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BRIEF REPORT

Immunogenicity of a 2-Dose Regimen of Moderna mRNA Beta/Omicron BA.1 Bivalent Variant Vaccine Boost in a Randomized Clinical Trial

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We compared the serologic responses of 1 dose versus 2 doses of a variant vaccine (Moderna mRNA-1273 Beta/Omicron BA.1 bivalent vaccine) in adults. A 2-dose boosting regimen with a variant vaccine did not increase the magnitude or the durability of the serological responses compared to a single variant vaccine boost.

Keywords. SARS-CoV-2; vaccine; variant.

INTRODUCTION

A single boost with currently available updated Omicron-containing vaccines leads to a serological advantage against Omicron subvariants compared to boosting with ancestral vaccine [1]. Although additional doses of variant boosters are recommended for individuals at risk for severe disease [2] and an updated Omicron XBB.1.5 formulation is recommended for the fall of 2023 [3] in the United States (US), it is unclear whether 2 doses of variant vaccines further boost humoral immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. The Coronavirus Variant Immunologic Landscape Trial (COVAIL) is an adaptive phase 2, open-label, randomized clinical trial assessing the immunogenicity of variant-containing SARS-CoV-2 vaccines. The objective of this report is to compare the magnitude and durability of the serologic response of 1 dose versus 2 doses of a variant nonancestral vaccine (Moderna mRNA-1273 Beta/Omicron BA.1 bivalent vaccine) in adults.

METHODS

Study Design and Eligibility Criteria

This phase 2, open-label, randomized clinical trial was performed at 22 US sites (Supplementary Table 7) enrolling all participants from March to May 2022. Eligible participants were healthy adults (with or without a history of prior SARS-CoV-2 infection) who had received a primary series and single homologous or heterologous boost with an approved or emergency use–authorized prototype coronavirus disease 2019 (COVID-19) vaccine (Supplementary Table 8). The most recent vaccine dose, and/or prior COVID-19 infection, must have occurred at least 16 weeks prior to randomization. Full eligibility criteria are described at ClinicalTrials.gov (identifier NCT05289037).

Two hundred two eligible participants were stratified by history of confirmed SARS-CoV-2 infection and randomized 1:1 to receive 1 or 2 doses (separated by 56 days) of Moderna mRNA Beta/Omicron BA.1 bivalent vaccine (50 μg). Beta/Omicron BA.1 was chosen to cover an antigenic space distant from D614G and from which new variants may emerge.

After informed consent, participants underwent screening, including confirmation of COVID-19 vaccination, medical history, a targeted physical examination, and a urine pregnancy test (if indicated). Samples were collected at days 1, 15, 29, 57 (2-dose arm only), and 85 (2-dose arm only) and 3, 6, 9, and 12 months after last dose of vaccine. Immunologic data are currently available up to day 181 for the 1-dose arm and through day 237 (180 days after second dose) for the 2-dose arm.

The trial was reviewed and approved by a central institutional review board and overseen by an independent data and safety monitoring board. Participants provided written informed consent before undergoing trial-related activities. The trial was sponsored and funded by the National Institutes of Health. The National Institute of Allergy and Infectious Diseases SARS-CoV-2 Assessment of Viral Evolution (SAVE) program team was consulted to inform study design and variant vaccine selection.

Trial Vaccine

The Beta/Omicron BA.1 bivalent trial vaccine was provided by Moderna (50 μg per dose; 25 μg of each component). The vaccine candidates were manufactured similarly to their corresponding authorized or approved vaccines in the US or Europe.

Study Outcomes

The primary objective was to evaluate humoral immune responses of candidate SARS-CoV-2 variant vaccines. Assessment of the safety of candidate variant vaccines was a secondary objective.

Immunogenicity Assays

SARS-CoV-2 neutralization titers [4], expressed as the serum inhibitory dilution required for 50% neutralization (ID_{50}), were assessed in the Monogram laboratory (San Francisco, California) using pseudotyped lentiviruses [4] presenting SARS-CoV-2 spike proteins of the following strains: D614G, B.1.617.2 (Delta), B.1.351 (Beta), Omicron BA.1, and Omicron BA.4/5.

Prespecified Immunogenicity Endpoints

Statistical Analysis

The magnitude and breadth of SARS-CoV-2–specific antibody titers in serum samples were evaluated by estimating 95% confidence intervals (CIs) for the geometric mean titer (GMT) at each timepoint when samples were collected. No formal hypothesis tests were planned.

