Supplementary Appendix

Supplement to: Winokur P, Gayed J, Fitz-Patrick D, et al. Bivalent omicron BA.1–adapted BNT162b2 booster in adults older than 55 years. N Engl J Med 2023;388:214-27. DOI: 10.1056/NEJMoa2213082

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

SUPPLEMENTARY APPENDIX

List of Investigators

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Cardona, Jose	Indago Research and Health Center	Hialeah, FL, USA
Chu, Laurence	Benchmark Research	Austin, TX, USA
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Gentry, Andrew	Bozeman Health Deaconess Hospital	Bozeman, MT, USA
Grasch, Anton	Confluence Health/Wenatchee Valley Hospital & Clinics	Wenatchee, WA, USA
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Rosen, Jeffrey	Clinical Research of South Florida	Coral Gables, FL, USA
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Usdan, Lisa	CNS Healthcare	Memphis, TN, USA
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Wadsworth, Larkin	Sundance Clinical Research	St Louis, MO, USA
Walsh, Edward	University of Rochester/Rochester General Hospital	Rochester, NY, USA
Walter, Emmanuel	Duke University	Durham, NC, USA
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Winokur, Patricia	University of Iowa	Iowa City, IA, USA

Eligibility Criteria

Participants were willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures; participants were healthy; and participants were capable of giving personal signed informed consent. For sentinel participants only, screening troponin levels had to be within normal range before randomization.

Participants were excluded if they had medical or psychiatric conditions that may increase the risk of study participation; history of severe adverse reactions associated with a vaccine and/or severe allergic reaction to any component of the study vaccination; previous clinical or microbiological diagnosis of COVID-19; immunocompromised individuals; or participants with bleeding diathesis. Participants were also excluded if they were pregnant or breastfeeding.

Participants could not have received or planned to receive radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids; blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19, from 90 days before study intervention administration; or any COVID-19 vaccine other than BNT162b2.

Ethical Conduct of the Study

Conduct of the study was in accordance with the study protocol and with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences Ethical Guidelines, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable laws and regulations, including applicable privacy laws. The study protocols and any amendments, informed consent documents, and other relevant documents were approved by institutional review board/ethics committees before study initiation. Before any study activity, written informed consent was obtained.

Blinding

Participants and site personnel were unaware of the trial group assignments, apart from staff members who prepared, dispensed, or administered the injections, and clinician(s), who were not direct members of the study team and did not participate in any other study-related activities, who reviewed unblinded

protocol deviations. Participants and the study team could become unblinded after the 3-month visit to confirm vaccine and dose.

Calculation of GMTs, GMRs, GMFRs, and Seroresponse

Geometric mean titers (GMTs) were calculated as the mean of the assay results after logarithmic transformation, and then exponentiating the mean to express results on the original scale. Geometric mean ratios (GMRs) were calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Geometric mean fold rises (GMFRs) were calculated as the mean of the difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean. Associated 2-sided 95% CIs for these parameters were obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's *t* distribution, and then exponentiating the confidence limits.

Seroresponse was defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement was below the lower limit of quantitation (LLOQ), the postvaccination measure of ≥4 × LLOQ was considered a seroresponse. The exact 95% CI for percentage of participants with seroresponse for each vaccine group was computed using the F distribution (Clopper-Pearson method). The primary approach to calculate the difference in percentages and the associated 2-sided 95% CI was calculated using the Miettinen and Nurminen method.

Surveillance for COVID-19 Cases

If a participant had a COVID-19 diagnosis, developed an acute respiratory illness, or experienced fever, new or increased cough or shortness of breath, chills, new or increased muscle pain, new loss of taste/smell, sore throat, diarrhea, or vomiting (irrespective of perceived etiology or clinical significance), the participant was to contact the site immediately. If COVID-19 was confirmed, the participant was to partake in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and 4 days after symptom resolution at the latest). If new symptoms were reported within 4 days after resolution of all previous symptoms, they were considered part of a single illness. Surveillance of potential COVID-19 symptoms continued even if a participant had a positive SARS-CoV-2 test earlier in

the study. Determination of SARS-CoV-2 infection and COVID-19 illness, and definition of COVID-19 severity, including FDA[1] and CDC[2] definitions, were described previously.[3]

Sample Size Determinations

A random sample of 230 participants was selected from each group in the expanded cohort as an immunogenicity subset to evaluate primary and secondary immunogenicity objectives. Assuming a 35% nonevaluable or previous infection rate, approximately 150 evaluable participants in each group would contribute to the primary immunogenicity evaluation.

