lipid nanoparticles (LNPs) as described previously.[3] The booster doses of mRNA-1273.214 and mRNA-1273 were administered by intramuscular injection at doses of 50-µg of mRNA in a 0.5 mL volume.

Immunogenicity Objectives and Endpoints

There were four pre-specified immunogenicity objectives at day 29 in the study (Table S1 and Fig. S2) including:

1) the second booster dose of 50-µg mRNA-1273.214 was non-inferior compared to the second booster dose of 50-µg mRNA-1273 based on the GMT ratio of mRNA-1273.214 against the omicron variant compared to mRNA-1273 against the omicron variant with a non-inferiority margin of 1.5
2) the second dose of 50-µg mRNA-1273.214 was non-inferior to the second booster dose of 50-µg mRNA-1273 against the omicron variant based on the difference in seroresponse rate (SRR) with a non-inferiority margin of 10%
3) the second booster dose of 50-µg mRNA-1273.214 was non-inferior to the second booster dose of 50-µg mRNA-1273 against the ancestral SARS-CoV-2 (D614G) based on the GMT ratio of mRNA-1273.214 against the ancestral SARS-CoV-2 (D614G) compared to mRNA-1273 against the ancestral SARS-CoV-2 (D614G) with a non-inferiority margin of 1.5
4) the second booster dose of 50-µg mRNA-1273.214 was superior to the second booster dose of 50-µg mRNA-1273 against omicron B.1.1.529 based on the GMT ratio of mRNA-1273.214 against the omicron variant compared to mRNA-1273 against the omicron variant. The fourth objective is only tested if the first 3 non-inferiority hypotheses are demonstrated (Fig. S1)

If all primary immunogenicity hypotheses are demonstrated, the key secondary objective, the second booster dose of 50-µg mRNA-1273.214 was non-inferior to the booster dose of 50-µg of mRNA-1273 against ancestral SARS-CoV-2 (D614G) based on the difference in SRR at day 29 with a non-inferiority margin of 10% is tested.

Statistical Analysis of Immunogenicity

In part G of the study, 50-µg mRNA-1273.214 as the second booster dose is compared to 50-µg mRNA-1273 as the second booster dose (active control arm in part F, Cohort 2). For the primary objective on immune response, 8 hypotheses (4 identical hypotheses each at days 29 and 91) are specified to be evaluated at days 29 and 91 (online protocol and SAP and Fig. S2). Only interim analysis results for the day 29 hypotheses are presented in this report; hypotheses for day 91 will be tested later when day 91 data become available.

Below are the 4 hypotheses for day 29 (day 91 hypotheses are provided in the online protocol and SAP).

1) 50-µg mRNA-1273.214, as a second booster dose, against the omicron (B.1.1.529) variant is non-inferior to the second booster dose of (50-µg) mRNA-1273 against the omicron (B.1.1.529) based on the GMT ratio of mRNA1273.214 compared to mRNA-1273 against omicron (B.1.1.529) at day 29 with a non-inferiority margin of 1.5.
2) 50-µg mRNA-1273.214, as a second booster dose, against the omicron (B.1.1.529) variant is non-inferior to the second booster dose of (50-µg) mRNA-1273 against omicron (B.1.1.529) based on the difference in SRR at day 29 with a non-inferiority margin of 10%.
3) 50-µg mRNA-1273.214, as a second booster dose, against ancestral SARS-CoV-2 (D614G) is non-inferior to the second booster dose of (50-µg) mRNA-1273 against ancestral SARS-CoV-2 (D614G) based on the GMT ratio of mRNA-1273.214 compared to mRNA-1273 against the ancestral SARS-CoV-2 (D614G) at day 29 with a non-inferiority margin of 1.5.
4) 50-µg mRNA-1273.214, as a second booster dose, against the omicron (B.1.1.529) variant is superior to the second booster dose of (50-µg) mRNA-1273 against B.1.1.529 based on

the GMT ratio of mRNA-1273.214 compared to mRNA-1273 against the omicron (B.1.1.529) at day 29.

For the primary immunogenicity objective, an alpha of 0.05 (two-sided) is allocated to the two time points (days 29 and 91). Days 29 and 91 each have an alpha of 0.025 (two-sided) for hypotheses testing. The primary immunogenicity objective is considered met if non-inferiority against omicron B.1.1.529 based on GMR and SRR difference, and non-inferiority against ancestral SARS-CoV-2 (D614G) based on GMR are demonstrated at days 29 or 91. The non-inferiority margins of 1.5 for GMR and 10% for SRR difference were chosen based on FDA guidelines.[4,5]

For the key secondary immunogenicity objective, there are 2 hypotheses to be tested (days 29 and 91 will each have alpha of 0.025 [two-sided] for hypotheses testing):

1) 50-µg mRNA-1273.214, as a second booster dose, against ancestral SARS-CoV-2 (D614G) is non-inferior to the booster dose of (50-µg) mRNA-1273 against ancestral SARS-CoV-2 (D614G) based on the difference in SRR at day 29 with a non-inferiority margin of 10%.
2) 50-µg mRNA-1273.214, as a second booster dose, against ancestral SARSCoV2 (D614G) is non-inferior to the booster dose of (50-µg) mRNA1273 against ancestral SARS-CoV-2 (D614G) based on the difference in SRR at day 91 with a non-inferiority margin of 10%.

Sample Size

The planned target enrollments are approximately 375 participants for 50-µg mRNA-1273.214 in part G and for the comparator 50-µg mRNA-1273 in part F (cohort 2). Hypotheses testing is performed at days 29 and 91, alpha of 0.025 (2-sided) will be allocated equally to each one of the two time points. Assuming 20% of participants will be excluded from the PP Set for Immunogenicity – SARS-CoV-2 negative, with approximately 300 participants in 50-µg mRNA-1273.214 and 300 participants in 50-µg mRNA-1273 (part F, Cohort 2, 50-µg mRNA-1273) in the PP Set for Immunogenicity and SARS-CoV-2 negative, there is approximately 71% global power to demonstrate the primary immunogenicity objectives with alpha of 0.025 (2-sided) at each time point. The assumptions are: the true GMR (mRNA-1273.214 second booster vs 50-µg mRNA-1273 second booster) against the omicron variant (B.1.1.529) is 1.5, the true GMR against ancestral SARS-CoV-2 (D614G) is 1, the standard deviation of the log-transformed titer is 1.5, and the non-inferiority margin for GMR is 1.5, the true SRR against B.1.1.529 after mRNA-1273.214 as a second booster dose is 90% (same assumption for both 50-µg mRNA-1273.214 and 50-µg mRNA-1273), and non-inferiority margin for SRR difference is 10%. With approximately 375 participants exposed to 50-µg mRNA-1273.214, there is at least 90% probability in this group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

An analysis of covariance (ANCOVA) model was performed to assess the difference in antibody responses between mRNA-1273.214 and mRNA-1273 booster doses, with antibody titers post-booster as a dependent variable, and a group variable (mRNA-1273.214 and mRNA-1273) as the fixed effect, adjusting for age groups (<65, ≥65 years) and pre-booster antibody titers. The GMTs (95% CI) estimated by the geometric least square mean (GLSM) from the model for each group and the GMR (mRNA-1273.214 compared with mRNA-1273) estimated by the ratio of GLSM from the model (97.5% CIs) are provided. The 97.5% CI for GMR was used to assess the between group difference in antibody responses.

Seroresponse is defined as ≥4 × LLOQ for those with a pre-dose 1 of a primary series baseline < LLOQ; ≥ 4-foldrise for those with pre-dose 1 of primary series baseline ≥ LLOQ. For participants without pre-dose 1 antibody titer information, seroresponse is defined as ≥4X LLOQ for those with negative SARS-CoV-2 status at pre-dose 1 of the primary series, and antibody titers are imputed as <LLOQ at pre-dose 1 of primary series. For participants who are 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 their pre-dose 1 of primary series.

The SRR of each arm against ancestral SARS-CoV-2 (D614G) and variants, defined as the percentage of participants achieving SRR against ancestral SARS-CoV-2 (D614G) and variants respectively, are provided for each arm with the 95% CI calculated using the Clopper Pearson method. The differences of SRR between mRNA-1273.214 and mRNA-1273 are calculated with 97.5% CI based on stratified Miettinen-Nurminen method adjusting for age groups.

An analysis of the primary immunogenicity endpoints was also performed in the per-protocol set for immunogenicity (participants with and without evidence of prior SARS-CoV-2 infection pre-booster), using an ANCOVA model, with antibody titers at day 29 post-booster as the dependent variable and the vaccine group variable as the fixed effect, adjusting for age groups (<65, ≥65 years), pre-booster SARS-CoV-2 infection status, and pre-booster titers. The SRR difference between the mRNA-1273.214 and mRNA-1273 groups was calculated with 97.5% CI based on stratified Miettinen-Nurminen method adjusted for the pre-booster SARS-CoV-2 infection status and age group. A pre-planned subgroup analysis of participants with prior evidence of SARS-CoV-2-infection pre-booster was performed using an ANCOVA model to assess neutralizing antibody differences between the mRNA-1273.214 and mRNA-1273 groups based on GMRs with 95% CIs. Lastly, a sensitivity analysis was performed excluding the participants with evidence of SARS-CoV-2-infection after the booster dose.