The geometric mean fold rise (GMFR) was calculated as the geometric mean of titers at a timepoint divided by titers at day 1. The geometric mean ratio to D614G (GMR_{D614G}) was the geometric mean of the ratio of titers against D614G to titers for a variant of concern. The geometric mean fold drop (GMFD) was calculated by dividing the result at day 29 by the result at each day after day 29 and then calculating the geometric mean. Seropositive rate was calculated as the proportion of participants with titers above the lower limit of detection. The 95% CIs for GMT, GMFR, GMFD, and GMR_{D614G} were calculated using the Student t distribution and 95% CIs for seropositive rate were calculated using the Clopper–Pearson binomial method.

Analysis of covariance (ANCOVA) models were used to estimate GMT ratios of the 2-dose arm compared to the 1-dose arm and included independent variables for age, previous infection history, and baseline titers. For modeling purposes, titers were $\log_{10}$ transformed and estimated mean differences were back-transformed to generate GMT ratios between vaccination arms. Unadjusted 97.5% CIs based on the t-distribution are reported.

For the purpose of analysis, participants were defined as previously infected by positive N- antibody at baseline or self-report of a positive antigen or polymerase chain reaction test. Participants were removed from analysis at timepoints following self-reported infection, N-antibody positivity, or receipt of an out-of-study COVID-19 booster (Supplementary Tables 10 and 11). Participants randomized to the 2-dose arm who did not receive the second dose were removed from the analysis after day 29. This consisted of participants who tested positive for COVID-19 prior to receiving the second dose, participants who had adverse events (AEs), and 1 participant who withdrew from the 2-dose arm due to reactogenicity experienced after the first dose.

RESULTS

Study Population

Previously vaccinated and boosted participants were enrolled between March and May 2022 and received either 1 dose or 2 doses of the Moderna mRNA Beta/Omicron BA.1 bivalent vaccine. Baseline characteristics were similar between the 2 study arms (Supplementary Table 9). Median age was 54 years (range, 19–81 years). Most participants (95% per arm) had received an mRNA-based primary series and booster vaccine. At enrollment, 19% had been previously infected (Supplementary Table 9). Median duration between study vaccination and the last previous vaccination or infection was 168 days (range, 112–244 days).

Safety

Solicited local and systemic AEs after vaccination were similar to other booster trials and did not differ between arms. The most frequently reported solicited local AE was injection-site pain (88% for both arms). The most common solicited systemic AEs were fatigue (66% for the 1-dose arm and 68% for the 2-dose arm). Most solicited AEs were mild to moderate; only 6% of solicited AEs were graded as severe (more frequently in the 1-dose arm). There were 16 unrelated AEs