Superiority and noninferiority of anti-Omicron BA.1 immunogenicity objectives

For comparisons based on the GMR, assuming common assay standard deviations of 1.05 in log scale, if the true GMR is 1.5, with 150 evaluable participants, the study would have 91.5% power to demonstrate superiority. If the true GMR is 2.0, the study would have 65.7% power to declare "super" superiority using a 1.5-fold margin. For seroresponse rate difference comparisons, if seroresponse rate is 70% in the BNT162b2-Omi.BA.1/30µg, BNT162b2-Omi.BA.1/60µg, bivalent-Omi.BA.1/30µg, or bivalent-Omi.BA.1/60µg) groups and 55% in the BNT162b2/30µg group, the study would have 94.9% power to demonstrate noninferiority using a 5% margin.

Noninferiority of anti-ancestral strain immunogenicity objectives

For comparisons based on GMR, common assay standard deviations of 1.05 and a GMR of 1 were assumed for each comparison. With 150 evaluable participants and the stated assumptions for the GMR and standard deviation, the study had 90.9% power to demonstrate noninferiority based on the GMR using a 1.5-fold margin.

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[1] US FDA Development and Licensure of Vaccines to Prevent COVID-19. Guidance for Industry. June 2020. Available at: www.fda.gov/media/139638/download (accessed September 27, 2022).
[2] US CDC People with Certain Medical Conditions. September 02, 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions (accessed September 27, 2022).
[3] Moreira et al. N Engl J Med 2022;386:1910-1921.

Adjustments for Multiplicity

Multiple primary and secondary immunogenicity objectives were assessed in a sequential order as listed below using a 1-sided alpha of 0.025.

- Superiority in GMR and noninferiority in seroresponse rate for Omicron BA.1 response versus BNT162b2/30µg: BNT162b2-Omi.BA.1/60µg → bivalent-Omi.BA.1/60µg → bivalent-Omi.BA.1/30µg →
- Noninferiority in GMR for ancestral strain response versus BNT162b2/30µg: bivalent-Omi.BA.1/60µg → bivalent-Omi.BA.1/30µg →
- "Super" superiority in GMR for Omicron BA.1 response versus BNT162b2/30µg: BNT162b2-Omi.BA.1/60µg → bivalent-Omi.BA.1/60µg → bivalent-Omi.BA.1/30µg →
- Superiority in GMR and noninferiority in seroresponse rate for Omicron BA.1 response versus BNT162b2/30µg: BNT162b2-Omi.BA.1/30µg (GMR and seroresponse)→ BNT162b2-Omi.BA.1/30µg ("super" superiority)

For objectives involving two hypotheses, hypotheses based on GMR and seroresponse rate differences were assessed sequentially in the order as stated. Both hypotheses within the objective had to be established before assessing the next objective in the sequence. Therefore, the overall type I error was fully controlled.

Table S1. Study populations

Population	Description
Enrolled	All participants who signed the informed consent document
Randomized/assigned	All participants who were assigned a randomization number in the interactive web response system
Evaluable immunogenicity	All eligible randomized/assigned participants who received the study intervention to which they were randomized or assigned, had a valid and determinate immunogenicity result from the blood sample collected within 28–42 days after vaccination, and no other important protocol deviations as determined by the clinician
Immunogenicity subset	Included 230 participants who were randomly selected from each group in the expanded cohort to evaluate primary and secondary immunogenicity objectives
Omicron BA.4/BA.5 neutralization assay subset	Included 100 participants (20 participants with baseline SARS-CoV-2 positive status and 80 participants with SARS-CoV-2 negative status up to 1 month after vaccination) who were randomly selected from each of the BNT162b2/30μg and bivalent-Omi.BA.1/30μg groups in the expanded cohort
Omicron BA.2.75 neutralization subset	Included 30 participants in each of the BNT162b2/30μg and bivalent-Omi.BA.1/ 30μg groups randomly selected from the Omicron BA.4/BA.5 neutralization assay subset, all without serological or virological evidence of previous SARS-CoV-2 infection up to 1 month after vaccination
Safety	All participants who received the study intervention

