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Omicron-BA.1-containing mRNA-1273 boosters compared with the original vaccine in the United Kingdom: a randomised, double-blind, active-control trial

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Abstract 300/300

Background

The Omicron-BA.1-bivalent booster is used globally. This large randomised, active-controlled trial compares the safety and immunogenicity of Omicron-BA.1-monovalent and -bivalent boosters with the original mRNA-1273 vaccine.

Methods

In this ongoing, phase 3 trial in the United Kingdom (28 sites), individuals ≥16 years who had previously received two injections of any authorized/approved coronavirus disease 2019 (COVID-19) vaccine with/without an mRNA-vaccine booster, were randomised to receive 50-µg Omicron-BA.1-monovalent or -bivalent vaccines or 50-µg mRNA-1273 administered as boosters. Primary objectives were safety and immunogenicity including prespecified non-inferiority and superiority of booster-immune responses.

Findings

Between February 16−March 24, 2022, 724 participants were randomised and received Omicron-BA.1-monovalent (n=366) or mRNA-1273 (n=357); between April 2−June 17, 2022, 2824 were randomised and received Omicron-BA.1-bivalent (n=1418) or mRNA-1273 (n=1395) as second boosters. Median durations (months) between the most recent COVID-19 vaccine and study boosters were similar for Omicron-BA.1-monovalent (4·0) and mRNA-1273 (4·1), and Omicron-BA.1-bivalent (5·5) and mRNA-1273 (5·4) boosters. Omicron-BA.1-monovalent and -bivalent boosters elicited superior neutralizing antibody geometric mean concentrations (GMC) against Omicron-BA.1 variant with GMC-ratios (99% CI) of 1·68 (1·45−1·95) and 1·53 (1·41−1·67) at day 29 post-boost in participants without prior SARS-CoV-2-infection. Both boosters induced non-inferior ancestral SARS-CoV-2 (D614G) immune responses with GMCs

(95% CI) that were similar for the bivalent (2987·2 [2814·9-3169·9] versus mRNA-1273 (2911·3 [2750·9-3081·0]) and lower for the monovalent (2699·7 [2431·3-2997·7] versus 3020·6 [2776·5-3286·2) boosters with GMC-ratios of 1·05 (99% CI 0·96-1·15) and 0·82 (95% CI 0·74-0·91) respectively. Results were comparable regardless of prior SARS-CoV-2-infection status. Incidences of solicited adverse reactions with Omicron-BA.1-monovalent (91·3% [335/367 participants]) and Omicron-BA.1-bivalent (90·4% [1285/1421 participants]) boosters were similar to those observed previously for mRNA-1273 with no new safety concerns identified and no occurrences of fatal adverse events.

Interpretation

Omicron-containing booster vaccines generated superior immunogenicity against BA.1 and comparable immunogenicity against the original strain with no new safety concerns.

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Research in Context

Evidence before this study

Variant-containing bivalent booster vaccines comprised of mRNAs encoding the original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Omicron BA.1 or BA.4/BA.5 have been deployed globally to prevent coronavirus disease 2019 (COVID-19) caused by the continuous emergence of Omicron variants. In prior non-randomised, open-label clinical studies, Omicron-BA.1-bivalent (mRNA-1273.214) and Omicron-BA.4/BA.5-bivalent (mRNA-1273.222) vaccines demonstrated superior immune responses compared to the original vaccine which supported authorization of the boosters; however, large randomised, active-controlled studies of the contemporaneous administration of the bivalent and original mRNA-1273 vaccine boosters had not been undertaken. We searched PubMed for research articles in English published between June 2022 and January 2023, using the terms COVID-19 booster vaccines, SARS-CoV-2 variants, randomised clinical trials and observational real-world effectiveness studies. In addition to previous studies describing the immune responses of mRNA-1273 vaccines and variant-containing boosters against SARS-CoV-2 variants, we identified prior publications describing the immune responses of other monovalent and bivalent COVID-19 vaccines including BNT-162b, AZD1222 and Ad26.COV2, against SAR-CoV-2 variants. Our search also identified one randomised phase 3 trial describing the immune responses of monovalent- and bivalent-omicron-BA.1-containing BNT-162b boosters against SARS-CoV-2 variants as well as several real-world studies demonstrating the effectiveness of booster vaccines against SARS-CoV-2 variants.

Added value of this study

Previous non-randomised, open-label clinical studies supported the authorization of the Omicron-BA.1- and Omicron-BA.4/BA.5-bivalent vaccines on the basis of improved immunogenicity compared with the original mRNA-1273 vaccine in rapid response to variant surges. Studies that further address whether vaccines modified to approximate circulating variants provide clinical benefit are needed. This is the first large (>3300 participants) randomised, observer-blind, active-controlled, phase 3 trial that compares the safety and immunogenicity of the Omicron-BA.1-monovalent and Omicron-BA.1-bivalent booster vaccines head-to-head with the original mRNA-1273 booster. The boosters were evaluated in individuals aged ≥16 years in the United Kingdom who had previously received two injections of any

authorized/approved COVID-19 primary series vaccine, with or without an mRNA-based booster (third) dose. Interim results of the study show that all boosters were well-tolerated, consistent with prior studies of the mRNA-1273 vaccine, and no new safety concerns were identified. Both Omicron-BA.1-monovalent and -bivalent vaccines administered as second booster (fourth) doses elicited immune responses that were superior against the Omicron-BA.1 variant and non-inferior against ancestral SARS-CoV-2 (D614G) compared with mRNA-1273 at 28 days post-booster doses. Additionally, the Omicron-BA.1-bivalent booster induced seroresponses as well as binding antibody levels that were higher across Omicron BA.1, SARS-CoV-2 (D614G), and alpha, delta, and gamma variants compared to mRNA-1273 28 days post-booster doses; whereas, the seroresponses and binding antibody responses of the Omicron-BA.1-monovalent booster against ancestral SARS-CoV-2 (D614G) and alpha, gamma, and delta variants were similar compared to mRNA-1273, suggesting a potentially narrower immune response. While the study was not powered to evaluate booster effectiveness, in an exploratory analysis, lower but statistically nonsignificant COVID-19 incidence rates were observed with the Omicron-BA.1-monovalent and -bivalent versus mRNA-1273 boosters for the Omicron BA.2 isolate and for the bivalent vaccine against BA.4 isolates, but not for BA.5 with either booster. No Omicron-BA.1 cases were observed in the study. The reduced incidence rates driven by lower incidence rates for the antigenically-similar Omicron BA.2 in both the Omicron-BA.1-monovalent and -bivalent group supports the importance of more closely matching sequence to the circulating variant in booster vaccines. These results extend the evidence for the clinical benefit of variant-containing boosters in a randomised, active-controlled study compared to the original vaccine booster.

Implications of all the available evidence

Variant-containing boosters have demonstrated an increased breath of immune responses against SARS-CoV-2 variants in clinical studies and effectiveness in preventing severe COVID-19 and hospitalizations in real-world observational studies. Our data support a more robust immune response generated by variant-containing vaccines and also suggest that booster vaccines modified to more closely match circulating variants may provide improved clinical benefit. Given the continuous evolution and emergence of antigenically divergent SARS-CoV-2 variants, it is imperative to remain vigilant in monitoring the neutralization ability and effectiveness of COVID-19 vaccines. Ensuring that practices and systems are in place to readily adapt vaccines,

if needed, in response to the emergence of new SARS-CoV-2 variant waves is also a matter of public health importance. Additional studies of the safety, durability, and effectiveness of variant-containing booster vaccines may help to better inform future vaccination strategies against this pathogen.

Introduction

Variant-containing bivalent booster vaccines comprised of mRNAs encoding the original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Omicron BA.1 or BA.4/BA.5 have been deployed to prevent coronavirus disease 2019 (COVID-19) caused by the continuous evolution and emergence of SARS-CoV-2-Omicron variants.[1-6] Prior non-randomised, open-label studies of Omicron-BA.1-bivalent mRNA-1273.214 and Omicron-BA.4/BA.5-bivalent mRNA-1273.222 booster vaccines demonstrated superior neutralizing antibody (nAb) responses against Omicron BA.1 and BA.4/BA.5, respectively, versus mRNA-1273 with no new safety concerns,[1-3] supporting authorization of the vaccines in rapid response to variant surges.[4,5] The Omicron-BA.1-bivalent booster was approved in August 2022 in the United Kingdom (UK) and has subsequently been authorized by the European Medicines Agency, the Swissmedic, and Health Canada amongst other regulatory agencies, and remains widely used around the world. Recent real-world data suggest that the BA.1 and BA.4/5-containing bivalent mRNA-boosters provide additional protection against COVID-19 compared with the original booster vaccine administered ≤6 months previously.[7-9] However, randomised, active-controlled studies of the contemporaneous administration of the Omicron-containing and original vaccine had not been undertaken.