Observed binding antibody GMTs and 95% CIs against variants are provided. Binding antibody level differences between the mRNA-1273.214 and mRNA-1273 groups based on GMRs with 95% CIs were assessed using an ANCOVA model, adjusting for age group and pre-booster titers.

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.[6] The PsVNA quantifies nAb using lentivirus particles that express ancestral SARS-CoV-2 Wuhan-Hu-1 full-length spike proteins with the following amino acid substitutions (prototype [D614G]; omicron [B.1.1.529; BA.1] with the following amino acid changes in the spike protein [A67V, ΔH69-V70, T95I, G142D, Δ143-145, Δ211/L212II, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F]; 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.

Omicron BA.4/BA.5 was assessed using a research grade pseudovirus lentivirus neutralization assay containing full-length spike protein for omicron subvariants BA.4 and BA.5 (designated BA.4/BA.5 for identical spike sequences between BA.4 and BA.5 [T191, L24S, ΔP25, ΔP26, ΔA27, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681G, N764K, D796Y, Q954H, N969K]). Experiments to assess the reproducibility of the omicron BA.4/BA.5 neutralization assay have been conducted that estimate the variability observed of samples measured in triplicate, by multiple operators and at different times (week-to-week) using three different sample types. Sample types utilized included the following: a) monoclonal antibody specific to the omicron BA.4/BA.5 spike protein b) a pooled control sample derived from patients who had infections that were confirmed as omicron by sequencing from other clinical studies, and c) samples from participants who were boosted with mRNA-1273.214. The variability assessed by the percent coefficient of variation (% CV) were similar to the neutralization assay specific to the original Wuhan strain (D614G assay). The BA.4/BA.5 assay is currently considered to be qualified and full assay validation is underway to assess additional parameters including limits of quantitation, accuracy, range, and dilutional linearity.

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

The validated Meso Scale Discovery (MSD, Rockville, MD) assay (SARSCOV2S2P [VAC123]; https://www.mesoscale.com/products/v-plex-sars-cov-2-panel-24-igg-kit-k15575u/) uses an indirect, quantitative, electrochemiluminescence method to detect SARS-CoV-2 binding IgG antibodies that bind to the SARS-CoV-2 full-length spike protein (Wuhan-Hu-1 ancestral SARS-CoV-2; beta [B.1.351] 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] with the following amino acid changes in the spike protein [ΔH69-V70, ΔY144, N501Y, A570D, D614G, P681H, T761I, S982A, and D1118H]; gamma [P.1] with the following amino acid changes in the spike protein [L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F]); delta [B.1.617.2; AY.4; Alt Seq 2] with the following amino acid changes in the spike protein [T19R, T95I, G142D, Δ156/157, R158G, L452R, T478K, D614G, P681R, and D950N]); omicron [B.1.1.529; BA.1] with the following amino acid changes in the spike protein [A67V, ΔH69-V70, T95I, G142D, Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F]) in human serum. The assay was performed by PPD, (Thermo Fisher Scientific Vaccines Laboratory Services, Richmond, Virginia). The assay is based on MSD technology which employs capture molecule MULTI-SPOT® microtiter plates fitted with a series of electrodes.

Incidence of SARS-CoV-2 Infection and Covid-19

Vaccine effectiveness was not assessed in this trial, but Covid-19 and SARS-CoV-2 infection were actively surveilled through weekly contact and blood draws. An exploratory objective of the study is to assess symptomatic and asymptomatic SARS-CoV-2 infection. SARS-CoV-2 infection is a combination of symptomatic infection (Covid-19) and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status pre-booster. Symptomatic infection was evaluated using the primary case definition in the COVE study[1,2] as well as a secondary case definition based on the Centers for Disease Control and Prevention (CDC) criteria.[7] Asymptomatic SARS-CoV-2 infection was defined as a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test or a positive serologic test for anti-nucleocapsid antibody after a negative test at the time of enrollment, in the absence of symptoms.

SARS-CoV-2 infection

SARS-CoV-2 infection is defined in participants with negative SARS-CoV-2 status pre-booster by either bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at day 1 that becomes positive (as measured by Roche Elecsys) starting at day 29 or later, OR a positive RT-PCR counted starting 14 days after the booster dose.

For the analysis, documented infection is counted starting 14 days after the booster dose, which requires positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid at day 29 or later, or a positive RT-PCR result starting 14 days after the booster dose.
The date of documented infection is the earlier of the date of a positive post-baseline RT-PCR result or of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid. The time to first SARS-CoV-2 infection is calculated as the date of the 1st documented infection minus the date of injection + 1. Cases are counted starting 14 days after the injection (date of documented infection minus date of the injection ≥14). SARS-CoV-2 infection cases are summarized based on tests performed at least 14 days after the booster dose.

Asymptomatic SARS-CoV-2 Infection

Asymptomatic SARS-CoV-2 infection is measured by RT-PCR of nasal swabs and/or serology tests obtained at post-baseline study visits counted starting 14 days after the injection in participants with negative SARS-CoV-2 status pre-booster. Asymptomatic SARS-CoV-2 infection is identified by the absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically, the absence of Covid-19 symptoms AND at least either a positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid protein day 29 or later, when blood samples for immunogenicity are collected, or a positive RT-PCR test at scheduled or unscheduled/illness visits. The date of documented asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid due to infection, or positive RT-PCR, with absence of symptoms. The time to the asymptomatic SARS-CoV-2 infection is calculated as the date of asymptomatic SARS-CoV-2 infection minus the date of injection + 1.

Symptomatic SARS-CoV-2 Infection (Covid-19)

Symptomatic SARS-CoV-2 Infection (Covid-19) is defined as the incidence of the first occurrence of symptomatic SARS-CoV-2 infection measured by RT-PCR of nasal swabs starting 14 days after the booster dose. Surveillance for Covid-19 symptoms is conducted via weekly contact and blood draw, and an illness visit to collect a nasopharyngeal swab was arranged for participants reporting Covid-19 symptoms.

Two definitions of symptomatic SARS-CoV-2 infection (Covid-19). This includes the primary case definition in the COVE trial[1,2] based on a positive post-baseline RT-PCR result AND at least TWO systemic symptoms (fever (≥ 38ºC/≥ 100.4ºF), chills, muscle and/or body aches [not related to exercise], headache, sore throat, new loss of taste/smell; OR at least ONE of respiratory signs/symptoms (cough, shortness of breath and/or difficulty breathing, OR clinical or radiographical evidence of pneumonia). The second case definition is based on CDC criteria for symptomatic disease defined as a positive post-baseline RT-PCR test AND at least ONE systemic or respiratory symptoms (fever [≥ 38ºC/≥100.4ºF], chills, cough, shortness of breath and/or difficulty breathing, fatigue, muscle and/or body aches [not related to exercise], headache, new loss of taste/smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhea).[7]

The date of a documented Covid-19 case is the later date of a symptom and the date of positive RT-PCR test, and the two dates should be within 14 days of each other. The time to the first occurrence of Covid-19 is calculated as the date of documented Covid-19 minus the date of injection + 1. Cases are counted starting 14 days after the injection (date of documented Covid-19 minus date of the injection ≥14).