Table S2. Representativeness of study participants*

Category	Details
Disease, problem, or condition under investigation	COVID-19 in adults older than 55 years
Special considerations related to	
Sex and gender	COVID-19 rates are similar between sexes, although men appear at increased risk for COVID-19-associated hospitalization, intensive care admission, and death.[1] Limited data are available on the relationship between gender identity and COVID-19.[2]
Age	The prevalence of COVID-19 is generally similar across adult age groups.[3] However hospitalization and mortality rates increase with older age.
Race or ethnic group	COVID-19 affects individuals of all races and ethnicities,[4] with racial and ethnic minority populations at increased risk for COVID-19–associated hospitalization and mortality.[5] In the United States, Black/African American, Hispanic/Latinx, and American Indian/Alaska Native individuals have higher COVID-19–associated hospitalization and mortality rates compared with White individuals.[4]
Geography	COVID-19 affects individuals worldwide, although the number of cases and outcomes have varied by country and geographic region.[6] As of September 14, 2022, the number of COVID-19 cases and attributed deaths in the United States were >94 million and >1 million, respectively.
Other considerations	As of September 2022 in the United States, Omicron SARS-CoV-2 BA.4 and BA.5 sublineages are the dominant circulating strains.[7]
Overall representativeness of this trial	The participants included in this study were older than 55 years, and half of participants were men. The trial disproportionately included White participants (87%), with 6%, 6%, and 15% of participants of Black/African American, Asian, and Hispanic/Latinx race/ethnicity. The study was conducted in the United States during the period of Omicron SARS-CoV-2 variant predominance.

1. Tharakan et al. Nat Rev Urol. 2021;19:47-63.
2. Morgan et al. Front Sociol. 2021;6:650729.
3. US Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group. Updated July 29, 2022. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed September 14, 2022.
4. US Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity. Updated July 28, 2022. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed September 14, 2022.
5. Khanijahani et al. Int J Equity Health. 2021;20:248.
6. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed September 14, 2022.
7. Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, September 15. https://covid.cdc.gov/covid-data-tracker. Accessed September 14, 2022.

* A literature search of PubMed and government sources was conducted to determine the representativeness of the participant population to the population of individuals with COVID-19.

Table S3. Demographic characteristics of the participants in the sentinel cohort

Characteristic	Original BNT162b2/ 30µg (N*=20)	BNT162b2/ 60µg (N*=20)	Monovalent BNT162b2-Omi.BA.1/30µg (N*=20)	Monovalent BNT162b2-Omi.BA.1/60µg (N*=20)	Bivalent BNT162b2/ 15µg + BNT162b2-Omi.BA.1/15µg (N*=20)	Bivalent BNT162b2/ 30µg + BNT162b2-Omi.BA.1/30µg (N*=20)	Total (N*=120)
Male, n (%)	12 (60.0)	11 (55.0)	6 (30.0)	8 (40.0)	13 (65.0)	9 (45.0)	59 (49.2)
Race, n (%)							
White	16 (80.0)	19 (95.0)	15 (75.0)	17 (85.0)	14 (70.0)	16 (80.0)	97 (80.8)
Black or African American	1 (5.0)	0	2 (10.0)	2 (10.0)	2 (10.0)	1 (5.0)	8 (6.7)
Asian	3 (15.0)	1 (5.0)	2 (10.0)	1 (5.0)	4 (20.0)	3 (15.0)	14 (11.7)
Multiracial	0	0	1 (5.0)	0	0	0	1 (0.8)
Ethnicity, n (%)							
Hispanic/Latinx	1 (5.0)	1 (5.0)	4 (20.0)	3 (15.0)	2 (10.0)	4 (20.0)	15 (12.5)
Non-Hispanic/non-Latinx	19 (95.0)	19 (95.0)	16 (80.0)	17 (85.0)	18 (90.0)	16 (80.0)	105 (87.5)
Age at vaccination, median (range), y	68.0 (56–79)	71.5 (57–84)	66.0 (56–78)	66.5 (58–78)	67.5 (57–74)	67.5 (56–85)	67.0 (56–85)
Baseline SARS-CoV-2 status, n (%)							
Positive†	2 (10.0)	0	3 (15.0)	2 (10.0)	4 (20.0)	1 (5.0)	12 (10.0)
Negative§	18 (90.0)	20 (100)	17 (85.0)	18 (90.0)	16 (80.0)	19 (95.0)	108 (90.0)
Months from dose 3 of BNT162b2 received before study vaccination							
Mean (SD)	8.4 (0.93)	8.7 (1.03)	8.1 (0.75	8.4 (0.97)	8.6 (0.98)	8.6 (0.93)	8.5 (0.94)
Median (range)	7.9 (7.3–10.0)	8.1 (7.4–10.0)	7.9 (7.4–9.9)	8.0 (7.3–10.0)	8.1 (7.4–10.0)	8.1 (7.3–10.0)	8.0 (7.3–10.0)
≥7 to <9, n (%)	14 (70.0)	12 (60.0)	17 (85.0)	14 (70.0)	13 (65.0)	13 (65.0)	83 (69.2)
≥9 to <11, n (%)	6 (30.0)	8 (40.0)	3 (15.0)	6 (30.0)	7 (35.0)	7 (35.0)	37 (30.8)