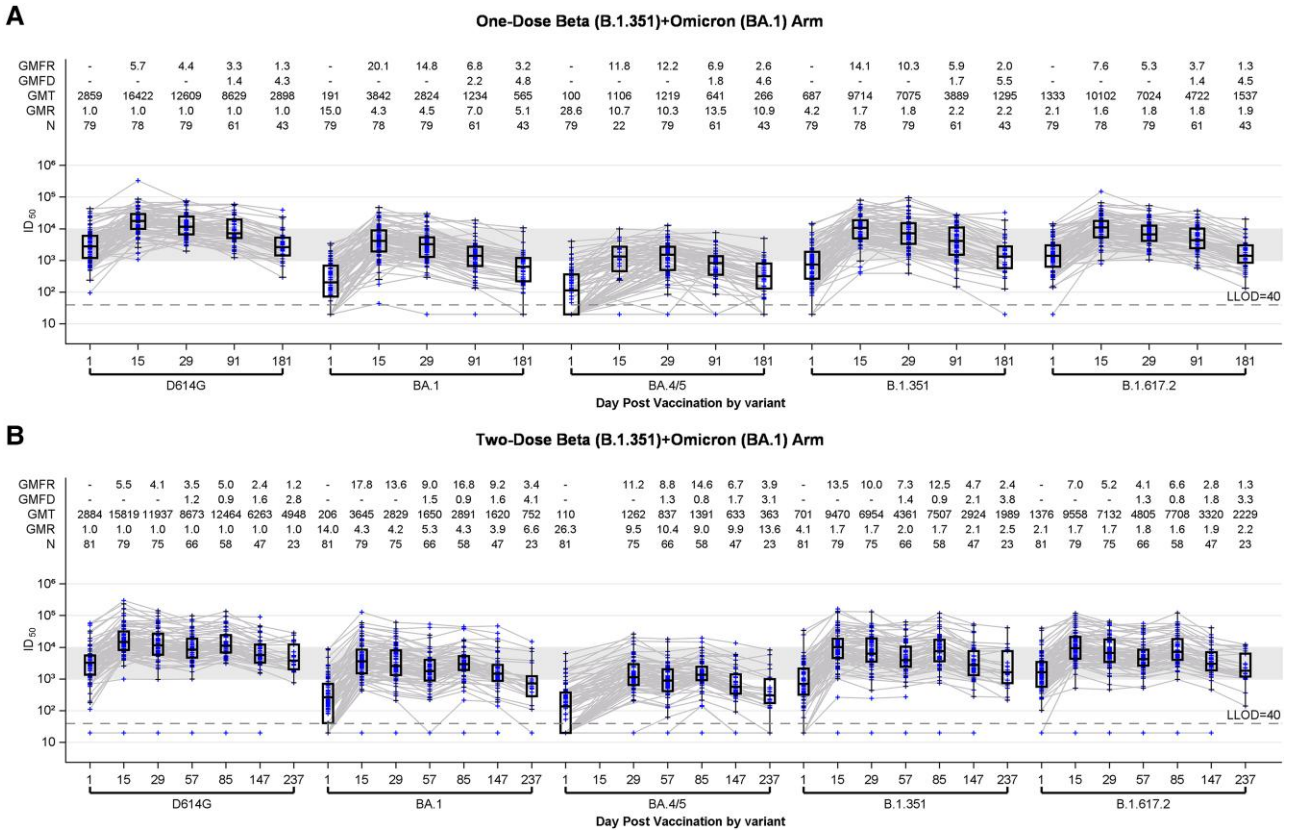

Figure 1. Pseudovirus neutralization serum inhibitory dilutions required for 50% neutralization (ID_{50}) titers by timepoint (baseline and days 15, 29, 91, and 181 for the 1-dose arm and days 15, 29, 57 [prior to receipt of the second dose], 85 [28 days after the second dose], 147 [90 days after the second dose], and 237 [180 days after the second dose] for the 2-dose arm) and variants (D614G, Omicron BA.1 [B.1.1.529], BA.4/BA.5, Beta [B.1.351], and Delta [B.1.617.2]) before and after vaccination with 1 dose of 50 μg of Moderna mRNA-1273 Beta/Omicron BA.1 (*A*) or 2 doses (given 56 days apart) of 50 μg Moderna mRNA-1273 Beta/Omicron BA.1 (*B*) in participants previously uninfected at baseline. Boxes with horizontal bars denote interquartile range and median ID_{50}, respectively. Whisker denotes 95% confidence interval. Abbreviations: GMFD, geometric mean fold decrease from baseline; GMFR, geometric mean fold rise from baseline; GMR, geometric mean ratio (relative to D614G); GMT, geometric mean titer; ID_{50}, serum inhibitory dilution required for 50% neutralization; LLOD, lower limit of detection of the assay.

of special interest, 12 unrelated serious AEs, and no AEs leading to study withdrawal at the time of interim analysis (Supplementary Figures 1 and 2 and Supplementary Tables 12 and 13).

Immunogenicity

One hundred participants were enrolled in the 1-dose arm and 102 in the 2-dose arm. In previously uninfected participants, day 29 ID_{50} GMTs in the 1-dose arm against D614G, BA.1, BA.4/5, B.1.351, and B.1.617.2 were 12 609, 2824, 1219, 7075, and 7024, respectively (Figure 1, Supplementary Tables 1 and 2). Corresponding ID_{50} GMTs in the 2-dose arm, 28 days after last dose, were 12 464, 2891, 1391, 7507, and 7708, respectively. To compare the degree of antibody waning, we used an ANCOVA model at 3 and 6 months since last vaccination and did not find any difference between 1- or 2-dose arms against BA.1, BA.4/5, or B.1.351 at 3 months (GMR estimates, 0.64–1.15) or at 6 months (GMR estimates, 1.08–1.36 with the unadjusted 97.5% CI including 1) (Supplementary Tables 5 and 6).

At enrollment, 18% and 21% of the 1- and 2-dose arms, respectively, had a prior SARS-CoV-2 infection by self-report or N-antibody testing (Supplementary Table 9). Titers were higher in these previously infected participants at all timepoints with similar findings following 1 or 2 doses (Supplementary Tables 3 and 4).