Here, we describe interim safety and immunogenicity results from a large, phase 3 randomised, observer-blind, active-controlled clinical trial that compares 50-µg of Omicron-BA.1 bivalent (25-µg ancestral SARS-CoV-2, 25-µg Omicron-BA.1 spike mRNAs) and Omicron-BA.1-monovalent (Omicron-BA.1 spike mRNA) booster vaccines with 50-µg of the original mRNA-1273 booster in individuals aged ≥16 years in the UK. Incidence rates of COVID-19 post-booster are also summarized.

Methods

Study Design

This large, phase 2/3 (designated phase 3, >3000 participants),[10] two-part, randomised, observer-blind, active-controlled, multicenter (28 sites) trial evaluated the immunogenicity and safety of 50-µg Omicron-BA.1-monovalent (part 1) and 50-µg Omicron-BA.1-bivalent (part 2) booster vaccines compared with 50-µg mRNA-1273 in medically-stable individuals aged ≥16 years in the UK (EudraCT;2022-000063-51) (Appendix, page 12). The trial was initiated in February of 2022 with a BA.1 monovalent booster vaccine in response to the emergence of the omicron variant. Thereafter, due to the rapid evolution of omicron sublineages, the enrollment of the Omicron-BA.1-monovalent portion of the trial (part 1) was stopped to expedite enrollment of an Omicron-BA.1-bivalent vaccine (part 2), which was hypothesized to induce better cross-protection.

The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice guidelines. The Derby Research Ethics Committee approved the protocol and consent forms. All participants provided written informed consent.

Participants

Eligible participants included those who previously received two injections of any authorized/approved COVID-19 primary series vaccine, including mixed regimens, with or without an mRNA-based booster as the third dose in the series ≥90 days prior. Participants who had previously received two injections of a COVID-19 vaccine as a primary series were eligible to receive Omicron-BA.1-monovalent vaccine, Omicron-BA.1-bivalent vaccine, or mRNA-1273 as first booster (third) doses. Participants who previously received a primary series and an

mRNA COVID-19 first booster (third) dose were eligible to receive a study vaccine as a second booster (fourth) dose. In part 1, one participant received Omicron-BA.1-monovalent vaccine as a third dose and in part 2, four and seven participants received Omicron-BA.1-bivalent and mRNA-1273 vaccines respectively as third doses. In part 1, 366 participants received Omicron-BA.1-monovalent and 357 received mRNA-1273 vaccines as second boosters, and in part 2, 1418 participants received Omicron-BA.1-bivalent vaccine and 1395 received mRNA-1273 vaccine as second booster doses. Those with histories of positive SARS-CoV-2-infection (≤90 days of screening) were ineligible for the study. Additional inclusion/exclusion criteria and details of study oversight, design and conduct are available in the Appendix, pages 4-10 and online study protocol.

Randomisation and masking

Participants were randomised 1:1 to receive a single dose of either 50-µg of Omicron-BA.1-monovalent or 50-µg of mRNA-1273 (active control) in part 1 and to receive a single dose of either 50-µg of Omicron-BA.1-bivalent or 50-µg of mRNA-1273 (active control) in part 2. In both parts, randomisation was stratified by age groups (16 to <65 years or ≥65 years) and number of booster doses received (to receive study vaccine as the second [fourth] booster dose or study vaccine as the first [third] booster dose). At least 90% of participants were prespecified to receive study vaccine as the fourth dose, as this was the booster dose anticipated to be received by the general population.

Randomisation was performed using an interactive response technology (Appendix, page 6). Enrollment was observer-blinded to treatment assignment. Dose preparation, administration, and accountability was performed by designated site personnel who did not participate in any clinical study evaluations and were responsible for only the management, documentation,

accountability, preparation, and administration of study vaccine. The unblinded site personnel prepared the dose out of view of participants and blinded site personnel, and did not reveal the identity of the study vaccine except in case of emergency. Blinding sleeves were applied to the contents of syringes and labels. Laboratory personnel responsible for immunogenicity testing were blinded to the treatment assignment of the samples tested throughout the study.

Procedures

Monovalent-mRNA-1273 and -Omicron-BA.1 vaccines contain single mRNAs (50-µg) encoding the prefusion-stabilized spike-glycoprotein of ancestral SARS-CoV-2 (Wuhan-Hu-1) or Omicron-BA.1 variant, respectively. Omicron-BA.1-bivalent vaccine (50-µg) contains two mRNAs (1:1, 25-µg each) encoding the prefusion-stabilized spike-glycoprotein of ancestral SARS-CoV-2 (Wuhan-Hu-1) and Omicron-BA.1 variant. The Omicron-BA.1-monovalent and the active comparator mRNA-1273 vaccines were administered at volumes of 0·25 mL, and the Omicron-BA.1-bivalent vaccine at 0·5 ml. All vaccines (50-µg) were administered via deltoid intramuscular injection.

Outcomes

The primary safety objective of both study parts was to evaluate the safety and reactogenicity of booster doses of Omicron-BA.1-monovalent, Omicron-BA.1-bivalent, and mRNA-1273 vaccines. Part 1 immunogenicity objectives included non-inferiority (primary) and superiority (key secondary) of Omicron-BA.1-monovalent vaccine-elicited immune responses against Omicron-BA.1 variant compared with mRNA-1273 when administered as booster doses at day 29 (Appendix, page 25-27). Secondary objectives include noninferiority of Omicron-BA.1-monovalent vaccine-elicited immune responses against ancestral SARS-CoV-2 with the D614G mutation (D614G) versus mRNA-1273 and seroresponses (SRR) at day 29.

Part 2 primary immunogenicity objectives included non-inferiority of Omicron-BA.1-bivalent vaccine-elicited immune responses against Omicron BA.1 and ancestral SARS-CoV-2 (D614G), and superiority of Omicron-BA.1-bivalent vaccine-elicited immune responses to Omicron BA.1, at day 29 compared with the mRNA-1273 booster. Non-inferiority and superiority in parts 1 and 2 were based on comparison of serum nAb for the monovalent and bivalent-boosters versus mRNA-1273, respectively. Evaluation of the immunogenicity of the Omicron-BA.1-monovalent and -bivalent vaccines against other variants (alpha, delta and gamma) based on binding antibody (bAb) geometric mean concentration (GMC) at day 29 versus mRNA-1273 were exploratory and secondary endpoints, respectively.

Incidences of symptomatic and asymptomatic SARS-CoV-2-infection post-booster vaccination were secondary (part 2) and exploratory (part 1) objectives (Appendix, page 25). Symptomatic SARS-CoV-2 infection is based on the protocol-defined COVID-19 primary case definition (Coronavirus Efficacy [COVE])[4,5] (≥two systemic symptoms, ≥one respiratory signs/symptoms and ≥one positive test for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction [RT-PCR]). Additionally, a secondary definition based on the Centers for Disease Control and Prevention (CDC) Case Definition of COVID-19[6] (≥one systemic symptoms; or ≥one respiratory signs/symptoms and a positive post-baseline RT-PCR test result). Asymptomatic SARS-CoV-2 infection is defined as the absence of symptoms and infections by RT-PCR or serology (bAb nucleocapsid protein [Roche Elecsys] negative at day 1 that become positive post-baseline. Exploratory endpoints included incidences of isolated SARS-CoV-2 variants (BA.2, BA.4 and BA.5) in parts 1 and 2.

Safety assessments included solicited local and systemic adverse reactions (ARs) recorded ≤seven days after booster vaccination; unsolicited adverse events (AEs) ≤28 days after

vaccination; and serious AEs (SAEs), medically-attended AEs (MAAEs), AEs leading to withdrawal, and AEs of special interest (Appendix, page 28) from vaccination to study end.

Serum nAb concentrations against Omicron BA.1 and/or ancestral SARS-CoV-2 (D614G) were measured by a validated pseudovirus neutralization assay.[11,12] Levels of serum bAb against Omicron BA.1, ancestral SARS-CoV-2 (D614G), and other variants were assessed using a validated SARS-CoV-2-specific spike-protein binding assay (Meso Scale Discovery). Results for both assays are reported as antibody geometric mean concentrations (GMC) in arbitrary units (AU)/mL. Immunogenicity assessment and assays are detailed in the Appendix, page 8.