Body mass index, n (%)							
<18.5 kg/m^2	0	0	1 (5.0)	0	0	0	1 (0.8)
≥18.5–24.9 kg/m^2	5 (25.0)	4 (20.0)	4 (20.0)	5 (25.0)	6 (30.0)	6 (30.0)	30 (25.0)
≥25.0–29.9 kg/m^2	6 (30.0)	8 (40.0)	8 (40.0)	9 (45.0)	6 (30.0)	8 (40.0)	45 (37.5)
≥30.0 kg/m^2	9 (45.0)	8 (40.0)	7 (35.0)	6 (30.0)	8 (40.0)	6 (30.0)	44 (36.7)

BNT162b2-Omi.BA.1=Omicron-BA.1-adapted BNT162b2 vaccine; N-binding=SARS-CoV-2 nucleoprotein–binding; NAAT=nucleic acid amplification test; SD=standard deviation.

Data are for the safety population (defined in **Table S1**).

* Number of participants in the specified group or total sample. This value is the denominator for the percentage calculations.

† Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

§ Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Table S4. SARS-CoV-2 neutralization assay results at 1 month after vaccination among participants with and without evidence of previous SARS-CoV-2 infection in the immunogenicity subset*

Endpoint	Original BNT162b2/ 30µg	BNT162b2/ 60µg	Monovalent BNT162b2-Omi.BA.1/30µg	Monovalent BNT162b2-Omi.BA.1/60µg	Bivalent BNT162b2/ 15µg + BNT162b2-Omi.BA.1/15µg	Bivalent BNT162b2/ 30µg + BNT162b2-Omi.BA.1/30µg
Omicron BA.1 neutralizing titers						
n†	201	205	211	208	207	208
GMT (95% CI)‡	663 (531, 829)	821 (684, 985)	1346 (1110, 1633)	1836 (1545, 2182)	884 (734, 1065)	1140 (931, 1397)
GMR vs BNT162b2/30µg (95% CI)§	-	-	2.03 (1.51, 2.72)	2.77 (2.09, 3.67)	1.33 (1.00, 1.78)	1.72 (1.27, 2.32)
Omicron BA.1 seroresponses‖						
n¶	186	195	200	195	196	192
Participants with seroresponses, n (%) (95% CI)#	97 (52.2) (44.7, 59.5)	116 (59.5) (52.2, 66.4)	143 (71.5) (64.7, 77.6)	160 (82.1) (75.9, 87.2)	131 (66.8) (59.8, 73.4)	122 (63.5) (56.3, 70.4)
Difference vs BNT162b2/30µg, % (95% CI)**	-	-	19.3 (9.7, 28.7)	29.9 (20.7, 38.7)	14.7 (4.8, 24.3)	11.4 (1.4, 21.1)
Ancestral strain neutralizing titers						
n†	221	220	222	218	216	216
GMT (95% CI)‡	7377 (6427, 8466)	8244 (7270, 9349)	6815 (5859, 7926)	8447 (7270, 9813)	6945 (6067, 7949)	9355 (8151, 10,736)
GMR vs BNT162b2/30µg (95% CI)§	-	-	-	-	0.94 (0.78, 1.14)	1.27 (1.04, 1.54)
Ancestral strain seroresponses‖						
n¶	218	219	218	215	216	214
Participants with seroresponses, n (%) (95% CI)#	102 (46.8) (40.0, 53.6)	121 (55.3) (48.4, 62.0)	110 (50.5) (43.6, 57.3)	121 (56.3) (49.4, 63.0)	102 (47.2) (40.4, 54.1)	123 (57.5) (50.6, 64.2)

BNT162b2-Omi.BA.1=Omicron-BA.1-adapted BNT162b2 vaccine; GMR=geometric mean ratio; GMT=geometric mean titer; LLOQ=lower limit of quantitation.