Figure S1. Trial Profile of Analysis Sets

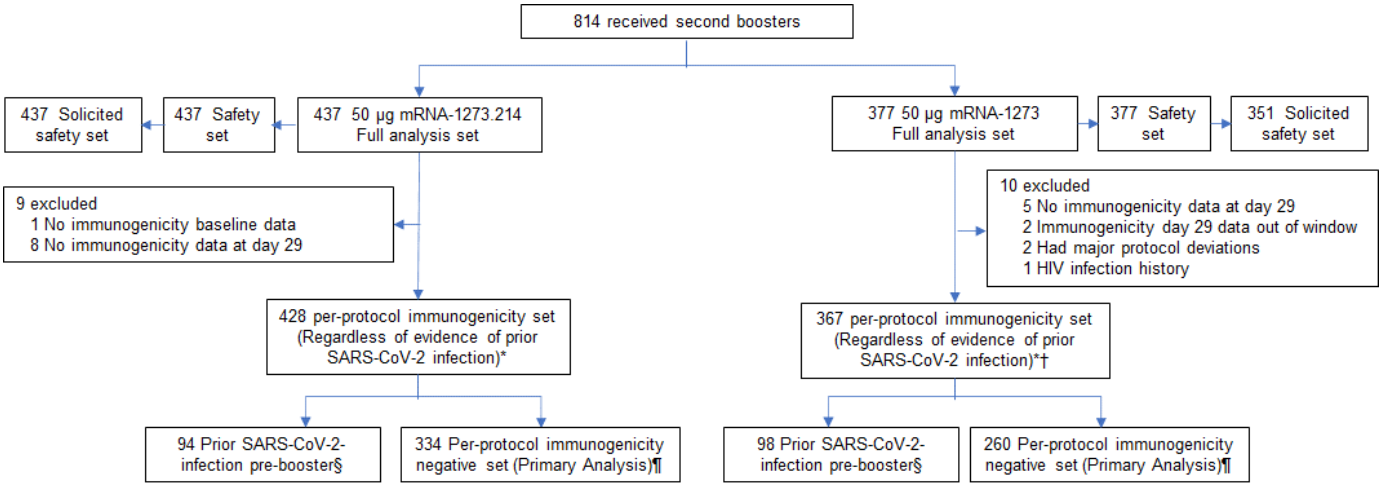


Figure S1. Trial Profile of Analysis Sets. The full analysis set consists of all participants who received study vaccine. The safety set consists of all participants who received study vaccine and was used for all analyses of safety except for solicited adverse reactions which were assessed in the solicited safety set. *The per-protocol set for immunogenicity consists of all participants in the full analysis set who received the planned dose of study vaccination and had antibody data available at pre-booster and day 29 and no major protocol deviations. †9 participants in the mRNA-1273 arm of the per-protocol immunogenicity set had missing pre-booster SARS-CoV-2 information. §Prior SARS-CoV-2-infection based on positive RT-PCR and/or serology test at baseline. ¶The per-protocol immunogenicity negative set consists of participants in the per-protocol set for immunogenicity who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline, i.e., who are SARS-CoV-2 infection negative, based on both negative RT-PCR tests for SARS-CoV-2 and negative SARS-CoV-2 nucleocapsid antibody test, and is the primary analysis set for immunogenicity analysis. A total of 379 participants received a second booster dose of 50-µg mRNA-1273; 1 participant had previously received the primary series but not a first booster dose, and another participant had a major protocol deviation. These two participants were excluded from all analysis sets. A total of 437 participants received a second booster dose of mRNA-1273.214; three participants had discontinued the study prior to dosing and were excluded from all analysis sets. Data-cut-off date was April 27th, 2022.

Figure S2: Statistical Testing Sequence for Immunogenicity Primary Objectives

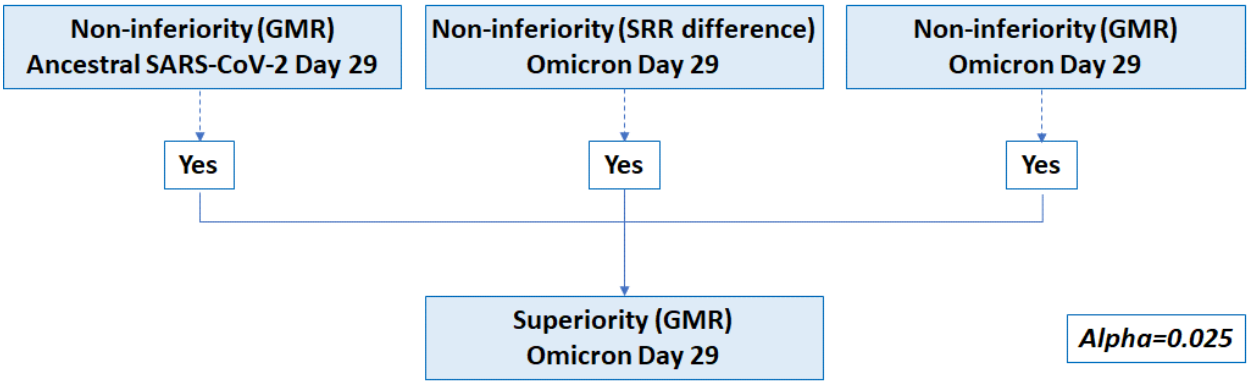
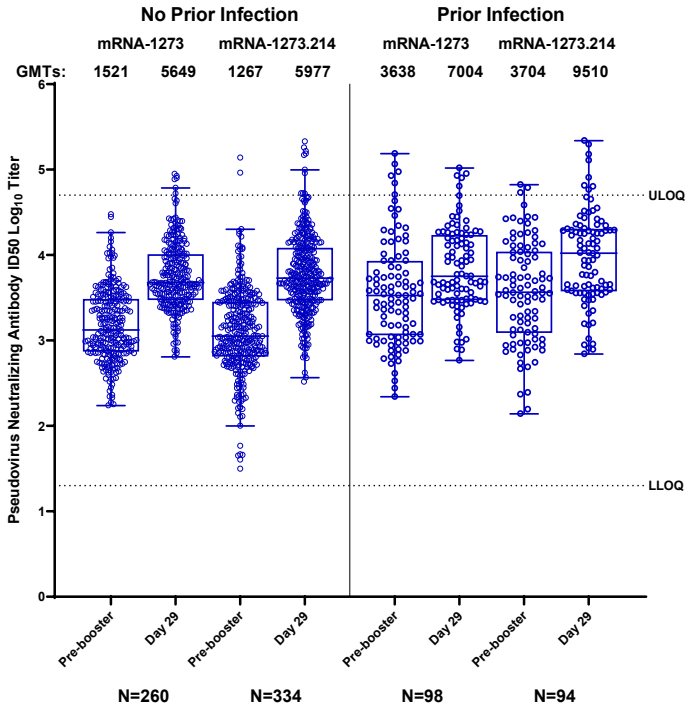


Figure S2. Statistical Hypotheses Testing Strategy. For part G of the study, immunogenicity objectives were tested at days 29 and 91 with the family-wise type I error controlled at 0.05 (2-sided) by equally splitting alpha to the two testing timepoints with alphas of 0.025 (2-sided) at each timepoint. The same testing strategy was applied to days 29 and 91. The figure above depicts the testing sequence for day 29 only. At day 29, there were 4 corresponding clinical endpoints for the pre-specified primary objectives: (1) non-inferiority of the antibody response of the second booster dose of 50-µg mRNA-1273.214 compared with the second booster dose of 50-µg mRNA-1273 based on the geometric mean ratio (GMR) against omicron; 2) non-inferiority of the antibody response of the second dose of 50-µg mRNA-1273.214 compared to the second booster dose of 50-µg mRNA-1273 against omicron based on the difference in seroresponse rate (SRR); 3) non-inferiority of the antibody response of the second booster dose of 50-µg mRNA-1273.214 compared to the second booster dose of 50-µg mRNA-1273 based on GMR against the ancestral SARS-CoV-2 (D614G) and, 4) superiority of the antibody response of the second booster dose of 50-µg mRNA-1273.214 compared to the second booster dose of 50-µg mRNA-1273 based on the GMR against omicron (detailed in Supplementary Statistical Methods). The endpoint testing sequence pre-specified that all 3 endpoints must first be met to test for the fourth endpoint and all tests were based on alpha of 0.025 (2-sided).[8] The immunogenicity endpoints are tested with an alpha of 0.025 (2-sided) for the interim analysis at 28 days after the booster dose (day 29). Non-inferiority is considered met when the lower bound of the 97.5% confidence interval (CI) of GMR is ≥0.67 and when SRR difference >-10%. Superiority is considered met when the lower bound of the 97.5% CI of GMR is >1. Superiority of the mRNA-1273.214 antibody response against omicron, compared to mRNA-1273, is considered demonstrated if superiority based on GMR is met at day 29. If non-inferiority is demonstrated for both omicron (based on GMR and SRR) and ancestral SARS-CoV-2 (D614G) (based on GMR), the lower bound of 97.5% CI of GMR is compared to 1, and if greater than 1, then superiority against omicron is demonstrated.

Figure S3. Observed Neutralizing Antibody Titers Against SARS-CoV-2 (D614G) and Omicron after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses in Participants with No Prior SARS-CoV-2 Infection