Active surveillance for COVID-19 and SARS-CoV-2-infection were performed in both study parts (Appendix, page 9). Illness visit at study sites were arranged as soon as possible and within 72 hours for participants who tested positive/equivocal for SARS-CoV-2 by local RT-PCR testing or using an authorized/approved lateral flow/rapid antigen if an RT-PCR SARS-CoV-2 test was unavailable, or if there was uncertainty on the test result. At this visit, a nasopharyngeal swab was collected to evaluate the presence of SARS-CoV-2 infection. SARS-CoV-2-infection status is based on positive post-baseline bAb against SARS-CoV-2-nucleocapsid (Roche Elecsys) or RT-PCR tests. SARS-CoV-2-variant sequences were obtained by RT-PCR of nasopharyngeal swabs positive for SARS-CoV-2-infection ≥14 days after vaccine administration on an ongoing, cumulative basis and were assessed through the data-cutoff date.

Statistical Analysis

Statistical analysis methods are detailed in the Appendix, pages 6-8 and analysis sets in the Appendix, page 30. Safety was assessed in the safety set (all participants who received first or second boosters) and solicited ARs in the solicited safety set. The per-protocol set for

immunogenicity (PPSI) consists of participants in the full analysis set who received the planned booster dose, had pre-booster and day 29 antibody data and no major protocol deviations. The primary immunogenicity objectives were assessed in the PPSI-SARS-CoV-2-negative set (PPSI-negative). Incidences of SARS-CoV-2-infection were evaluated in the per-protocol set for efficacy comprising all participants in the modified-intent-to-treat population who received the planned study vaccination with no major protocol deviations. In both study parts, immunogenicity was evaluated in those who received second booster (fourth) doses as prespecified, and the efficacy analysis was restricted to participants who received second booster (fourth) doses as the sample size of participants eligible for the per-protocol efficacy set of those who received the first booster (third) doses was limited.

The GMCs with 95% confidence intervals (CIs), the geometric mean fold-rise (GMFR) of post-booster/pre-booster GMCs with 95% CIs, SRRs with 95% CI (Clopper-Pearson), and SRR differences with 95% CI (Miettinen-Nurminen) of nAb and bAb for Omicron-BA.1-monovalent vaccine, Omicron-BA.1-bivalent vaccine, and mRNA-1273 vaccine at day 29 are provided. In part 1, the non-inferiority of nAb GMC against Omicron BA.1 and ancestral SARS-CoV-2 (D614G), and superiority against Omicron BA.1 (dependent on demonstration of non-inferiority) are based on GMC-ratios (GMRs) of Omicron-BA.1-monovalent vaccine versus mRNA-1273 boosters at day 29 estimated using an Analysis of Covariance (ANCOVA) model (Appendix, pages 6-8). Part 2 primary immunogenicity objectives were evaluated using a prespecified hypothesis-testing sequence (Appendix, page 14) that included non-inferiority of Omicron-BA.1-bivalent vaccine versus mRNA-1273 antibody responses against Omicron BA.1 and ancestral SARS-CoV-2 (D614G) based on day 29 GMRs, and testing of superiority against Omicron BA.1 (day 29 GMR) if both non-inferiority objectives are met. Criteria for non-

inferiority of Omicron-BA.1-monovalent vaccine and non-inferiority and superiority of Omicron-BA.1-bivalent vaccine versus mRNA-1273 against Omicron BA.1 were considered met if the lower bounds of the 99% CI of the GMR from the ANCOVA models are ≥0·67 and >1 at day 29, respectively, with 1·5 margins (2-sided alpha=0·01). Non-inferiority against ancestral SARS-CoV-2 (D614G) was met if lower bounds of the 95% (Omicron-BA.1-monovalent) and 99% (Omicron-BA.1-bivalent) CIs of the GMR are ≥0·67. Observed nAb GMC (95% CI) in all participants regardless of SARS-CoV-2-infection status and those with evidence of prior SARS-CoV-2-infection in part 2 and in age subgroups (16-<65 years and ≥65 years) in both parts 1 and 2 are provided. Binding antibody GMCs (95% CI) and GMRs (95% CI) against Omicron BA.1, SARS-CoV-2 (D614G) and alpha, delta and gamma variants assessed by ANCOVA (parts 1 and 2) are summarized.

Percentages of participants with SARS-CoV-2-infection and COVID-19 events ≥14 days after randomisation are summarized. Incidence rates of COVID-19 cases (primary definition in COVE trial and CDC definition),[13-15] SARS-CoV-2-infection regardless of symptoms and asymptomatic infection adjusting for person-time with 95% CIs (Poisson distribution), as well as cumulative event rates (Kaplan-Meier method) and relative vaccine efficacy (VE) (1-hazard ratio [HR]) of Omicron-BA.1-monovalent and -bivalent vaccine versus mRNA-1273 (Cox proportional hazards model) starting 14 days after randomisation, are provided; a statistical comparison between arms was not performed. COVID-19 cases having variant sequences (BA.2, BA.4, BA.5) were explored using a competing-risk method to analyze sublineage-specific events, where competing events were not censored. The Fine-Gray proportional hazards model for subdistribution of a competing-risk was used to estimate the hazard ratio and relative VE (1-HR).[16]

All analyses were conducted using SAS Version 9·4 or higher.

Role of the funding source

The study sponsor, Moderna, Inc. funded the study and was involved in the study design as well as the collection, analysis, and interpretation of the data.

Results

Between February 16−March 24, 2022 and April 2−June 17, 2022, 724 participants were randomised and received Omicron-BA.1-monovalent vaccine (n=366) or mRNA-1273 (n=357), and 2,824 participants were randomised and received Omicron-BA.1-bivalent vaccine (n=1418) or mRNA-1273 vaccine (n=1395) as second booster doses in parts 1 and 2, respectively (figure 1). The mean age of participants was 57 years (standard deviations 12·9 and 13·2 and 12·5 and 12·8) in the Omicron-BA.1-monovalent versus mRNA-1273 [part 1] and Omicron-BA.1-bivalent versus mRNA-1273 [part 2]) groups respectively (table 1), and ~34% (127/367 and 124/357, and 477/1422 and 469/1402) were ≥65 year of age. In both study parts, ~50% of the participants in the Omicron-BA.1-monovalent (200/367) and mRNA-1273 (202/357) part 1 groups and in the Omicron-BA.1-bivalent (695/1422) and mRNA-1273 (694/1402) part 2 groups were female, and the majority were white (~94-96%) in those groups respectively (353, 335, 1346 and 1312). Baseline characteristics were similar in PPSI-negative primary immunogenicity analysis set (appendix, page 31). Proportions of participants with prior SARS-CoV-2-infection pre-booster were 12·8% (47/367) and 12·0% (43/357) in the Omicron-BA.1-monovalent and mRNA-1273 arms, and 22·6% (322/1422) and 26·0% (364/1402) in the Omicron-BA.1-bivalent and mRNA-1273 arms, respectively. Median duration times (months [interquartile range]) between the most recent COVID-19 vaccine and study boosters were similar in the Omicron-

BA.1-monovalent (4·0 [3·6-4·7]) and mRNA-1273 (4·1 [3·5-4·7]) and in the Omicron-BA.1-bivalent (5·5 [4·8-6·2]) and mRNA-1273 (5·4 [4·8-6·2]) arms. Most participants received Vaxzevria (52% (374/724) and 63% (1779/2824)) or Comirnaty (46% [334/724] and 34% [965/2824]) as primary COVID-19 vaccinations, and Comirnaty (81% [586/724] and 77% [2178/2824]) as first boosters in parts 1 and 2, respectively (table 1 and Appendix, page 15).

In the part 1 primary immunogenicity analysis in participants with no evidence of SARS-CoV-2-infection (PPSI-negative), baseline nAb GMCs were comparable in the Omicron-BA.1-monovalent and mRNA-1273 groups. The observed nAb GMCs (95% CI) against Omicron BA.1 were higher at day 29 following the Omicron-BA.1-monovalent (537·7 [478·2-604·6]) compared to the mRNA-1273 (307·4 [279·5-338·2]) booster (table 2, Appendix, page 16). The ANCOVA-modeled GMR (99% CI) at day 29 was 1·68 (1·45−1·95) for Omicron-BA.1-monovalent versus mRNA-1273 booster, meeting pre-specified criterion for non-inferiority (lower bound of CI ≥0·67). Additionally, the key secondary endpoint of superiority of the immune responses against Omicron BA.1 for Omicron-BA.1-monovalent compared to mRNA-1273 was demonstrated (lower bound of CI >1). The observed ancestral SARS-CoV-2 (D614G) GMCs (95% CI) were similar for Omicron-BA.1-monovalent (2699·7 [2431·3-2997·7] and mRNA-1273 (3020·6 [2776·5-3286·2]) at day 29 with a GMR (95% CI) of 0·82 (0·74−0·91) that met criteria for non-inferiority.