Data are for the evaluable immunogenicity population (defined in **Table S1**).
* Immunogenicity subset refers to a random sample of 230 participants in each vaccine group selected from the expanded cohort.
† Number of participants in the specified group with valid and determinate assay results for the specified assay at 1 month postvaccination.
‡ GMTs and associated 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student *t* distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
§ GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding column − BNT162b2 [30-μg]) and the corresponding CI (based on the Student *t* distribution).
‖ Seroresponse was defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered a seroresponse.
¶ Number of participants in the specified group with valid and determinate assay results for the specified assay at both baseline and 1 month postvaccination.
# 2-sided CI based on the Clopper–Pearson method.
** 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Table S5. Seroresponse rates 1 month after vaccination for SARS-CoV-2 Omicron BA.4/BA.5

Baseline SARS-CoV-2 status	n	Seroresponse, % (95% CI)	
		Original BNT162b2/30µg	Bivalent BNT162b2/15µg + BNT162b2-Omi.BA.1/15µg
All	100	42.0 (32.2, 52.3)	56.0 (45.7, 65.9)
Positive	20	25.0 (8.7, 49.1)	50.0 (27.2, 72.8)
Negative	80	46.3 (35.0, 57.8)	57.5 (45.9, 68.5)

Data are for the Omicron BA.4/BA.5 neutralization assay subset (**Table S1**). Positive SARS-CoV-2 status was defined as N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19. Seroresponse was defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement was below the LLOQ, the postvaccination measure of ≥4 × LLOQ was considered a seroresponse. 95% CIs for seroresponse rates were calculated based on the Clopper–Pearson method. BNT162b2-Omi.BA.1=Omicron BA.1-adapted BNT162b2 vaccine; LLOQ=lower limit of quantitation; N-binding=SARS-CoV-2 nucleoprotein–binding; NAAT=nucleic acid amplification test.

Table S6. Summary of adverse events in the expanded cohort

	Original BNT162b2/ 30µg (N*=305) n† (%)	BNT162b2/ 60µg (N*=302) n† (%)	Monovalent BNT162b2-Omi.BA.1/30µg (N*=307) n† (%)	Monovalent BNT162b2-Omi.BA.1/60µg (N*=306) n† (%)	Bivalent BNT162b2/ 15µg + BNT162b2-Omi.BA.1/15µg (N*=305) n† (%)	Bivalent BNT162b2/ 30µg + BNT162b2-Omi.BA.1/30µg (N*=316) n† (%)
Adverse event through 1 month after vaccination	18 (5.9)	20 (6.6)	26 (8.5)	11 (3.6)	19 (6.2)	33 (10.4)
Related‡§	4 (1.3)	13 (4.3)	10 (3.3)	5 (1.6)	7 (2.3)	16 (5.1)
Severe	0	0	1 (0.3)	0	1 (0.3)	3 (0.9)
Life-threatening	0	0	0	0	0	1 (0.3)
Serious adverse event through data cutoff date|	2 (0.7)	0	3 (1.0)	0	1 (0.3)	2 (0.6)
Related‡	0	0	1 (0.3)	0	0	0
Severe	2 (0.7)	0	1 (0.3)	0	1 (0.3)	0
Life-threatening	0	0	0	0	0	1 (0.3)
Any adverse event leading to withdrawal through data cutoff date	0	0	0	0	0	0
Death through data cutoff date	0	0	0	0	0	0

BNT162b2-Omi.BA.1=Omicron-BA.1-adapted BNT162b2 vaccine.

Data are for the safety population (defined in **Table S1)**. Adverse events in the sentinel cohort are shown in **Table S7**.

* Number of participants in the specified group. This value is the denominator for the percentage calculations.

† Number of participants reporting ≥1 occurrence of the specified adverse event category.

‡ Assessed by the investigator as related to study intervention.

§ Includes adverse events of injection-site pruritus (n=1, BNT162b2-Omi.BA.1/30µg); rash (n=1, BNT162b2/60µg; n=3, bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg), urticaria (n=1, bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg).

| Includes one event each of severe pneumonia (BNT162b2/30µg; unrelated), severe ischemic stroke (BNT162b2/30µg; unrelated), severe dehydration (BNT162b2-Omi.BA.1/30µg; related), prostate cancer (BNT162b2-Omi.BA.1/30µg; unrelated), moderate nephrolithiasis (BNT162b2-Omi.BA.1/30µg; unrelated), severe gastroesophageal reflux disease (bivalent BNT162b2/15µg + BNT162b2-Omi.BA.1/15µg; unrelated), mild atrial fibrillation (bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg; unrelated), and Grade 4 atrial fibrillation (bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg; unrelated).

Table S7. Summary of adverse events through 1 month after vaccination in the sentinel cohort

	Original BNT162b2/ 30µg (N*=20) n† (%)	BNT162b2/ 60µg (N*=20) n† (%)	Monovalent BNT162b2-Omi.BA.1/30µg (N*=20) n† (%)	Monovalent BNT162b2-Omi.BA.1/60µg (N*=20) n† (%)	Bivalent BNT162b2/15µg + BNT162b2-Omi.BA.1/15µg (N*=20) n† (%)	Bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg (N*=20) n† (%)
Adverse event	2 (10.0)	0	3 (15.0)	1 (5.0)	1 (5.0)	1 (5.0)
Related‡	0	0	1 (5.0)	1 (5.0)	0	0
Severe	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Serious adverse event	0	0	0	0	0	0
Adverse event leading to withdrawal	0	0	0	0	0	0
Death	0	0	0	0	0	0

BNT162b2-Omi.BA.1=Omicron-BA.1-adapted BNT162b2 vaccine.