A. Ancestral SARS-CoV-2 (D614G)



B. Omicron

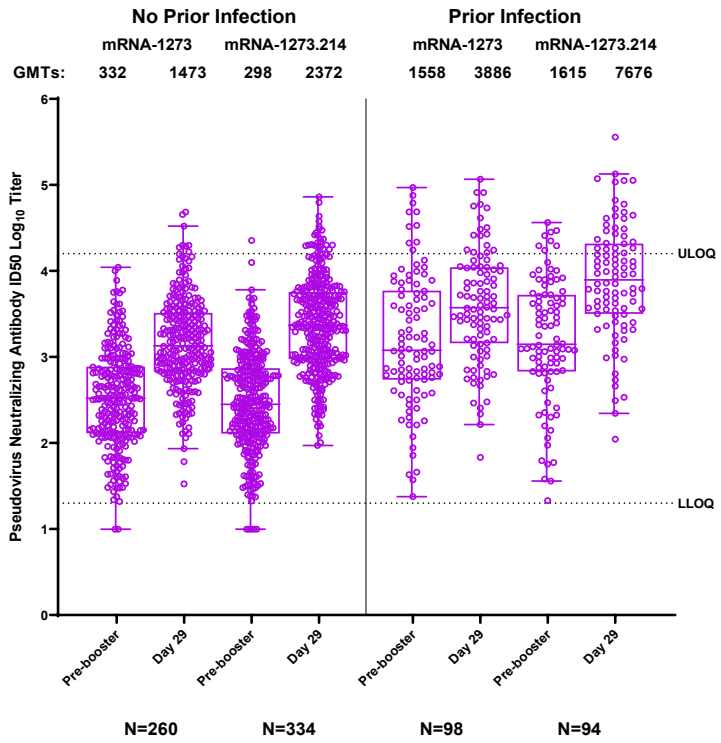


Figure S3. Observed Neutralizing Antibody Titers Against SARS-CoV-2 (D614G) and Omicron after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses. Neutralizing antibody titers (ID50 $\log_{10}$) in the pseudovirus assay against the ancestral SARS-CoV-2 (D614G) (Panel A; blue) or the omicron variant (Panel B; purple) are shown for serum samples collected before the second booster dose of 50-µg of mRNA-1273 or 50-µg of mRNA-1273.214 (pre-booster), and at 28 days after the second booster dose (day 29) in those without prior SARS-Cov-2 infection. The circles are values from individual serum samples. Pseudovirus neutralizing antibody assay lower limits of quantification (LLOQ) are 18.5 for ancestral SARS-CoV-2 [D614G] and 19.9 for omicron; upper limits of quantification (ULOQ) are 45,118 for ancestral SARS-CoV-2 [D614G] and 15,502.7 for omicron. Corresponding $\log_{10}$ values for LLOQs for the pseudovirus neutralizing antibody assay are 1.3 for both ancestral [D614G] and omicron, and ULOQs are 4.7 for ancestral SARS-CoV-2 [D614G] and 4.2 omicron. Boxes and horizontal bars denote interquartile (IQR) ranges and median endpoint titers; whisker endpoints are the maximum and minimum values within 1.5 times the IQR above the 75% and below the 25% percentiles. Refer to Table 2 for the observed geometric mean titers (GMTs) and geometric mean fold rises, and the estimated neutralizing antibody geometric mean titers and geometric mean ratios (ANCOVA model-based) following the second booster doses of 50-µg mRNA-1273 or 50-µg of mRNA-1273.214.

Figure S4. Observed Neutralizing Antibody Titers Against Omicron BA.4 and BA.5 Subvariants after 50-µg of mRNA-1273.214 Administered as a Second Booster Dose

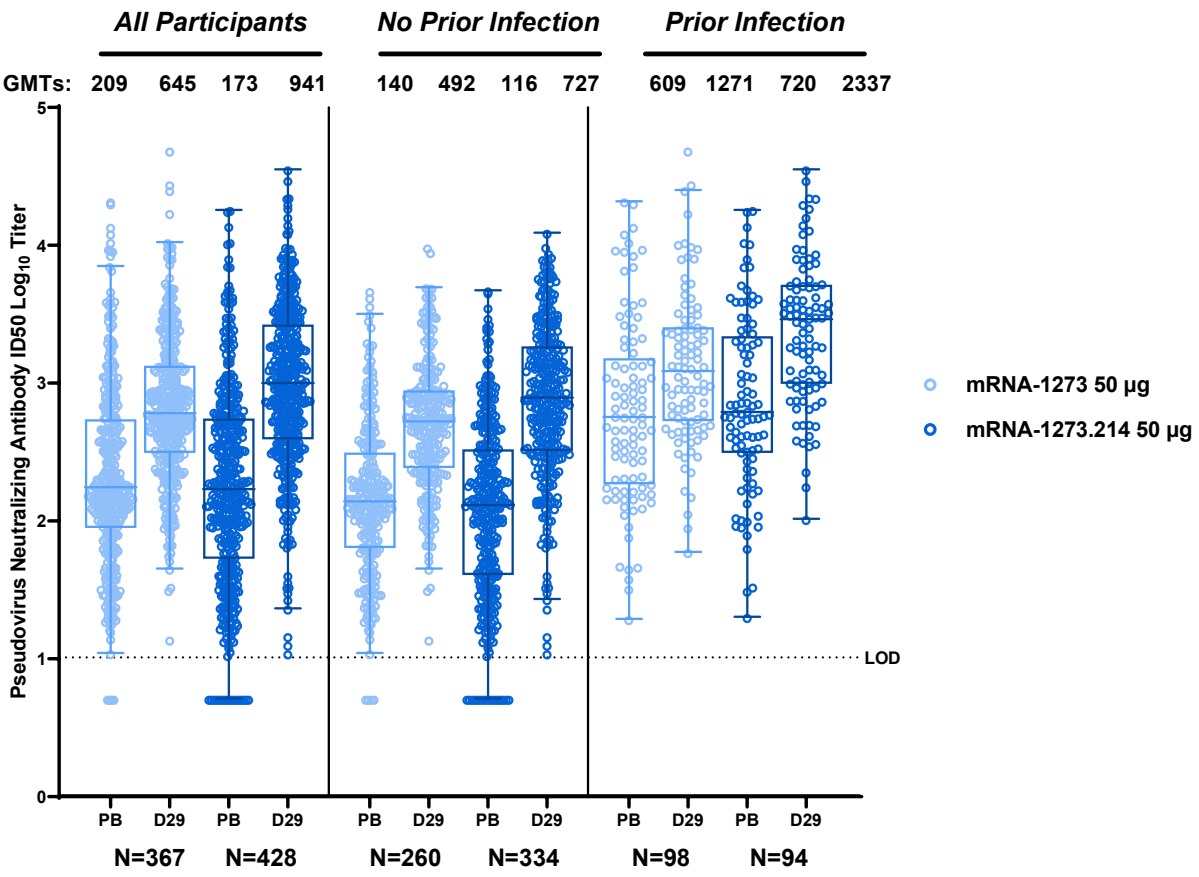


Figure S4. Observed Neutralizing Antibody Titers Against Omicron BA.4 and BA.5 Subvariants after 50-µg of mRNA-1273.214 Administered as a Second Booster Dose. PB=pre-booster; D29=day 29. The neutralizing antibody titers (ID50 $\log_{10}$) in the research grade pseudovirus assay against the omicron BA.4/BA.5 variants are shown for serum samples collected before the second booster dose of mRNA-1273.214 (pre-booster), and at 28 days after the second booster dose (day 29) in all participants, and those with and without prior SARS-Cov-2-infection. Assay limit of detection (LOD) is 10 ($\log_{10}$=1). The circles are the values from individual serum samples. Boxes and horizontal bars denote interquartile (IQR) ranges and median endpoint titers; whisker endpoints are the maximum and minimum values within ±1.5 times the IQR above the 75% and below the 25% percentiles. Observed geometric mean titers (GMTs) are provided in Table S8.

Figure S5. Observed Binding Antibody Levels Against Variants After 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses in All Participants

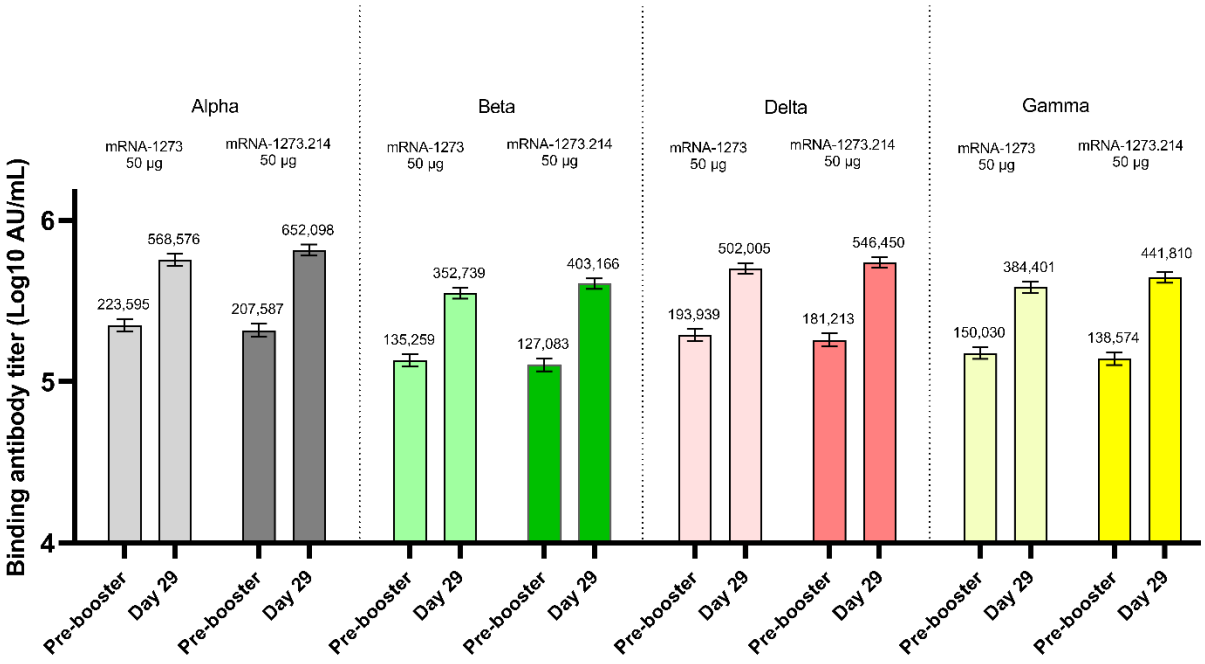


Figure S5. **Observed Binding Antibody Levels Against Variants After 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses in All Participants.** The levels (AU/mL) of antibodies that specifically bind to the alpha, beta, delta, or gamma spike proteins were determined by the Mesoscale Discovery (MSD) Multiplex (VAC123) assay in all participants. Serum samples were collected before the second booster dose of 50-µg of mRNA-1273 or 50-µg of mRNA-1273.214 (pre-booster), and at 28 days after the second booster injection (day 29). Number of participants (n) ranges from 350 to 365 in mRNA-1273 group, and n ranges from 398 to 423 in mRNA-1273.214 group. Antibody values reported as below the lower limit of quantification (LLOQ) were 52 for alpha, 111 for beta, 150 for delta, 143 for gamma and were replaced by 0.5 times the LLOQ. Antibody values reported as greater than the upper limit of quantification (ULLQ) were 8,800,000 for alpha, 5,000,000 for beta, 8,000,000 for delta, 5,800,000 for gamma and were converted to the ULOQ if the actual values were not available. Error bars are 95% confidence intervals. The 95% confidence intervals were calculated based on the t-distribution of the log-transformed values for the geometric mean value then back transformed to the original scale for presentation. Observed binding antibody titers are summarized in table S10.