In part 2 participants in the primary analysis PPSI-negative set, pre-booster baselines were similar for the Omicron-BA.1-bivalent and mRNA-1273 groups. The observed GMCs for the Omicron-BA.1-bivalent (466·8 [438·0-497·4]) booster were higher than those of mRNA-1273 (311·8 [293·8-330·9]) with a GMR (99% CI) of 1·53 (1·41−1·67) which met prespecified criteria for both non-inferiority and superiority. For the co-primary endpoint of the Omicron-

BA.1-bivalent versus mRNA-1273 antibody response against ancestral SARS-CoV-2 (D614G) at day 29, GMCs were 2987·2 (2814·9-3169·9) and 2911·3 (2750·9-3081·0), respectively, with a GMR (99% CI) of 1·05 (0·96-1·15) meeting the non-inferiority criterion.

The SRRs ([number/participants assessed]; 95% CI) against Omicron BA.1 were 82·7% (220/266; 77·6−87·1%) and 55·7% (151/271; 49·6−61·7%) and against ancestral SARS-CoV-2 (614G) were 43·1% (115/267; 37·1−49·2%) and 59·0% (160/271; 52·9−65·0%) at day 29 after the Omicron-BA.1-monovalent and mRNA-1273 boosters, respectively, with SRR (95% CI) differences of 27·0 (19·4−34·3) for Omicron-BA.1 and -16·0 (-24·2−-7·5) for ancestral SARS-CoV-2 (D614G) versus mRNA-1273 (table 2). Following the Omicron-BA.1-bivalent and mRNA-1273 boosters at day 29, respectively, SRRs (95% CI) were 84·5% (813/962; 82·1−86·7%) and 70·6% (631/894; 67·5−73·6%) for Omicron BA.1 and 70·9% (670/945; 67·9−73·8%) and 68·5% (600/876; 65·3−71·6%) for ancestral SARS-CoV-2 (D614G) with SRR differences (95% CI) of 13·9 (10·2−17·7) for Omicron-BA.1 and of 2·4 (-1·8−6·6) for ancestral SAR-CoV-2 (D614G) versus mRNA-1273.

In all participants regardless of SARS-CoV-2-infection status and only those with evidence of prior SARS-CoV-2-infection, GMCs were also higher following the Omicron-BA.1-bivalent than mRNA-1273 boosters against both Omicron BA.1 and ancestral SARS-CoV-2 (D614G) (Appendix, pages 17 and 33). Neutralizing antibodies were also higher against Omicron BA.1 in both younger and older participants for Omicron-BA.1-monovalent and Omicron-BA.1-bivalent versus mRNA-1273 boosters, and were similar against SARS-CoV-2 (D614G) for the boosters (Appendix, pages 18 and 34).

Spike bAb GMCs were higher against Omicron BA.1 after the Omicron-BA.1-monovalent than mRNA-1273 booster at day 29 (GMR 1·18 [95% CI, 1·05−1·32]) and were

similar against ancestral SARS-CoV-2, and alpha, gamma, and delta variants with GMRs (95% CI) ranging from 0·91 (0·84−0·99) to 1·00 (0·92−1·08) for both boosters (Appendix, pages 19 and 35). The bAb GMCs were higher after the Omicron-BA.1-bivalent versus the mRNA-1273 booster across Omicron BA.1, ancestral SARS-CoV-2, and alpha, gamma, and delta variants (Appendix, pages 20 and 36) with GMRs (95% CI) ranging from 1·04 (0·98−1·10) to 1·13 (1·06−1·21).

The median (interquartile range) safety follow-up times were 156 (148−161) days for both Omicron-BA.1-monovalent and mRNA-1273 in part 1, and 102 (91−114) days for both Omicron-BA.1-bivalent and mRNA-1273 in part 2. The safety data for the Omicron-BA.1-monovalent were similar to those of Omicron-BA.1-bivalent and are provided in the Appendix, pages 11, 21 and 37-39).

In part 2, the frequencies of solicited local (83·5% [1187/1421] and 89·8% [1256/1398]) and systemic (70·2% [997/1421] and 75·3% [1052/1398]) ARs ≤7 days post-booster dose were comparable for the Omicron-BA.1-bivalent and mRNA-1273 groups, respectively (figure 2, Appendix, page 37). The most commonly reported ARs were pain, fatigue, and headache. Most reactions were grades 1-2. Grade 3 events were similar across study arms, and no grade 4 events were reported. Frequencies of any unsolicited AEs reported ≤28 days after the booster dose were also comparable in the Omicron-BA.1-bivalent (31·5% [448/1422]) and mRNA-1273 (29·7% [417/1402]) groups (Appendix, page 39). The incidences of AEs considered related to study vaccine by the investigators were 4·9% (69/1422) and 5·1% (71/1402) in the Omicron-BA.1-bivalent and mRNA-1273 groups, respectively. Related MAAEs occurred in 6 (0·4%) of 1422 participants and 7 (0·5%) of 1402 participants in the Omicron-BA.1-bivalent and mRNA-1273 recipients, respectively. None of the AEs led to study discontinuation. Serious AEs occurred in 6

(0·4%) of 1422 participants in the Omicron-BA.1-bivalent and 5 (0·4%) of 1402 participants in the mRNA-1273 groups; none were considered by the investigator to be related to study vaccine among Omicron-BA.1-bivalent recipients. One related SAE (multiple pulmonary emboli) occurred in the mRNA-1273 arm.

As of the interim analysis data-cutoff date, no fatal AEs occurred. After the interim analysis data-cutoff date, two deaths (sudden unexpected death in epilepsy, sudden cardiac death due to arrhythmia) were observed in the mRNA-1273 arm of part 2 and were determined by the investigators to be unrelated to the study vaccine.

The total overall person-years at the data-cutoff date were 113·3 and 111·8 in the Omicron-BA.1-monovalent and mRNA-1273 arms, and 249·6 and 233·3 in the Omicron-BA.1-bivalent and mRNA-1273 arms, respectively, per the primary case definition for COVID-19. As a secondary objective in part 2, incidence rates/1,000 person-years (95% CI) of COVID-19 (COVE primary case definition)[13,14] ≥14 days after randomisation were 633·0 (538·1−739·7) for Omicron-BA.1-bivalent and 711·6 (607·5−828·5) for mRNA-1273 (figure 3, Appendix, page 40). Incidence rates/1,000 person-years (95% CI) were 739·2 (635·7−854·8) and 755·4 (647·6−876·0) for COVID-19 (CDC definition),[15] and for overall SARS-CoV-2-infection were 1010·5 (887·5−1145·9) and 1099·1 (966·5−1244·7) in the Omicron-BA.1-bivalent and mRNA-1273 arms, respectively. Part 1 incidence rates of COVID-19 ≥14 days after randomisation for the Omicron-BA.1-monovalent booster, an exploratory objective, were generally similar to those of part 2 (figure 3, Appendix, pages 11 and 40). The relative VEs (95% CI) based on a proportional hazards model in the Omicron-BA.1-bivalent and -monovalent groups compared to mRNA-1273 were 11.4% (-10.2−28.7%) and 13.5% (-17.8−36.5%), respectively (Appendix,

page 41). No cases of RT-PCR-diagnosed severe cases and COVID-19-related hospitalization were reported.

The majority of the 850 available variant sequences obtained by RT-PCR from nasopharyngeal swabs positive for SARS-CoV-2-infection (February−September 2022) in the study were of the Omicron BA.4 and BA.5 lineages which predominated during June and July of 2022 (Appendix, page 22). In parts 1 and 2, a total of 162 and 324 COVID-19 cases occurred ≥14 post-randomisation to data-cutoff date, respectively. Variant sequences were detected in 68/76 (89·5%) COVID-19 cases in the Omicron-BA.1-monovalent, 80/86 (93.0%) in the mRNA-1273, 135/158 (85·4%) in the Omicron-BA.1-bivalent and 154/166 (92·8%) in the mRNA-1273 arms (Appendix, page 42). In part 1, the majority of the cases in the Omicron-BA.1-monovalent and mRNA-1273 groups, respectively, were of the BA.2 (43% [29/68] and 58% [46/80]) and BA.5 (49% [33/68] and 34% [27/80]) Omicron lineages and 9% [6/68 and 7/80] were BA.4 in both arms. The majority of part 2 cases were BA.5 (70% [94/135] and 60% [93/154]), 13% [18/135] and 19% [29/154] were BA.4, and 17% [23/135] and 21% [32/154] were BA.2 Omicron lineages in the Omicron-BA.1-bivalent and mRNA-1273 groups, respectively. There were no BA.1 cases detected in either part of the trial.