Data are for the safety population (defined in **Table S1)**.

* Number of participants in the specified group. This value is the denominator for the percentage calculations.

† Number of participants reporting ≥1 occurrence of the specified adverse event category.

‡ Assessed by the investigator as related to study intervention.

Table S8. Severity grading for local reactions and systemic events

	Mild	Moderate	Severe	Potentially life threatening (Grade 4)
Local reactions				
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Systemic events				
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Vomiting	1–2 times in 24 hours	≥2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools in 24 hours	4–5 loose stools in 24 hours	≥6 loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Figure S1. Randomization and vaccine administration in the sentinel cohort

The figure shows all participant dispositions as of the database cutoff date of April 5, 2022. BNT162b2-Omi.Ba.1=Omicron BA.1-adapted BNT162b2 vaccine.

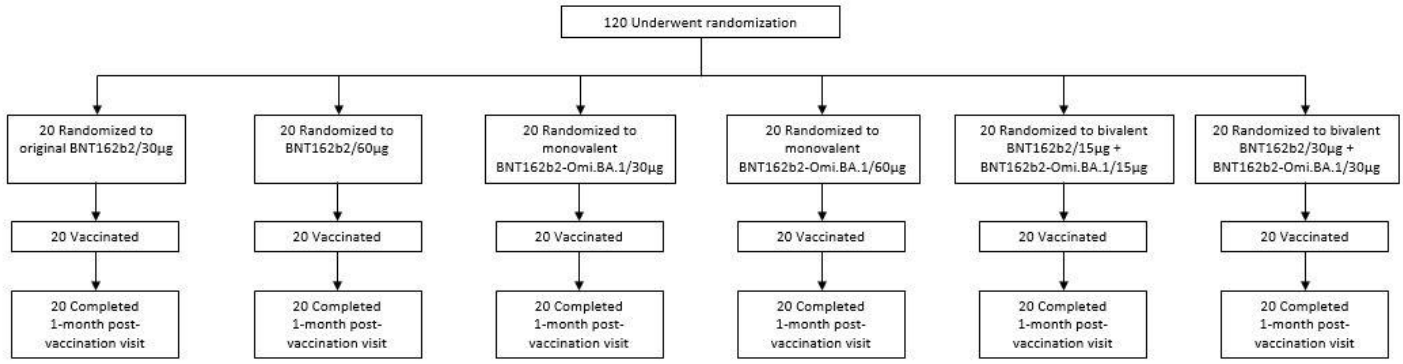

Figure S2. SARS-CoV-2 neutralization GMTs before and at 1 month after vaccination among participants with and without evidence of previous SARS-CoV-2 infection in the immunogenicity subset

Panel (A) shows results from the assay using the Omicron BA.1 strain, while panel (B) shows results from the assay using the ancestral strain. Data are for the evaluable population (defined in **Table S1**). Immunogenicity subset refers to random sample of 230 participants in each vaccine group selected from the expanded cohort. Previous SARS-CoV-2 infection was defined based on serological or virological evidence (before the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] result positive at the study vaccination or the 1-month post–study vaccination visits, positive NAAT [nasal swab] result at the study vaccination visit or any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) or medical history of COVID-19. GMTs are shown within the bars and GMFRs from before to 1 month after vaccination are shown above the bars for each group. GMTs, GMFRs, and associated 95% CIs were calculated by exponentiating the mean logarithm of the titers (GMTs) or fold rises (GMFRs) and the corresponding CIs (based on the Student *t* distribution). Assay results below the LLOQ were set to 0.5 × LLOQ. BNT162b2-Omi.BA.1=Omicron BA.1-adapted BNT162b2 vaccine; GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; N-binding=SARS-CoV-2 nucleoprotein–binding; NAAT=nucleic acid amplification test.