Table S1. Objectives and Endpoints for Part G Second Booster Doses of 50-µg mRNA-1273.214 in Participants Who Received 100 µg mRNA-1273 Primary Series and a Booster Dose of 50 µg mRNA-1273

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50-µg) when administered as a second booster dose against the omicron variant (B.1.1.529) at Day 29 or Day 91 based on GMT ratio and SRR difference at Day 29 or Day 91 To demonstrate superiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50-µg) administered as a second booster dose against the omicron variant (B.1.1.529) based on GMT ratio at Day 29 or Day 91 To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50-µg) when administered as a second booster dose against ancestral SARS-CoV-2 (D614G) based on GMT ratio at Day 29 or Day 91	GMT ratio of omicron-specific GMT of mRNA-1273.214 over the omicron-specific GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91 SRR difference between mRNA-1273.214 against omicron variant and mRNA-1273 against omicron variant at Day 29 and Day 91 GMT ratio of ancestral SARS-CoV-2 (D614G) GMT of mRNA-1273.214 over ancestral SARS-CoV-2 (D614G) GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 or Day 91
To evaluate the safety and reactogenicity of mRNA-1273.214	Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination Unsolicited AEs during the 28-day follow-up period after vaccination Serious AEs (SAEs), MAAEs, AEs leading to withdrawal and AESIs from Day 1 to EoS
Key Secondary	
To demonstrate non-inferiority based on the SRR against ancestral SARS-CoV-2 (D614G) of a second booster dose of mRNA-1273.214 compared to a second booster dose of mRNA-1273 (50-µg) at Day 29 or Day 91	SRR difference between mRNA-1273.214 against ancestral SARS-CoV-2 (D614G) and mRNA-1273 against ancestral SARS-CoV-2 (D614G) at Day 29 and Day 91
Secondary	
To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a	• GMT ratio of mRNA-1273.214 and mRNA-1273 against the omicron variant at all timepoints post-boost

Objectives	Endpoints
second booster dose at all timepoints post-boost	• SRR difference between mRNA-1273.214 against the omicron variant and mRNA-1273 against the omicron variant at all timepoints post-boost • GMT ratio of mRNA-1273.214 and mRNA-1273 against ancestral SARS-CoV-2 (D614G) and other variants at all timepoints post-boost • SRR difference between mRNA-1273.214 against ancestral SARS-CoV-2 (D614G) and other variants and mRNA-1273 against ancestral SARS-CoV-2 (D614G) and other variants at all timepoints post-boost
To compare the immune response of mRNA-1273.214 as a second dose against the omicron variant compared to the priming series of mRNA-1273	• GMT ratio and SRR difference of mRNA-1273.214 as a second booster dose against the omicron variant compared to the priming series of mRNA-1273 against ancestral SARS-CoV-2 (D614G) (historical control group)
Exploratory	
• To assess for symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants: Primary case definition per the (COVE) study Secondary case definition based on the CDC criteria: the presence of one of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive reverse transcriptase polymerase chain reaction (RT-PCR) test on a respiratory sample • Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test at time of enrollment
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 genomic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates
• To characterize the cellular immune response of mRNA-1273.214 as a booster against SARS-CoV-2 and other variants	• T-cell and B-cell response after the mRNA-1273.214 booster

Table S2. Analysis Sets

Set	Description
Full Analysis Set (FAS)	The FAS consists of all participants who receive investigational product (IP).
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.
PP Set for Immunogenicity – SARS-CoV-2 negative (PPSI-Neg)	Participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline, i.e., who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid PPSI-Neg will be the primary analysis set for analyses of immunogenicity for between booster comparisons.
Solicited Safety Set	The Solicited Safety Set consists of all participants who receive IP and contribute any solicited 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.

Table S3. Solicited Local and Systemic Adverse Reactions Within 7 Days Following the Second Booster Injections of mRNA-1273.214 (50 µg) and mRNA-1273 (50 µg), Solicited Safety Set

Adverse Reaction, N (%)	mRNA-1273.214 Second Booster Dose (50 µg) N=437	mRNA-1273 Second Booster Dose (50 µg) N=351
Solicited AR, N1	437	351
Any Solicited AR	380 (87.0)	301 (85.8)
Grade 1	220 (50.3)	184 (52.4)
Grade 2	125 (28.6)	89 (25.4)
Grade 3	35 (8.0)	28 (8.0)
Grade 4	0	0
Any Solicited Local AR, N1	437	351
Any Solicited Local AR	347 (79.4)	279 (79.5)
Grade 1	291 (66.6)	239 (68.1)
Grade 2	41 (9.4)	28 (8.0)
Grade 3	15 (3.4)	12 (3.4)
Local AR, Pain, N1	437	351
Pain	338 (77.3)	269 (76.6)
Grade 1	303 (69.3)	241 (68.7)
Grade 2	31 (7.1)	24 (6.8)
Grade 3	4 (0.9)	4 (1.1)
Erythema, N1	437	351
Erythema	30 (6.9)	13 (3.7)
Grade 1	15 (3.4)	5 (1.4)
Grade 2	6 (1.4)	6 (1.7)
Grade 3	9 (2.1)	2 (0.6)
Swelling, N1	437	351
Swelling	30 (6.9)	23 (6.6)
Grade 1	17 (3.9)	13 (3.7)
Grade 2	8 (1.8)	5 (1.4)
Grade 3	5 (1.1)	5 (1.4)
Axillary Swelling or Tenderness, N1	437	351
Axillary Swelling or Tenderness	76 (17.4)	54 (15.4)
Grade 1	71 (16.2)	46 (13.1)
Grade 2	4 (0.9)	4 (1.1)
Grade 3	1 (0.2)	4 (1.1)
Any Systemic AR, N1	437	351
Any Systemic AR	307 (70.3)	232 (66.1)
Grade 1	167 (38.2)	124 (35.3)
Grade 2	116 (26.5)	92 (26.2)
Grade 3	24 (5.5)	16 (4.6)

Fever, N1	436	351
Fever	19 (4.4)	12 (3.4)
Grade 1	14 (3.2)	9 (2.6)
Grade 2	4 (0.9)	3 (0.9)
Grade 3	1 (0.2)	0
Headache, N1	437	350
Headache	192 (43.9)	144 (41.1)
Grade 1	150 (34.3)	112 (32.0)
Grade 2	37 (8.5)	30 (8.6)
Grade 3	5 (1.1)	2 (0.6)
Fatigue, N1	437	350
Fatigue	240 (54.9)	180 (51.4)
Grade 1	125 (28.6)	95 (27.1)
Grade 2	100 (22.9)	74 (21.1)
Grade 3	15 (3.4)	11 (3.1)
Myalgia, N1	437	350
Myalgia	173 (39.6)	135 (38.6)
Grade 1	101 (23.1)	68 (19.4)
Grade 2	62 (14.2)	54 (15.4)
Grade 3	10 (2.3)	13 (3.7)
Arthralgia, N1	437	350
Arthralgia	136 (31.1)	111 (31.7)
Grade 1	93 (21.3)	70 (20.0)
Grade 2	39 (8.9)	38 (10.9)
Grade 3	4 (0.9)	3 (0.9)
Nausea/ vomiting, N1	437	350
Nausea / vomiting	45 (10.3)	35 (10.0)
Grade 1	39 (8.9)	27 (7.7)
Grade 2	5 (1.1)	8 (2.3)
Grade 3	1 (0.2)	0
Chills, N1	437	350
Chills	104 (23.8)	74 (21.1)
Grade 1	65 (14.9)	46 (13.1)
Grade 2	38 (8.7)	27 (7.7)
Grade 3	1 (0.2)	1 (0.3)

AR=adverse reaction. Any=Grade 1 or higher. N1=Number of exposed participants with any information about the adverse event. Percentages are based on the number of participants who submitted any data for the event. Data cutoff date was April 27, 2022.

Table S4. Summary of Unsolicited Adverse Events ≤28 Days Post-booster Dose, Safety Set

n (%)	mRNA-1273.214 50 µg (N=437)	mRNA-1273 50 µg (N=377)
Unsolicited AEs Regardless of Relationship to Study Vaccination		
All	81 (18.5)	78 (20.7)
Serious	2 (0.5)	1 (0.3)
Fatal	0	0
Medically attended	43 (9.8)	52 (13.8)
Leading to discontinuation from study	0	0
Grade 3 or higher	4 (0.9)	3 (0.8)
Unsolicited AEs related to study vaccination		
All	25 (5.7)	22 (5.8)
Serious	0	0
Fatal	0	0
Medically attended	2 (0.5)*	2 (0.5)*
Leading to discontinuation from study	0	0
Grade 3 or higher	1 (0.2)	2 (0.5)

AE=adverse event. 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. *Medically attended AEs of fatigue (grade 2) and dermatitis (grade 1) occurred in the mRNA-1273.214 group and of hypertension and urticaria (both grade 1) in the mRNA-1273 groups.