An exploratory analysis of COVID-19 cases having BA.2, BA.4 or BA.5 sublineage sequences, using the Fine-Gray proportional hazards model for subdistribution of a competing risk,[16] showed non-statistically significant lower incidence rates for the BA.2 and BA.4 sublineages in the Omicron-BA.1-bivalent arm versus mRNA-1273. A numerically lower incidence rate was also observed for the BA.2 sublineage in the Omicron-BA.1 monovalent arm versus mRNA-1273; this observation was less clear for the BA.4 sublineage due to the limited sample size in part 1. Incidence rates were similar for the BA.5 sublineage across study arms

(Appendix, pages 22 and 23). Relative VE estimates (95% CI) were 37·7% (0·9-60·9%), 13·3% (-157·7−70·8%) and -24·5% (-106·8−25·1%) for Omicron-BA.1-monovalent versus mRNA-1273 and were 32·6% (-15·1−60·5%), 41·6% (-5·1−67·5%), and 4·4% (-27·2−28·2%) for Omicron-BA.1-bivalent versus mRNA-1273 for the BA.2, BA.4, and BA.5 sublineages, respectively (Appendix, page 41). A sensitivity analysis of non-BA.5 variant sublineages resulted in relative VEs of 35·0% and 37·3% for the Omicron-BA.1-monovalent and -bivalent boosters versus mRNA-1273, respectively with corresponding 95% CIs excluding zero (0·4−57·6% and 6·9−57·8%).

Discussion

This is the first large randomised, observer-blind, active-controlled, trial comparing variant-containing mRNA-1273 booster vaccines head-to-head with the original mRNA-1273 vaccine. In the trial, the Omicron-BA.1-bivalent (mRNA-1273.214) vaccine elicited nAb responses that were superior against Omicron BA.1 and non-inferior against ancestral SARS-CoV-2 (D614G), and bAb responses that were higher across Omicron BA.1, SARS-CoV-2, and alpha, delta, and gamma variants compared to mRNA-1273 28 days post-booster doses, consistent with previous studies.[1-3,17] The Omicron-BA.1-monovalent (mRNA-1273.529) booster also elicited superior nAb responses against Omicron BA.1 versus mRNA-1273; however, the ancestral SARS-CoV-2 (D614G) nAb, bAb and SRRs as well as alpha, gamma, and delta variant bAb responses were similar compared to mRNA-1273, suggesting a more restricted immune response with monovalent variant-containing boosters.[18,19]

In previous open-label studies of the omicron-BA.1-bivalent (mRNA-1273.214) vaccine administered as second boosters to those who had received a primary series and a first booster

dose of mRNA-1273, nAb responses against omicron variants at day 29 and day 91 post-booster doses were superior to those of mRNA-1273.[1,3] Differences in absolute GMC values observed in this trial compared with those studies comparing Omicron-BA.1-bivalent versus mRNA-1273 may be attributed to the distinct trial design, the first of its size to evaluate participants who received mixed primary COVID-19 vaccination regimens including non-mRNA-based vaccines, as well as disparate laboratories and immunoassays utilized.[1,3] Of note, lower SRRs in this trial are likely due to measurement of changes in antibody levels from pre-booster to day 29 rather than changes from pre-primary series levels assessed in other studies.[1,3] Nonetheless, the Omicron-BA.1-bivalent booster elicited antibody responses that were superior against Omicron BA.1 and non-inferior against ancestral SARS-CoV-2.

Emerging observational data suggest a clinical benefit of bivalent booster vaccines in preventing COVID-19 against emergent variants beyond Omicron BA.1.[7-9,20] In this trial, both the Omicron-BA.1-monovalent and -bivalent boosters showed numerically lower COVID-19 incidence rates compared with mRNA-1273. In an exploratory analysis, COVID-19 incidence rates were non-statistically significantly lower with the Omicron-BA.1-monovalent and -bivalent versus mRNA-1273 boosters for the Omicron BA.2 isolate and for the bivalent vaccine against the BA.4 isolate, but not for BA.5 with either booster, although small sample sizes limit interpretation. Omicron BA.4- and BA.5-variants have identical spike-protein sequences and neutralization results have been typically reported together for both sublineages (BA.4/BA.5) in the same assay.[1-3,21,22] Potential factors explaining the different estimated VEs between the Omicron BA.4- and BA.5-sublineages include increased BA.5 viral fitness compared to other sublineages (including BA.4), the later emergence of BA.5 relative to time of study vaccination, and differences in relative VE that may not be detectable given the limited follow-up time in this

509 interim analysis. Overall, the post-booster COVID-19 incidence rates suggest a clinical benefit of
510 the Omicron-BA.1-bivalent vaccine, especially against variants (e.g. BA.2) that are antigenically
511 closer to the variant sublineage contained in the vaccine. In line with this notion, a previous
512 study showed that the Omicron-BA.4/BA.5-bivalent booster elicited cross-neutralization against
513 more recent divergent variants not contained in the vaccine (BQ.1.1, XBB.1 and XBB.1.5) in a
514 small subset of participants, irrespective of prior SARS-CoV-2-infection status, although the
515 antibody titers for these variants were lower compared to BA.4/BA.5.[2] Further monitoring of
516 vaccine effectiveness in real-world studies in parallel with assessing the cross-neutralization
517 ability of previously authorized vaccines is needed, given the continual evolution of divergent
518 variants that can confer antibody escape leading to re-infections and COVID-19.[21-23]
519 The incidences of solicited ARs with Omicron-BA.1-monovalent and Omicron-BA.1-
520 bivalent vaccines were similar to those of mRNA-1273 observed in prior studies.[1-3] No new
521 safety concerns were identified in this interim analysis, and the safety data presented here,
522 together with the previously reported longer-term safety follow-up on the Omicron-BA.1
523 bivalent booster,[1-3] extend the body of safety information available for Omicron-containing
524 bivalent vaccines.
525 Limitations include that the present randomised trial, designed to evaluate Omicron
526 BA.1-containing versus the original mRNA-1273 vaccine in response to the emergence of
527 Omicron BA.1-variants, was initiated February 2022 with results available late November 2022
528 (August 4, 2022 data-cutoff date) and it was no longer feasible to randomise additional
529 participants to more updated Omicron strains when Omicron-containing COVID-19 booster
530 vaccines became authorized. The analysis of participants without previous SARS-CoV-2
531 infection may be affected by mild and/or asymptomatic infections that were potentially not

detected at study screening or post-randomization, although this distinction is becoming less relevant as a large proportion of the population has been infected.[24-26] The trial was powered to detect immunogenicity differences between the two vaccines but not COVID-19 event rates which were subject to the evolving epidemiology of Omicron subvariants. While secondary and exploratory analyses suggest that Omicron-containing boosters reduce COVID-19 incidence rates versus the mRNA-1273, these results were not statistically significant. Further, interpretation of cumulative COVID-19 event curve data is limited by low numbers of participants at longer follow-up times. Additionally, the trial population was limited to predominantly white participants, aged ≥16 years in the UK and did not include immunocompromised individuals. Evaluation of the longer-term safety of the variant-containing boosters and durability of the immune response is ongoing in the trial.

In conclusion, the Omicron-BA.1-monovalent and -bivalent boosters elicited superior nAb responses against Omicron BA.1 with numerically lower incidences of COVID-19 compared to the original mRNA-1273 booster in a head-to-head comparison. The data suggest a clinical benefit in protection against COVID-19 with variant-containing vaccines that more closely match the circulating variant and that modified-monovalent boosters may have more limited immune responses than modified-bivalent boosters. Given the continuous emergence of SARS-CoV-2 variants, it remains important to continue monitoring the neutralization ability as well as vaccine effectiveness of COVID-19 boosters towards planning updates of vaccines containing variant modifications that more closely match circulating strains. Due to the rapid emergence of viral subvariants, the interval between identifying an epidemiologically-dominant strain and developing modified variant-containing boosters will not permit adequate time to

554 conduct large-scale randomised controlled trials like this one. Thus, decision-making may need
555 to rely on both epidemiological data and prior studies of variant-containing vaccines.
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Contributors

ITL, CAC, ASFR, PTH, SC, JF, LT, HZ, JMM, and RD contributed to the design of the study. ITL, CAC, CP, DR, SM, EdW, AS, JMM, and RD contributed to study oversight. ITL, CAG, PM, CB, RN, MB, PAK, RC, PID, MB, RS, EM, TCD, FB, DS, CJAD, PL, ASFR, EG, PTH, EdW, and AS contributed to data collection and data cleaning. JF, LT, and HZ conducted statistical analyses and verified all the data. BG was responsible for immunogenicity assays and variant sequencing, and WD, XC, LT, and HZ for variant sequencing-related data and statistical analyses. ITL, BG, EdW, AS, JET, SC, WD, XC, JF, LY, HZ, JMM, and RD interpreted the data and results. ITL, JET, and LT drafted the manuscript with contributions from SC, HZ, JMM, and RD, and FJD provided editorial support and development of data displays. All the authors contributed to the review and editing of the manuscript and approved the final version for submission to the journal. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