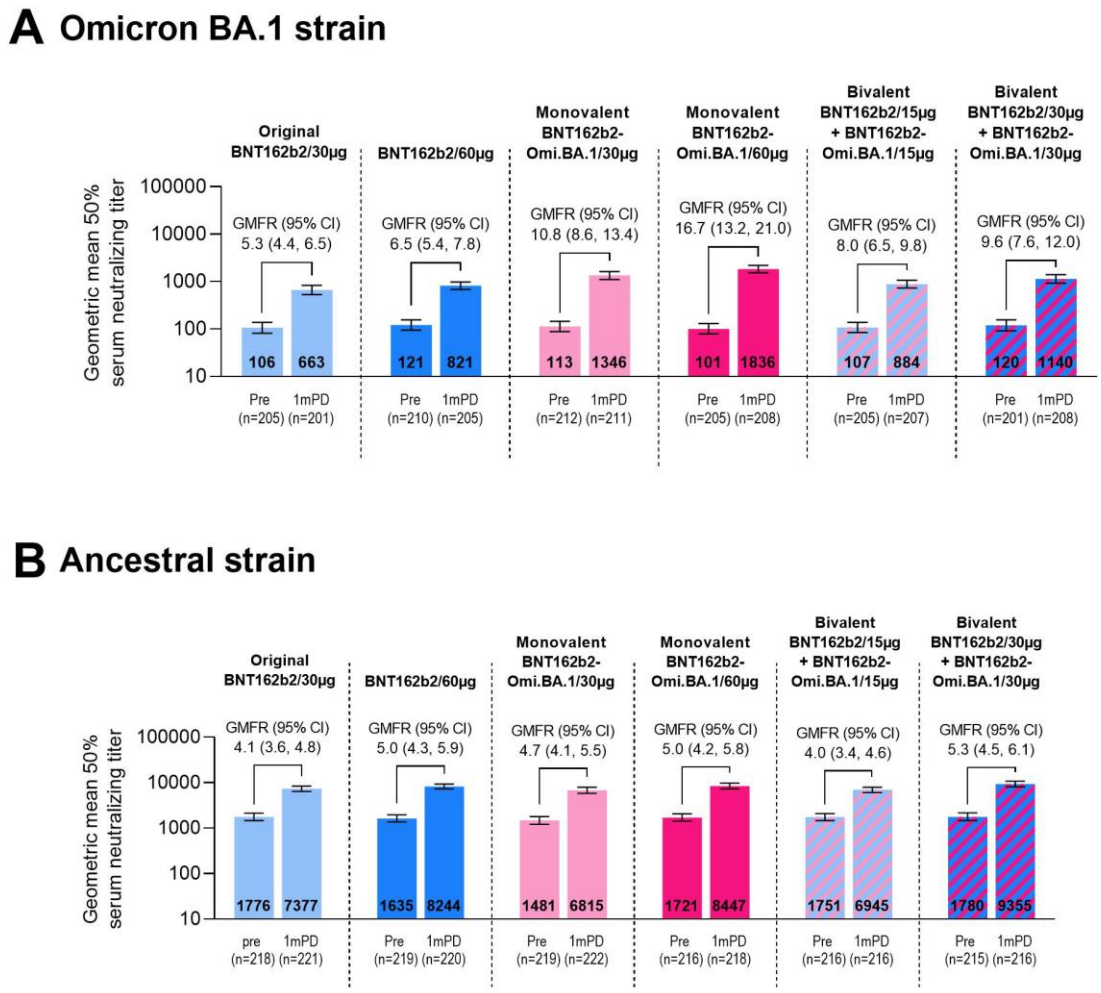

Figure S3. (A) Local reactions and (B) systemic events reported within 7 days of vaccination

Data are for the safety population (defined in **Table S1)**. Severity grading is provided in **Table S8**. Error bars represent 95% CIs, and numbers above the error bars indicate the percentage of participants in each group reporting the specified event. Reactogenicity results in the sentinel cohort are shown in **Figure S4**. Bivalent BNT-Omi/30=bivalent BNT162b2/15µg+BNT162b2-Omi.BA.1/15µg (n=301); Bivalent BNT-Omi/60=bivalent BNT162b2/30µg+BNT162b2-Omi.BA.1/30µg (n=312); BNT/30=BNT162b2/30µg (n=298); BNT/60=BNT162b2/60µg (n=298); BNT162b2-Omi.BA.1=Omicron BA.1-adapted BNT162b2 vaccine; Mono BNT/30=monovalent BNT162b2-Omi.BA.1/30µg (n=301); Mono BNT/60=monovalent BNT162b2-Omi.BA.1/60µg (n=301).