Table S5. Geometric Mean Neutralizing Antibody Titer Ratio and Seroresponse Difference Against Ancestral SARS-CoV-2 (D614G) and Omicron after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses in All Participants Regardless of Evidence of Prior SARS-CoV-2 Infection

	Ancestral SARS-CoV-2 (D614G)		Omicron	
	50 µg mRNA-1273.214 Booster Dose*	50 ug mRNA-1273 Booster dose*	50 µg mRNA-1273.214 Booster Dose*	50 ug mRNA-1273 Booster dose*
	N=428	N=367	N=428	N=367
Pre-booster n†	428	367	428	367
Observed GMT (95% CI)§	1603.4 (1420.3-1810.0)	1944.8 (1725.4-2192.1)	432.1 (372.5-501.2)	512.0 (433.4-604.8)
Day 29, n†	428	367	428	367
Observed GMT (95% CI)§	6619.0 (5941.7-7373.5)	6047.5 (5465.9-6691.0)	3070.4 (2685.4-3510.6)	1932.8 (1681.2-2222.0)
GMFR (95% CI)§	4.1 (3.8-4.4)	3.1 (2.9-3.4)	7.1 (6.5-7.8)	3.8 (3.4-4.2)
Estimated GMT (95% CI)¶	6555.7 (6122.3-7019.7)	5301.4 (4931.8-5698.7)	3232.5 (2951.8-3539.9)	1815.1 (1650.0-1996.7)
GMR (97.5% CI)¶	1.24 (1.12-1.37)		1.78 (1.56-2.04)	
Day 29 SRR, n/N1 %‖	383/383, 100	347/347, 100	380/380, 100	340/342, 99.4
(95% CI)	(99.0-100)	(98.9-100)	(99.0-100)	(97.9-99.9)
Difference (97.5% CI)‡	0		1.2 (-1.3, 3.7)	

ANCOVA=analysis of covariance, CI=confidence interval, GMT=geometric mean titer, GMFR= geometric mean fold rise (post-baseline/baseline titers), GMR=geometric mean ratio (mRNA-1273.214 vs mRNA-1273). ID50=50% inhibitory dose; LLOQ=lower limit of quantification; LS=least squares; SRR=seroresponse rate; ULOQ, upper limit of quantification. Antibody values assessed by pseudovirus neutralizing antibody assay reported as below the LLOQ (18.5 for ancestral [D614G] and 19.9 for omicron are replaced by 0.5 × LLOQ. Values greater than ULOQ (45,118) for ancestral [D614G] and (15,502.7) for omicron are replaced by the ULOQ if actual values are not available.

†Number of participants with non-missing data at the timepoint (baseline or post-baseline).

§95% CI based on the t-distribution of log-transformed values or difference in the log-transformed values for GMT value and GMFR, respectively, then back transformed to the original scale.

¶Log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years), pre-booster titers and prior SARS-CoV-2 infection. The resulting LS means and the 95% confidence intervals, difference of LS means and 97.5% confidence intervals are back transformed to the original scale.

‖Seroresponse at a participant level defined as a change from <LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ; comparison to pre-vaccination baseline. Percentages were based on the number of participants with non-missing data at baseline and the corresponding time point. 95% CI calculated using the Clopper-Pearson method.

‡The SRR difference is a calculated common risk difference adjusted by age group using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate and the CI cannot be calculated when the seroresponse rate in both groups is 100%, absolute difference is reported.

Table S6. Geometric Mean Neutralizing Antibody Titer Ratio and Seroresponse Difference Against Ancestral SARS-CoV-2 (D614G) and Omicron after 50-µg of mRNA-1273.214 and mRNA-1273 administered as Second Booster Doses in Participants with Evidence of Prior SARS-CoV-2 Infection

	Ancestral SARS-CoV-2 (D614G)		Omicron	
	50 µg mRNA-1273.214 Booster Dose*	50 ug mRNA-1273 Booster dose*	50 µg mRNA-1273.214 Booster Dose*	50 ug mRNA-1273 Booster dose*
	N=94	N=98	N=94	N=98
Pre-booster n†				
Observed GMT (95% CI)§	3704.0 (2793.2-4911.7)	3638.0 (2742.0-4826.6)	1614.6 (1149.7-2267.7)	1558.4 (1088.9-2230.1)
Day 29, n†				
Observed GMT (95% CI)§	9509.7 (7345.9-12,310.9)	7003.5 (5592.6-8770.4)	7676.2 (5618.2-10,488.1)	3885.6 (2877.8-5246.4)
GMFR (95% CI)§	2.6 (2.2-2.9)	1.9 (1.6-2.2)	4.8 (4.0-5.7)	2.5 (2.1-3.0)
Estimated GMT (95% CI)¶	9891.5 (8732.2-11204.8)	7776.5 (6813.0-8876.3)	7669.2 (6470.7-9089.6)	4041.5 (3375.1-4839.5)
GMR (95.0% CI)¶	1.27 (1.07-1.51)		1.90 (1.50-2.40)	
Day 29 SRR, n/N1 %‖ (95% CI)	49/49, 100 (92.7-100.0)	79/79, 100 (95.4-100.0)	47/47, 100 (92.5-100.0)	76/76, 100 (95.3-100.0)
Difference (95.0% CI)‡	0		0	

ANCOVA=analysis of covariance, CI=confidence interval, GMT=geometric mean titer, GMFR= geometric mean fold rise (post-baseline/baseline titers), GMR=geometric mean ratio (mRNA-1273.214 vs mRNA-1273). ID50=50% inhibitory dose; LLOQ=lower limit of quantification; LS=least squares; SRR=seroresponse rate; ULOQ=upper limit of quantification. Antibody values assessed by pseudovirus neutralizing antibody assay reported as below the LLOQ (18.5 for ancestral SARS-CoV-2 [D614G] and 19.9 for omicron are replaced by 0.5 × LLOQ. Values greater than ULOQ (45,118) for ancestral SARS-CoV-2 [D614G] and (15,502.7) for omicron are replaced by the ULOQ if actual values are not available.

†Number of participants with non-missing data at the timepoint (baseline or post-baseline).

§95% CI based on the t-distribution of log-transformed values or difference in the log-transformed values for GMT value and GMFR, respectively, then back transformed to the original scale.

¶Log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years) and pre-booster titers. The resulting LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

‖Seroresponse at a participant level defined as a change from <LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ; comparison to pre-vaccination baseline. Percentages were based on the number of participants with non-missing data at baseline and the corresponding time point. 95% CI calculated using the Clopper-Pearson method.

‡The SRR difference is a calculated common risk difference adjusted by age group using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate and the CI cannot be calculated when the seroresponse rate in both groups is 100%, absolute difference is reported.

Table S7. Observed Neutralizing Antibody Geometric Mean Titers Against Ancestral SARS-CoV-2 (D614G) and Omicron after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses by Prior SARS-CoV-2 Infection at Pre-Booster

	All participants		No prior SARS-CoV-2 infection		Prior SARS-CoV-2 infection	
	mRNA-1273.214 50 µg Booster Dose	**mRNA-1273 50 µg Booster Dose**	**mRNA-1273.214 50 µg Booster Dose**	**mRNA-1273 50 µg Booster Dose**	**mRNA-1273.214 50 µg Booster Dose**	**mRNA-1273 50 µg Booster Dose**
Ancestral SARS-CoV-2 (D614G)	**N=428**	**N=367**	**N=334**	**N=260**	**N=94**	**N=98**
Pre-booster						
Observed GMT (95% CI)	1603.4 (1420.3-1810.0)	1944.8 (1725.4-2192.1)	1266.7 (1120.2-1432.5)	1521.0 (1352.8-1710.2)	3704.0 (2793.2-4911.7)	3638.0 (2742.0-4826.6)
Day 29						
Observed GMT (95% CI)	6619.0 (5941.7-7373.5)	6047.5 (5465.9-6691.0)	5977.3 (5321.9-6713.3)	5649.3 (5056.8-6311.2)	9509.7 (7345.9-12,310.9)	7003.5 (5592.6-8770.4)
GMFR (95% CI)	4.1 (3.8-4.4)	3.1 (2.9-3.4)	4.7 (4.4-5.1)	3.7 (3.4-4.0)	2.6 (2.2-2.9)	1.9 (1.6-2.2)
Omicron (B.1.1.529)	**N=428**	**N=367**	**N=334**	**N=260**	**N=94**	**N=98**
Pre-booster						
Observed GMT (95% CI)	432.1 (372.5-501.2)	512.0 (433.4, 604.8)	298.1 (258.8-343.5)	332.0 (282.0-390.9)	1614.6 (1149.7-2267.7)	1558.4 (1088.9-2230.1)
Day 29						
Observed GMT (95% CI)	3070.4 (2685.4-3510.6)	1932.8 (1681.2-2222.0)	2372.4 (2070.6-2718.2)	1473.5 (1270.8-1708.4)	7676.2 (5618.2-10488.1)	3885.6 (2877.8-5246.4)
GMFR (95% CI)	7.1 (6.5-7.8)	3.8 (3.4-4.2)	8.0 (7.2-8.8)	4.4 (4.0-5.0)	4.8 (4.0-5.7)	2.5 (2.1-3.0)

SARS-CoV-2 infection baseline info missing for 9 participants in mRNA-1273 50 µg group. CI = confidence interval, GMFR= geometric mean fold rise (post-baseline/baseline titers), GMT=geometric mean titer; LLOQ=lower limit of quantification ULOQ=upper limit of quantification. Antibody values assessed by pseudovirus neutralizing antibody assay reported as below the LLOQ (18.5 for ancestral SARS-CoV-2 [D614G] and 19.9 for omicron B.1.1.529) are replaced by 0.5 × LLOQ. Values greater than ULOQ (45,118) for ancestral SARS-CoV-2 [D614G] and 15,502.7 for omicron B.1.1.529) are replaced by the ULOQ if actual values are not available. 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 GMFR, respectively, then back transformed to the original scale.