Data Sharing Statement

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

Declaration of Interests

PM reports being a speaker/advisor and/or research grants from GSK, Sanofi, Novavax, Moderna, MSD, Janssen, Medicago, and AstraZeneca; PK reports being a speaker/advisor/travel grants and/or research grants from GSK, Pfizer, Pharmacosmos, Astellas, Vifor, Astra Zeneca, Bayer, Unicyte, Evotec, Fresenius, and Otsuka; PD reports research grants for COVID-19 research studies from Moderna, Astra Zeneca, Janssen, and Atea; MBoffito reports being an advisor/speaker for GSK, Atea, ViiV, MSD, Janssen, Gilead, Cipla, Mylan, Roche and has received research grants from ViiV, MSD, Janssen, Gilead, Novavax, Valneva, and Moderna; FB reports receiving speaker fees and a research grant to institution from Gilead Sciences Ltd; CD reports receiving Grants from Wellcome Trust and MRC; DC reports receiving research grants to institution from Gilead Sciences Ltd, ViiV Healthcare, Moderna, Janssen, GSK, and Novavax; ASR received research grants (to my Organisation) from Pfizer, Novavax, Valneva, Moderna, and Janssen; PH reports being a speaker/advisor and/or research grants from Pfizer, Novavax, Valneva, Moderna, and Janssen. CG, CB, RN, MBula, RC, RS, EM, TD, DS, PL and EG report no conflicts. ITL, SC, BG, CP, DR, SM, EW, AS, WD, XC, LT, HZ, JM, and RD are employees of Moderna, Inc. and hold stock/stock options in the company. JET and FJD are Moderna contractors.

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Figure Legends

Figure 1. Eligible participants who previously received any COVID-19 primary-series vaccination with or without a prior booster dose, were randomised in a 1:1 ratio to receive either a Omicron-BA.1-monovalent or a mRNA-1273 booster (part 1) or to receive either a Omicron-BA.1-bivalent or a mRNA-1273 booster (part 2) in the safety set. The trial was initiated in February 2022 with the Omicron-BA.1-monovalent booster vaccine in response to the emergence of the Omicron variant; thereafter due to the rapid evolution of Omicron sublineages, enrollment of the Omicron-BA.1-monovalent portion of the trial (part 1) was stopped to expedite enrollment of an Omicron-BA.1-bivalent vaccine (part 2), which was hypothesized to induce better cross-protection. Randomisation was stratified by age group (16 to <65 or ≥65 years) and number of prior booster doses received (received study vaccine as the fourth dose or as the third dose). Participants who received the second booster (fourth) dose as part of the study must have previously received a mRNA vaccine as the first booster (third) dose of a COVID-19 vaccine. Participants who received the first booster (third) dose may have previously received two injections of an approved/authorized mRNA or non-mRNA COVID-19 vaccine. In part 1, *4 participants who received Omicron-BA.1-monovalent were included in the safety set but not in the full analysis set; †1 participant received Omicron-BA.1-monovalent as a third dose and was included in the safety set but excluded from the immunogenicity and efficacy analyses. §In part 2, 4 participants who received Omicron-BA.1-bivalent as a third dose and 7 participants who received mRNA-1273 as a third dose were excluded from the immunogenicity and efficacy analyses. The data-cutoff date was August 4, 2022.

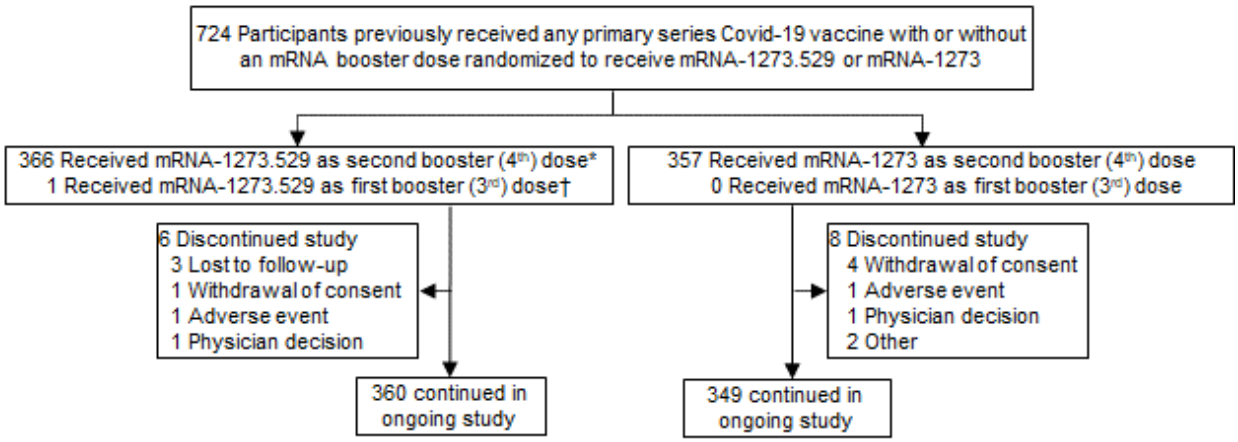
Figure 2. Shown are the percentages of participants in whom solicited local or systemic adverse reactions occurred within 7 days after the booster dose in the solicited safety set (part 2, n=1421

in the Omicron-BA.1-bivalent and n=1398 in the mRNA-1273 groups) and includes those with first and second booster doses.

Figure 3. Shown are the cumulative event rates of COVID-19 per the primary case definition of the COVE trial[13,14] based on assessment starting 14 days after randomisation in the per-protocol efficacy population of parts 1 (Panel A) and 2 (Panel B). Tick marks indicate censored data. The incidence rate was defined as the number of events divided by number of participants at risk and adjusted by 1,000 person-years. Arrow denotes that as of the data-cutoff date for the interim analysis <50% of participants had follow-up beyond 150 days in part 1 and beyond 100 days in part 2.

Figure 1: Trial profile

A. Part 1



B. Part 2

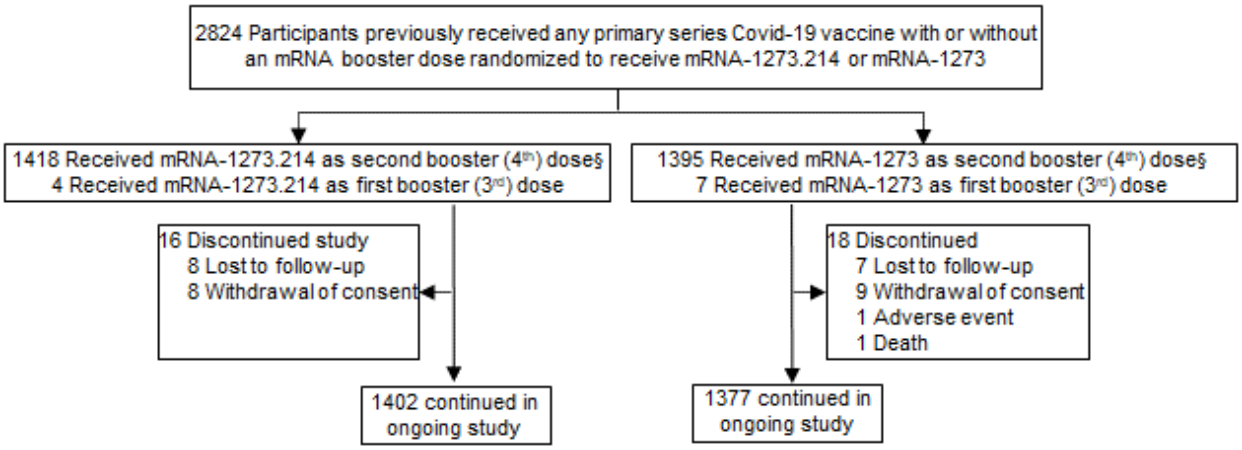


Figure 2: Solicited adverse reactions after receipt of Omicron-BA.1-Bivalent or mRNA-1273 boosters, part 2 solicited safety set

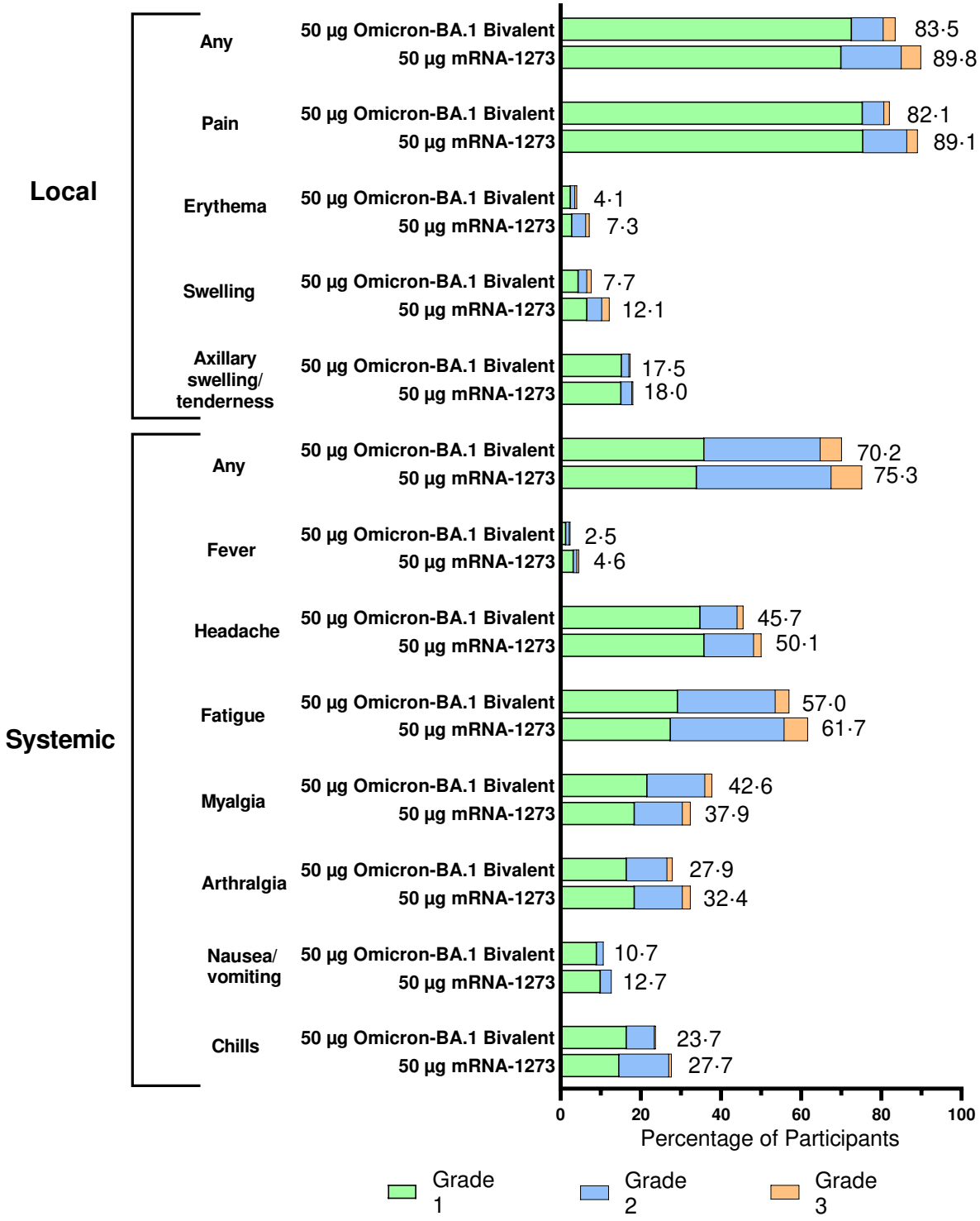
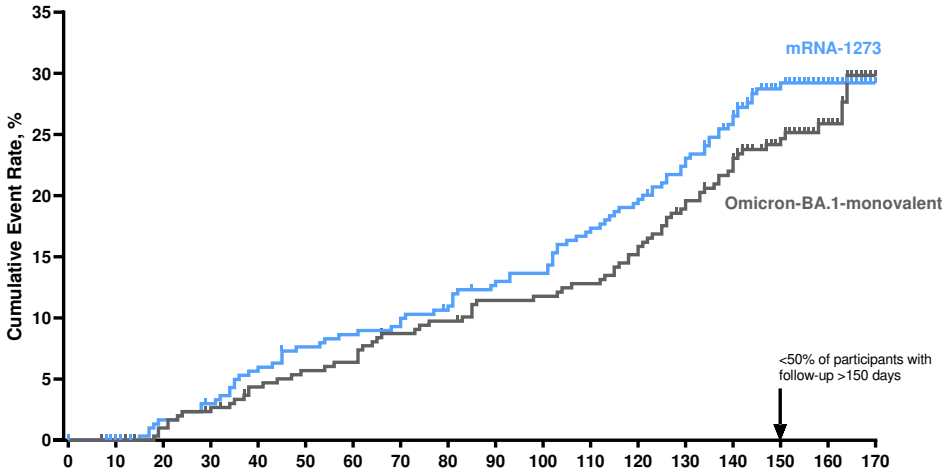


Figure 3. Cumulative event rates of COVID-19 starting ≥14 days after randomisation following receipt of Omicron-BA.1-monovalent, Omicron-BA.1-bivalent, or mRNA-1273 boosters

A. Part 1

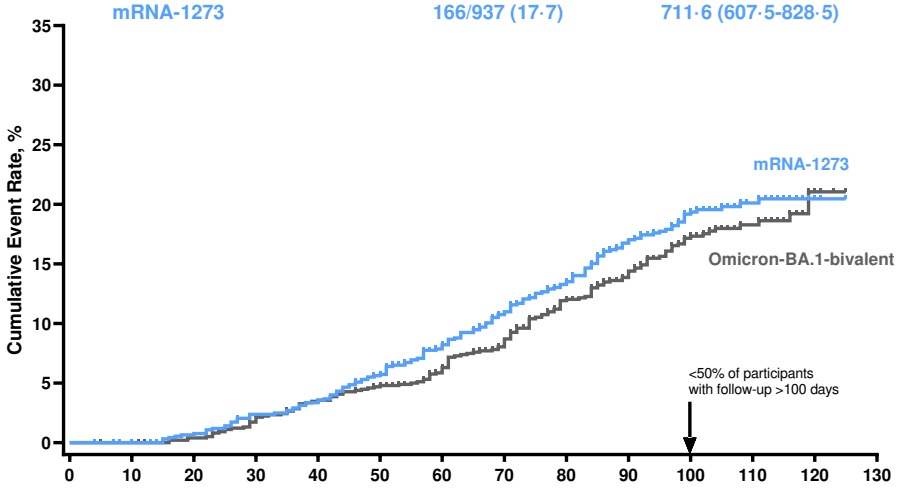
	n/N (%) Participants	Incidence rate/ 1000 person-yr (95% CI)
Omicron-BA.1-monovalent	76/312 (24·4)	670·5 (528·3-839·3)
mRNA-1273	86/312 (27·6)	769·3 (615·4-950·1)



Number at risk																	
BA.1-monovalent	312	308	297	292	284	280	278	270	267	261	260	257	250	238	223	154	87	5
mRNA-1273	312	309	297	292	284	277	274	272	267	260	257	247	240	230	213	145	84	5

B. Part 2

	n/N (%) Participants	Incidence rate/ 1000 person-yr (95% CI)
Omicron-BA.1-bivalent	158/997 (15·8)	633·0 (538·1-739·7)
mRNA-1273	166/937 (17·7)	711·6 (607·5-828·5)



Number at risk														
BA.1-bivalent	997	994	980	964	945	921	870	827	754	654	488	234	30	0
mRNA-1273	937	931	919	902	893	863	806	758	701	601	452	229	27	0