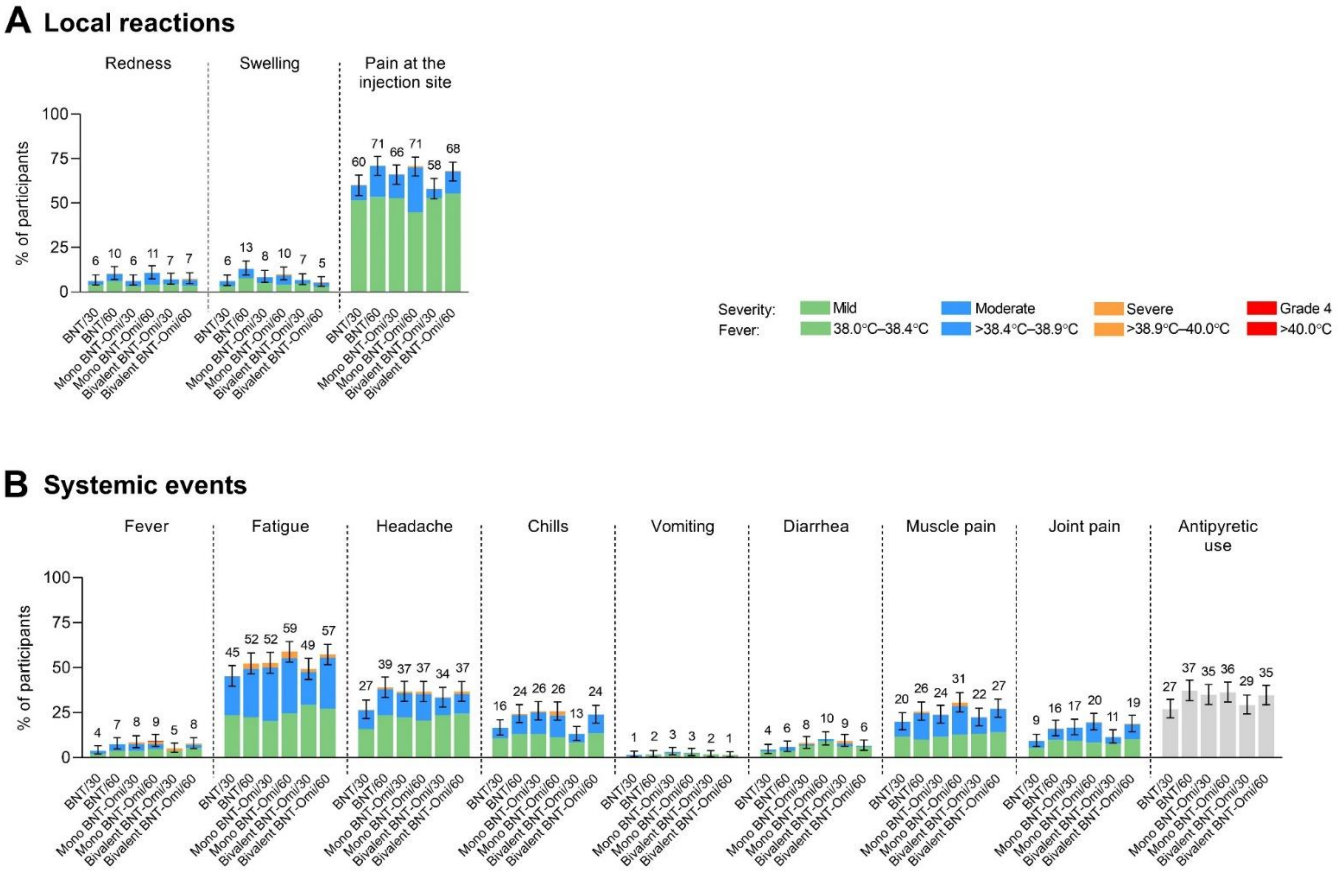

Figure S4. (A) Local reactions and (B) systemic events reported within 7 days of vaccination in the sentinel cohort

Data are for the safety population (defined in **Table S1**). Severity grading for each event is provided in **Table S8**. Error bars represent 95% CIs, and numbers above the error bars indicate the percentage of participants in each group reporting the specified local reaction or systemic event. Twenty participants were evaluated in each group for each local reaction or systemic event. Bivalent BNT-Omi/30=bivalent BNT162b2/15µg+BNT162b2-Omi.BA.1/15µg; Bivalent BNT-Omi/60=bivalent BNT162b2/30µg + BNT162b2-Omi.BA.1/30µg; BNT/30=BNT162b2/30µg; BNT/60=BNT162b2/60µg; BNT162b2-Omi.BA.1=Omicron BA.1-adapted BNT162b2 vaccine; Mono BNT/30= monovalent BNT162b2-Omi.BA.1/30µg; Mono BNT/60=monovalent BNT162b2-Omi.BA.1/60µg.