Table S8. Observed Neutralizing Antibody Geometric Mean Titers Against Omicron BA.4 and BA.5 Subvariants after 50-µg of mRNA-1273.214 Administered as Second Booster Doses by Prior SARS-CoV-2 Infection at Pre-Booster

	All participants		No prior SARS-CoV-2 infection		Prior SARS-CoV-2 infection	
	mRNA-1273.214 50 µg Booster Dose	**mRNA-1273 50 µg Booster Dose**	**mRNA-1273.214 50 µg Booster Dose**	**mRNA-1273 50 µg Booster Dose**	**mRNA-1273.214 50 µg Booster Dose**	**mRNA-1273 50 µg Booster Dose**
	N=428	**N=367**	**N=334**	**N=260**	**N=94**	N=98
Pre-booster, n†	428	367	334	260	94	98
Observed GMT (95% CI)§	172.7 (147.4-202.3)	209.3 (179.5-244.1)	115.6 (98.5-135.6)	139.7 (119.5-163.3)	719.5 (531.6-973.9)	609.1 (448.1-828.1)
Day 29, n†	427	367	333	260	94	98
Observed GMT (95% CI)§	940.6 (826.3-1070.6)	645.4 (570.1-730.6)	727.4 (632.8-836.1)	492.1 (431.1-561.9)	2337.4 (1825.5-2992.9)	1270.8 (987.3-1635.8)
GMFR (95% CI)§	5.4 (5.0-5.9)	3.1 (2.8-3.3)	6.3 (5.7-6.9)	3.5 (3.2-3.9)	3.2 (2.8-3.8)	2.1 (1.8-2.4)
Estimated GMT (95% CI)¶	985.4 (914.8-1061.4)	588.4 (544.1-636.2)	776.4 (719.5-837.9)	458.3 (420.6-499.3)	2246.3 (1975.5-2554.1)	1406.9 (1227.9-1612.0)
GMR (95.0% CI)¶	1.68 (1.52-1.84)		1.69 (1.51-1.90)		1.60 (1.34-1.91)	

CI=confidence interval, GMFR=geometric mean fold rise (post-baseline/baseline titers), GMR=geometric mean ratio (mRNA-1273.214 vs mRNA-1273), GMT=geometric mean titer. n=Number of participants with non-missing data at baseline and the corresponding post-baseline timepoint. Antibody values assessed by a research-grade pseudovirus neutralizing antibody ID50 assay for omicron (BA.4/BA.5) reported as below the lower limit of detection ([LOD] 10) are replaced by 0.5 x LOD.

†Number of participants 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 GMT and GMFR, respectively, then back transformed to the original scale for presentation.

¶The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years) and pre-booster antibody titer level (in $\log_{10}$ scale). The treatment variable corresponds to each individual study arm dose. The resulting LS means, difference of LS means, and confidence intervals are back transformed to the original scale for presentation.

Table S9. Binding Antibody Titers and Geometric Mean Ratios Against Ancestral SARS-CoV-2 and Variants after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses in Participants with No Evidence of Prior SARS-CoV-2 Infection at Pre-Booster

	Ancestral SARS-CoV-2 (D614G)		Omicron		Beta	
	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260
Pre-booster, n†	332	259	331	256	332	259
Observed GM levels§	253,732 (230,053-279,847)	280,187 (255,546-307,204)	50,656 (45,583-56,293)	55,962 (50,769-61,686)	113,986 (103,401-125,656)	125,812 (114,408-138,352)
Day 29, n†	313	251	292	239	306	252
Observed GM Level (95% CI)§	850,554 (780,987-926,317)	783,449 (714,773-858,725)	201,643 (183,823-221,191)	173,721 (157,525-191,582)	393467 (362,016- 427,651)	363114 (331,815-397,366)
GMFR (95% CI)§	3.4 (3.2-3.6)	2.8 (2.7-3.0)	4.0 (3.7-4.2)	3.1 (2.9-3.4)	3.5 (3.3- 3.7)	3.0 (2.8-3.2)
Estimated GM Level (95% CI)¶	884,978 (839,674-932,727)	761,984 (718,961-807,582)	209,859 (198,170-222,237)	168,687 (158,454-179,580)	408,455 (387,526-430,513)	354,483 (334,714-375,419)
GMR (95% CI)¶	1.16 (1.07-1.26)		1.24 (1.14-1.35)		1.15 (1.07-1.25)	
	Delta		**Gamma**		**Alpha**	
	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260	mRNA-1273.214 50 µg N=334	mRNA-1273 50 µg N=260
Pre-booster, n†	332	259	332	259	332	259
Observed GM levels§	160,021 (145,267- 176,274)	176,051 (160,245-193,415)	121,087 (109,783-133,556)	136,347 (124,199-149,684)	183,545 (166,029-202,909)	207,233 (188,611-227,693)
Day 29, n†	310	252	307	252	308	250
Observed GM Level (95% CI)§	527,855 (486,349-572,904)	507,471 (465,240- 553,536)	424,440 (389,001-463,108)	386785 (353150- 423624)	638,782 (585,808-696,546)	584,312 (532,975-640,594
GMFR (95% CI)§	3.3 (3.1-3.5)	3.0 (2.8-3.1)	3.5(3.3-3.8)	2.9 (2.7-3.1)	3.5 (3.3- 3.7)	2.9 (2.7-3.1)
Estimated GM Level (95% CI)¶	546,567 (520,178-574,295)	494,689 (468,536-522,302)	443,655 (420,473, 468,114)	374,273 (352,956-396,878)	668,710 (634,902-704,319)	562,715 (531,544-595,715)
GMR (95% CI)¶	1.11 (1.03-1.19)		1.19 (1.10-1.28)		1.19 (1.10-1.28)	

CI=confidence interval, GM=geometric mean, GMFR=geometric mean fold rise (post-baseline/baseline titers), GMR=geometric mean ratio (mRNA-1273.214 relative to mRNA-1273), LLOQ=lower limit of quantification; Meso Scale Discovery =MSD; ULOQ=upper limit of quantification. Binding antibody values assessed by MSD assay reported as below the LLOQ (69 for ancestral SARS-CoV-2; 102 for omicron, 111 for beta; 150 for delta; 143 for gamma; and 52 for alpha) were replaced by 0.5 × LLOQ. Values greater than ULOQ (14,400,000 for ancestral SARS-CoV-2; 1,180,000 for omicron; 5,000,000 for beta; 8,000,000 for delta; 5,800,000 for gamma; 8,800,000 for alpha) were replaced by the ULOQ if actual values are not available.

†Number of participants with non-missing data at the timepoint (baseline or post-baseline).

§95% CI based on the t-distribution of log-transformed values or difference in the log-transformed values for GM value and GMFR, respectively, then back transformed to the original scale.