731 **Table 1: Demographics and participant characteristics, safety set**

Characteristics n (%)*	Part 1		Part 2	
	Omicron-BA.1-Monovalent 50 µg N=367	mRNA-1273 50 µg N=357	Omicron-BA.1-Bivalent 50 µg N=1422	mRNA-1273 50 µg N=1402
Age at Screening (yr)				
Mean (SD)	57·6 (12.9)	57·3 (13.2)	57·4 (12.5)	57·0 (12.8)
Age subgroup				
≥16 and <65 years	240 (65·4)	233 (65·3)	945 (66·5)	933 (66·5)
≥65 years	127 (34·6)	124 (34·7)	477 (33·5)	469 (33·5)
Sex				
Male	167 (45·5)	155 (43·4)	727 (51·1)	708 (50·5)
Female	200 (54·5)	202 (56·6)	695 (48·9)	694 (49·5)
Race or ethnic group†				
White	353 (96·2)	335 (93·8)	1346 (94·7)	1312 (93·6)
Black	0	0	6 (0·4)	6 (0·4)
Asian	10 (2·7)	10 (2·8)	31 (2·2)	41 (2·9)
Mixed or multiple ethnic groups	3 (0·8)	5 (1·4)	21 (1·5)	28 (2·0)
Other	1 (0·3)	5 (1·4)	4 (0·3)	7 (0·5)
Not reported, unknown or missing	0	2 (0·6)	14 (1·0)	8 (0·6)
Body mass index (kg/m2)				
Mean (SD)	27·7 (5·7)	28·3 (5·8)	27·7 (5·5)	27·6 (5·7)
Time from most recent COVID-19 vaccine to booster dose (months)				
Median (Interquartile range)§	4·0 (3·6-4·7)	4·1 (3·5-4·7)	5·5 (4·8-6·2)	5·4 (4·8-6·2)
Prior vaccination received (primary series)				
Vaxzevria	196 (53·4)	178 (49·9)	907 (63·8)	872 (62·2)
Comirnaty	164 (44·7)	170 (47·6)	472 (33·2)	493 (35·2)
Spikevax	2 (0·5)	2 (0·6)	21 (1·5)	19 (1·4)
Jcovden	-	-	4 (0·3)	5 (0·4)
Mixed regimen/other	5 (1·3)	7 (2·0)	18 (1·3)	13 (0·9)
Prior first booster received				
Comirnaty	296 (80·9)	290 (81·2)	1110 (78·1)	1068 (76·6)
Spikevax	70 (19·1)	67 (18·8)	308 (21·7)	327 (23·5)
Pre-booster RT-PCR assay for SARS-CoV-2				
Negative	363 (98·9)	351 (98·3)	1302 (91·6)	1291 (92·1)
Positive	4 (1·1)	6 (1·7)	19 (1·3)	15 (1·1)
Missing	0	0	101 (7·1)	96 (6·8)
Pre-booster antibody to SARS-CoV-2 nucleocapsid¶				
Negative	319 (86·9)	318 (89·1)	1093 (76·9)	1034 (73·8)
Positive	44 (12·0)	37 (10·4)	313 (22·0)	357 (25·5)
Missing	4 (1·1)	2 (0·6)	16 (1·1)	11 (0·8)
Pre-booster SARS-CoV-2 status‖				
Negative	316 (86·1)	312 (87·4)	1004 (70·6)	957 (68·3)
Positive	47 (12·8)	43 (12·0)	322 (22·6)	364 (26·0)
Missing	4 (1·1)	2 (0·6)	96 (6·8)	81 (5·8)

SD=standard deviation. Percentages are based on the number of participants in the safety set. In part 1, one participant received Omicron-BA.1-monovalent as a third dose, 366 participants received Omicron-BA.1-monovalent as a fourth dose, and 357 participants received mRNA-1273 as a fourth dose. In part 2, four participants received Omicron-BA.1-bivalent as a third dose, 1418 received Omicron-BA.1-bivalent as a fourth dose, seven participants received mRNA-1273 as a third dose, and 1395 participants received mRNA-1273 as a fourth dose.

*Percentages may not total 100% due to rounding. RT-PCR: reverse-transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

† Race and ethnic group were reported by the participant.

§ Participants with <3 months duration between 3rd and 4th doses were excluded from the per-protocol sets

¶The Elecsys assay for binding antibody to SARS-CoV-2 nucleocapsid was used.

[ll]Pre-booster SARS-CoV-2 status was positive if there was evidence of previous SARS-CoV-2 infection, defined as positive binding antibody against the SARS-CoV-2 nucleocapsid or positive RT-PCR assay 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 assay at day 1. The data-cutoff date was August 4, 2022

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Table 2. Pseudovirus neutralizing antibodies against Omicron BA.1 or ancestral SARS-CoV-2 (D614G) after receipt of Omicron-BA.1-Monovalent, Omicron-BA.1-Bivalent, or mRNA-1273 second boosters administered to participants with no prior SARS-CoV-2-infection

	Omicron BA.1			
	Part 1		Part 2	
	Omicron-BA.1-Monovalent 50 µg N=274	mRNA-1273 50 µg N=277	Omicron-BA.1 Bivalent 50 µg N=969	mRNA-1273 50 µg N=902
Baseline (Day 1) n*	266	273	966	901
Observed GMC (95% CI)†	71·2 (63·6-79·8)	67·6 (60·3-75·9)	50·9 (47·7-54·2)	52·1 (48·7-55·8)
Day 29, n*	274	275	965	895
Observed GMC (95% CI)†	537·7 (478·2-604·6)	307·4 (279·5-338·2)	466·8 (438·0-497·4)	311·8 (293·8-330·9)
GMFR (95% CI)†	7·5 (6·8-8·2)	4·5 (4·1-4·9)	9·2 (8·7-9·7)	5·9 (5·6-6·3)
Estimated GMC (99% CI)§	525·5 (472·0-585·0)	312·8 (281·4-347·7)	496·4 (339·1-726·6)	323·9 (221·2-474·2)
GMR (99% CI)§	1·68 (1·45-1·95)		1·53 (1·41-1·67)	
Day 29 SRR n/N1,%¶	220/266, 82·7	151/271, 55·7	813/962, 84·5	631/894, 70·6
(95% CI)‖	(77·6-87·1)	(49·6-61·7)	(82·1-86·7)	(67·5-73·6)
Difference (95% CI)‡	27·0 (19·4-34·3)		13·9 (10·2-17·7)	
	Ancestral (D614G)			
	Part 1		Part 2	
	Omicron-BA.1-Monovalent 50 µg N=274	mRNA-1273 50 µg N=277	Omicron-BA.1 Bivalent 50 µg N=969	mRNA-1273 50 µg N=902
Baseline (Day 1) n*	271	276	953	885
Observed GMC (95% CI)†	731·7 (662·2-808·5)	634·3 (575·6-699·0)	501·6 (471·8-533·2)	518·1 (486·9-551·4)
Day 29, n*	270	276	955	886
Observed GMC (95% CI)†	2699·7 (2431·3-2997·7)	3020·6 (2776·5-3286·2)	2987·2 (2814·9-3169·9)	2911·3 (2750·9-3081·0)
GMFR (95% CI)†	3·7 (3·4-4·0)	4·8 (4·4-5·2)	6·0 (5·6-6·3)	5·6 (5·3-6·0)
Estimated GMC (95%/99% CI)§	2563·9 (2381·8-2760·0)	3127·5 (2907·4-3364·3)	3217·3 (2381·2-4347·1)	3069·5 (2271·5-4147·9)
GMR (99% CI)§	-		1·05 (0·96-1·15)	
GMR (95% CI)§	0·82 (0·74-0·91)		-	
Day 29 SRR n/N1, %¶	115/267, 43·1	160/271, 59·0	670/945, 70·9	600/876, 68·5
(95% CI)‖	(37·1-49·2)	(52·9-65·0)	(67·9-73·8)	(65·3-71·6)
Difference (95% CI)‡	-16·0 (-24·2 − -7·5)		2·4 (-1·8−6·6)	

ANCOVA=analysis of covariance; CI=Confidence interval; GMC=geometric mean concentration; GMFR=geometric mean fold-rise; GMR=geometric mean ratio of GMCs for Omicron-BA.1-monovalent vs mRNA-1273 or Omicron-BA.1-bivalent vs mRNA-1273; LLOQ=lower limit of quantification; LS=least squares; SRR=seroresponse rate; ULOQ=upper limit of quantification.
Antibody values assessed by means of pseudovirus neutralizing antibody assay reported as <LLOQ (8 for Omicron BA.1; 10 for ancestral SARS-CoV-2 [D614G]) were replaced by 0·5 times the LLOQ. Values >ULOQ (41,984 for Omicron BA.1; 4,505,600 for ancestral SARS-CoV-2 [D614G]) were replaced by the ULOQ if actual values were not available. Included are participants with no evidence of SARS-CoV-2 infection from baseline through day 29 (primary analysis set, PPSI-negative) who received second booster doses.
*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 GMC value and GMFR, respectively, then back transformed to the original scale for presentation.
§The log-transformed antibody concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (16 to <65, ≥65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The Least Squares means, difference of Least Squares means, and 95% CI (GMC and GMR part 1 for ancestral SARS-CoV-2 [D614G]) and 99% CI (GMC and GMR parts 1 and 2 for Omicron BA.1 and part 2 for ancestral SARS-CoV-2 [D614G]) are back transformed to the original scale for presentation.

¶SRR at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. 95% CI is calculated using the Clopper-Pearson method.
‡95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
||Number of participants with non-missing data at baseline and the corresponding timepoint.

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