DISCUSSION

To our knowledge, this study is the first in humans to show serological responses after a 2-dose boost with the same nonancestral SARS-CoV-2 variant–based vaccine. A 2-dose boosting regimen with a variant vaccine, albeit given 2 months apart, did not increase the magnitude or the durability of the serological responses compared to a single-variant vaccine boost, contrary to what has been observed for other pandemic vaccines (eg, AS03-adjuvanted H5N1 influenza virus vaccine). It is possible that a boost with more contemporary variant vaccines, or 2 doses given with a longer interval, could lead to different results. Vaccine regimens that require dosing more than

once annually will be extremely hard to sustain over the long term, underscoring the importance of ongoing efforts toward optimizing effectiveness toward emerging variants. The limitations of our study include small sample size, differential follow-up due to the 2-dose arm dosing interval, and the absence of memory B-cell data. Although antibody levels play a major role in vaccine effectiveness [5], we do not currently have precise immune correlates of protection for emerging SARS-CoV-2 variants, and we do not have efficacy data from this phase 2 trial. While vaccination has played a significant role in decreasing morbidity and mortality related to SARS-CoV-2 [6], efforts are currently under way to develop next-generation COVID-19 vaccines focusing on improving durability and breadth of immune responses and ultimately decreasing acquisition and transmission [7].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. A. R. B. has received research support from NIH-NIAID, grants from Pfizer, Cyanvac, Moderna, Vaccine.co and Merck as well as consulting fees from Janssen and GSK. She serves as DSMB member for NIH, IDSA Public Health Committee. Honoraria as a speaker from Virology Education. L. R. B. has received grants from Wellcome Trust, Gates Foundation, NIH/Harvard Medical School through institution. Serves as member of DSMB for NIH and AMDAC for FDA. Dr Baden is involved in HIV and SARS-CoV-2 vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), Covid Vaccine Prevention Network (CoVPN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Moderna, Military HIV Research Program (MHRP), the Gates Foundation, and Harvard Medical School. D. J. D. has received a contract from Leidos Biomedical/NIH research to conduct the clinical trial through institution. A. R. F. has received grants from Janssen, Pfizer, Merck, BioFire Diagnostics, Moderna, Vaccine company and CyanVac through institution. Consultant fees from Arrow Pharmaceutical, ADMA biologics, GSK, and honoraria as a speaker from Sanofi and GlaxoSmithKline. Serves as DSMB advisory boards for Novavax and received travel/meeting support from GlaxoSmithKline. S. E. F. has received funding from Leidos to Saint Louis University to conduct Protocol DMID 22-0004. Funding was also received to conduct the Moderna and Janssen trials phase 3 SARS-CoV-2 trials. Serves as DSMB for HVTN Safety Monitoring Board. D. N. F. has as a contract from CDC and is the site PI for DN Fusco study of COVID in Special Populations. D. N. F. served on an HBV Advisory board for Gilead related to hepatitis C & B viruses and Axcella related to Long COVID. P. A. G. has received funding from NIH. PAG has a patent for COVID-19 monoclonal not developed clinically and received consulting fees from International AIDS Society as speaker. L. C. I. has received support from NIH, Moderna, Pfizer, and Sanofi. L. C. I. has also received grants from GSK, Merck, Sharpe & Dohme Corp, CDC, Novavax, Pediatric Emergency Medicine Associates, and NIH/NLM/National Institute on Minority Health and Health Disparities as well as consulting fees from Moderna. L. C. I. has received honoraria as a speaker from American Academy of Pediatrics, Rockefeller University, Moderna, CDC and American Academy of Pediatrics- Georgia Chapter. L. C. I. Serves on Data Safety Monitoring for NIH-Phase 2 Vaccine Trial for Monkeypox, Moderna Scientific Advisory Board- North America, and CoVID-19 Task Force, Georgia. L. C. I. has a leadership role Break the Cycle of Health Disparities Inc, the Center for Spatial Analytics of the Georgia Institute of Technology, and the American Academy of Pediatrics (Executive Board for Section on Infectious Diseases). L. C. I. has received travel/meeting support from the American Academy of Pediatrics and Moderna. L. A. J. has received funding from NIH for support for this study, funding from Pfizer to support a clinical trial and contract funding for research support from the CDC and the NIH, all through institution. L. A. J. also reports unpaid participation on Data Safety Monitoring Boards for NIH funded clinical trials. S. K.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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