¶Log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years) and pre-booster titers. The resulting LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Table S10. Binding Antibody Levels and Geometric Mean Ratios Against Ancestral SARS-CoV-2 and Variants after 50-µg of mRNA-1273.214 and mRNA-1273 Administered as Second Booster Doses, Regardless of Evidence of Prior SARS-CoV-2 Infection

	Ancestral SARS-CoV-2		Omicron		Beta	
	mRNA-1273.214 50 µg N=428	**mRNA-1273 50 µg N=367**	**mRNA-1273.214 50 µg N=428**	**mRNA-1273 50 µg N=367**	**mRNA-1273.214 50 µg N=428**	**mRNA-1273 50 µg N=367**
Pre-booster, n†	423	365	420	360	423	365
Observed GM levels§	282,635 (257,514-310,207)	299,028 (274,090-326,237)	54,956 (49,719-60,745)	58,640 (53,339-64,469)	127,083 (115,948-139,288)	135,259 (123,818-147,756)
Day 29, n†	405	353	384	334	398	350
Observed GM Level (95% CI)§	856,394 (791,569-926,528)	753,438 (694,045-817,914)	201,367 (185,010-219,170)	163,486 (149,305-179,013)	403,166 (373,553-435,126)	352,739 (325,581-382,162)
GMFR (95% CI)§	3.0 (2.8-3.2)	2.6 (2.4-2.7)	3.6 (3.4-3.8)	2.8 (2.7-3.0)	3.1 (3.0-3.3)	2.7 (2.6-2.9)
Estimated GM Level (95% CI)¶	797,188 (758,939-837,365)	700,606 (665934-737,084)	187,826 (178,054-198,134)	152,403 (144,175-161,100)	382,058 (363,634-401,415)	334,638 (317,957-352,195)
GMR (95% CI)¶	1.14 (1.07-1.21)		1.23 (1.15-1.32)		1.14 (1.07-1.22)	
	Delta		**Gamma**		**Alpha**	
	mRNA-1273.214 50 µg N=428	**mRNA-1273 50 µg N=367**	**mRNA-1273.214 50 µg N=428**	**mRNA-1273 50 µg N=367**	**mRNA-1273.214 50 µg N=428**	**mRNA-1273 50 µg N=367**
Pre-booster, n†	423	365	423	365	423	364
Observed GM levels§	181,213 (165,495-198,424)	193,939 (177,757-211,594)	138,574 (126,336-151,998)	150,030 (137,680-163,486)	207,587 (188,619-228,462)	223,595 (204,443-244,541)
Day 29, n†	402	351	399	350	400	350
Observed GM Level (95% CI)§	546,450 (507,230-588,702)	502,005 (465,032-541,917)	441,810 (408,370-477,989)	384,401 (354,977-416,264)	652,098 (602,056- 706,299)	568,576 (523,291-617,779)
GMFR (95% CI)§	3.0 (2.8-3.2)	2.7 (2.5-2.8)	3.1 (3.0-3.3)	2.7 (2.5-2.8)	3.1 (2.9-3.3)	2.6 (2.5-2.7)
Estimated GM Level (95% CI)¶	516,916 (493,390-541,564)	472,237 (450,021-495,549	419,813 (399,165-441,528)	361,839 (343,419- 381,246))	610,201 (581,170, 640,682)	523,953 (498,178-551,061)
GMR (95% CI)¶	1.10 (1.03-1.16)		1.16 (1.09-1.24)		1.17 (1.09-1.24)	

ANCOVA=analysis of covariance, CI=confidence interval, GM=geometric mean, GMFR=geometric mean fold rise (post-baseline/baseline titers), GMR=geometric mean ratio, mRNA-1273.214 vs mRNA-1273. LLOQ=lower limit of quantification; LS=least squares; ULOQ=upper limit of quantification. Binding antibody values assessed by MSD assay reported as below the LLOQ (69 for ancestral SARS-CoV-2; 102 for omicron, 111 for beta; 150 for delta; 143 for gamma; and 52 for alpha) were replaced by 0.5 × LLOQ. Values greater than ULOQ (14,400,000 for ancestral SARS-CoV-2; 1,180,000 for omicron; 5,000,000 for beta; 8,000,000 for delta; 5,800,000 for gamma; 8,800,000 for alpha) were replaced by the ULOQ if actual values are not available.

†Number of participants with non-missing data at the timepoint (baseline or post-baseline).

§95% CI based on the t-distribution of log-transformed values or difference in the log-transformed values for GM value and GMFR, respectively, then back transformed to the original scale.

¶Log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years), pre-booster titers and prior SARS-CoV-2 infection. The resulting LS means, difference of LS means, and 95% CI are back transformed to the original scale.

Table S11. Observed Binding Antibody Geometric Mean Levels Against Ancestral SARS-CoV-2 and Omicron After Second 50-µg Boosters of mRNA-1273.214 and mRNA-1273 by Prior SARS-CoV-2 Infection at Pre-Booster

	All participants		No prior SARS-CoV-2 infection		Prior SARS-CoV-2 infection	
	mRNA-1273.214 50 µg Booster Dose	mRNA-1273 50 µg Booster Dose	mRNA-1273.214 50 µg Booster Dose	mRNA-1273 50 µg Booster Dose	mRNA-1273.214 50 µg Booster Dose	mRNA-1273 50 µg Booster Dose
Ancestral SARS-CoV-2	**N=428**	**N=367**	**N=334**	**N=260**	**N=94**	**N=98**
Pre-booster						
n	423	365	332	259	91	97
Observed GM level (95% CI)	282,635 (257,514-310207)	299,028 (274,090-326,237)	253,732 (230,053-279,847)	280,187 (255,546-307,204)	418,947 (332,856-527,305)	349,738 (283,191-431,922)
Day 29						
n	405	353	313	251	92	95
Observed GM level (95% CI)	856,394 (791,569-926,528)	753,438 (694,045-817,914)	850,554 (780,987-926,317)	783,449 (714,773-858,725)	876,567 (723,100-1,062,604)	682,474 (567,428-820,846)
GMFR (95% CI)	3.0 (2.8-3.2)	2.6 (2.4-2.7)	3.4 (3.2-3.6)	2.8 (2.7-3.0)	2.0 (1.8-2.2)	1.9 (1.8-2.1)
Omicron (B.1.1.529)	**N=428**	**N=367**	**N=334**	**N=260**	**N=94**	**N=98**
Pre-booster						
n	420	360	331	256	89	95
Observed GM level (95% CI)	54,956 (49,719-60,745)	58,640 (53,339-64,469)	50,656 (45,583-56,293)	55,962 (50,769-61,686)	74,410 (57,476-96,333)	65,018 (51,139-82,664)
Day 29						
n	384	334	292	239	92	88
Observed GM level (95% CI)	201,367 (185,010-219,170)	163,486 (149,305-179,013)	201,643 (183,823-221,191)	173,721 (157,525-191,582)	200,491 (164,075-244,991)	139,392 (112,194-173,182)
GMFR (95% CI)	3.6 (3.4-3.8)	2.8 (2.7-3.0)	4.0 (3.7-4.2)	3.1 (2.9-3.4)	2.5 (2.3-2.8)	2.2 (2.0-2.4)

SARS-CoV-2 infection baseline info missing for 9 participants in mRNA-1273 50 µg group. CI=confidence interval, GM=geometric mean, GMFR=geometric mean fold rise (post-baseline/baseline titers), LLOQ=lower limit of quantification. Meso Scale Discovery=MSD; ULOQ=upper limit of quantification. Binding IgG antibody values assessed by MSD assay reported as below the LLOQ (69 for ancestral SARS-CoV-2; 102 for omicron B.1.1.529) are replaced by 0.5 × LLOQ. Values greater than ULOQ (14,400,000 for ancestral SARS-CoV-2; 1,180,000 for omicron) are replaced by the ULOQ if actual values are not available. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GMFR respectively, and then back transformed to the original scale for presentation.

Table S12. Incidences of SARS-CoV-2-infection and Covid-19

	Per-protocol Efficacy Set No Prior SARS-CoV-2 Infection		Full Analysis Set Prior SARS-CoV-2 Infection		Full Analysis Set All Participants	
n (%)	**mRNA-1273.214 50 µg N=339**	**mRNA-1273 50 µg N=266**	**mRNA-1273.214 50 µg N=96**	**mRNA-1273 50 µg N=101**	**mRNA-1273.214 50 µg N=437**	**mRNA-1273 50 µg N=377**
Covid-19 (COVE definition)*						
Cases	4 (1.2)	1 (0.4)	0	0	4 (0.9)	2 (0.5)
Covid-19 (CDC definition)*						
Cases	5 (1.5)	1 (0.4)	0	0	5 (1.1)	2 (0.5)
SARS-CoV-2 infection (regardless of symptoms)						
Cases	11 (3.2)	5 (1.9)	0	3 (3.0)	11 (2.5)	9 (2.4)
Asymptomatic SARS-CoV-2 infection						
Cases	6 (1.8)	4 (1.5)	0	3 (3.0)	6 (1.4)	7 (1.9)

*Covid-19 cases based on 1 symptom per CDC definition; Covid-19 primary case definition based on 2 systemic symptoms or at least one of the respiratory symptoms used in the Coronavirus Efficacy (COVE) trial.[1,2] The full analysis set consists of all participants who received study vaccine. The per-protocol set for efficacy consists of all participants in the full analysis set (FAS) who are SARS-CoV-2 negative pre-booster and have no major protocol deviations. There was one participant in the mRNA-1273.214 50 µg group and 9 participants in the mRNA-1273 50 µg group with missing pre-booster information in the full analysis set. One participant with missing pre-booster SARS-CoV-2 status had Covid-19 infection (per COVE and CDC definitions). Table includes all events starting 14 days after the booster dose. Data-cut-off April 27th, 2022.

Supplement References

1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-16.
2. El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med 2021;385:1774-85.
3. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383:1920-31.
4. FDA U. Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry file:///C:/Users/Owner/Downloads/FDA-2020-D-1137-0019_attachment_2%20(1)pdf May 25, 2021.
5. FDA U. Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry https://wwwfdagov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19 March 2022.
6. Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science 2022;375:43-50.
7. Symptoms of COVID-19. 2021. (Accessed October, 2021, at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.)
8. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Multiple Endpoints in Clinical Trials Guidance for Industry. 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry.