16.1.11 PUBLICATIONS BASED ON THE STUDY

1. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;10.1038/s41586-020-2639-4.

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Article

Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults

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Check for updates

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In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], a pandemic. With rapidly accumulating numbers of cases and deaths reported globally[2], a vaccine is urgently needed. Here we report the available safety, tolerability and immunogenicity data from an ongoing placebo-controlled, observer-blinded dose-escalation study (ClinicalTrials.gov identifier NCT04368728) among 45 healthy adults (18–55 years of age), who were randomized to receive 2 doses—separated by 21 days—of 10 μg, 30 μg or 100 μg of BNT162b1. BNT162b1 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes the trimerized receptor-binding domain (RBD) of the spike glycoprotein of SARS-CoV-2. Local reactions and systemic events were dose-dependent, generally mild to moderate, and transient. A second vaccination with 100 μg was not administered because of the increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared with the 30-μg dose. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level and after a second dose. Geometric mean neutralizing titres reached 1.9–4.6-fold that of a panel of COVID-19 convalescent human sera, which were obtained at least 14 days after a positive SARS-CoV-2 PCR. These results support further evaluation of this mRNA vaccine candidate.

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. By January 2020, a new coronavirus was identified as the aetiological agent. Within a month, the genetic sequence of the virus became available (MN908947.3). Infections with SARS-CoV-2 and the resulting disease, COVID-19, have spread globally. On 11 March 2020, the WHO declared the COVID-19 outbreak a pandemic[1]. So far, the United States has reported the highest number of cases globally[2,3]. No vaccines are currently available to prevent SARS-CoV-2 infection or COVID-19.

The RNA vaccine platform has enabled rapid vaccine development in response to this pandemic. RNA vaccines provide flexibility in the design and expression of vaccine antigens that can mimic the structure and expression of the antigen during natural infection. RNA is required for protein synthesis, does not integrate into the genome, is transiently expressed, is metabolized and eliminated by the natural mechanisms of the body and is therefore considered safe[4–7]. RNA-based prophylactic infectious-disease vaccines and RNA therapeutic agents have been shown to be safe and well-tolerated in clinical trials. In general, vaccination with RNA elicits a robust innate immune response. RNA directs the expression of the vaccine antigen in host cells and has intrinsic adjuvant effects[8]. A strength of the RNA-vaccine manufacturing platform—irrespective of the encoded pathogen antigen—is the ability to rapidly produce large quantities of vaccine doses against a new pathogen[9,10].

Vaccine RNA can be modified by incorporating 1-methyl-pseudouridine, which dampens innate immune sensing and increases mRNA translation in vivo[11]. The BNT162b1 vaccine candidate that is currently investigated clinically incorporates such nucleoside-modified mRNA and encodes the RBD of the spike protein of SARS-CoV-2, a key target of virus-neutralizing antibodies[12–14]. The RBD antigen expressed by BNT162b1 is modified by the addition of a T4 fibritin-derived foldon trimerization domain to increase its immunogenicity[15] by multivalent display[16]. The proper folding of the RBDs in the resulting protein construct has been confirmed by high resolution structural analysis (A.B.V. et al., manuscript in preparation). The vaccine RNA is formulated in lipid nanoparticles for more-efficient delivery into cells after intramuscular injection[17]. BNT162b1 is one of several RNA-based SARS-CoV-2 vaccine candidates[18] that are studied in parallel for selection to advance

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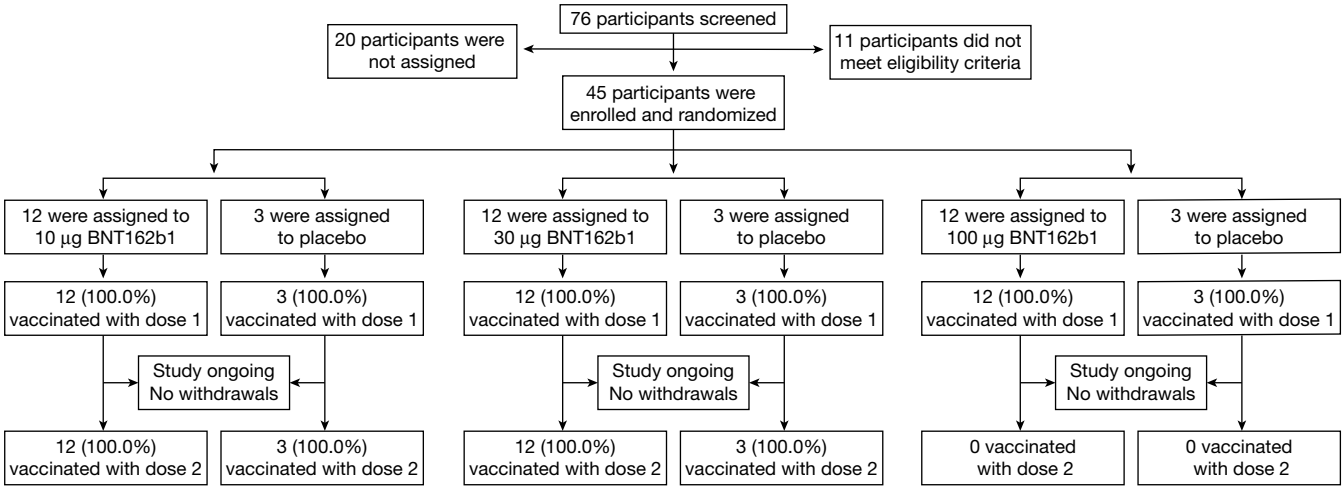

Fig. 1 | Study design. Participants who were not assigned ($n = 20$) were screened but not randomized because enrolment had closed.

to a safety and efficacy trial. Here, we present the available data, up to 14 days after a second dose in adults (18–55 years of age) from an ongoing phase I/II vaccine study with BNT162b1, which is also enrolling adults who are 65–85 years of age (ClinicalTrials.gov identifier, NCT04368728).

Study design and demographics

Between 4 May 2020 and 19 June 2020, 76 participants were screened, and 45 participants were randomized and vaccinated. Per dose level (10 μg and 30 μg), 12 participants were vaccinated with BNT162b1 on days 1 and 21, 12 participants received a 100-μg dose on day 1 and 9 participants received placebo (Fig. 1). The study population consisted of healthy male and female participants with a mean age of 35.4 years (range, 19–54 years); 51.1% were male and 48.9% were female. Most participants self-reported as white (82.2%) and non-Hispanic/non-Latinx (93.3%) (Extended Data Table 1).

Safety and tolerability

In the 7 days after vaccination doses 1 and 2, pain at the injection site was the most-frequent solicited local reaction, reported after the first dose by 58.3% (7 out of 12) in the 10-μg BNT162b1 group, 100.0% (12 out of 12 each) in the 30-μg and 100-μg BNT162b1 groups, and 22.2% (2 out of 9) in the placebo group. After the second dose, pain was reported by 83.3% (10 out of 12) and 100.0% of individuals who received 10 μg and 30 μg BNT162b1, respectively, and by 16.7% of individuals who received the placebo. All local reactions were mild or moderate in severity except for one report of severe pain after the first dose of 100 μg BNT162b1 (Fig. 2).

The most-common systemic events reported in the 7 days after each vaccination in both BNT162b1 and placebo groups were mild to moderate fatigue and headache. Reports of fatigue and headache were more common in the BNT162b1 groups than in the placebo group. In addition, chills, muscle pain and joint pain were reported by individuals who received BNT162b1 but not by individuals who received the placebo. Systemic events increased with dose level and were reported in a greater number of participants after the second dose (10-μg and 30-μg groups). After the first dose, fever (defined as ≥38.0 °C) was reported by 8.3% (1 out of 12) of participants who received 10 μg and 30 μg BNT162b1 and by 50.0% (6 out of 12) of individuals who received 100 μg BNT162b1. After the second dose, 8.3% (1 out of 12) of participants who received 10 μg BNT162b1 and 75.0% (9 out of 12) of participants who received 30 μg BNT162b1 reported fever of ≥38.0 °C. On the basis of the reactogenicity reported after the first dose of 100 μg and the second dose of 30 μg, participants who received an initial 100-μg dose did not receive a second 100-μg dose. Fevers generally resolved within 1 day of onset. No grade 4 systemic events or fever were reported (Fig. 3a, b). Most local reactions and systemic events peaked by day 2 after vaccination and resolved by day 7.

Adverse events (Extended Data Table 2) were reported by 50.0% (6 out of 12) of participants who received either 10 or 30 μg of BNT162b1, 58.3% (7 out of 12) of participants who received 100 μg of BNT162b1, and 11.1% (1 out of 9) of placebo recipients. Two participants reported a severe adverse event: grade 3 fever 2 days after vaccination in the 30-μg group, and sleep disturbance 1 day after vaccination in the 100-μg group. Related adverse events were reported by 25% (3 out of 12 in the 10-μg group) to 50% (6 out of 12 each in the 30-μg and 100-μg groups) of individuals who received BNT162b1 and by 11.1% (1 out of 9) of participants who received the placebo. No serious adverse events were reported.

No grade 1 or greater change in routine clinical laboratory values or laboratory abnormalities were observed for most participants after either of the BNT162b1 vaccinations. Of those with laboratory changes, the largest changes were decreases in the lymphocyte count after the first dose in 8.3% (1 out of 12), 45.5% (5 out of 11) and 50.0% (6 out of 12) of participants who received 10 μg, 30 μg and 100 μg BNT162b1, respectively. One participant each in the 10-μg (8.3% (1 out of 12)) and 30-μg (9.1% (1 out of 11)) groups and 4 participants in the 100-μg group (33.3% (4 out of 12)) had grade 3 decreases in the lymphocyte count. These decreases in lymphocyte count after the first dose were transient and returned to normal 6–8 days after vaccination (Extended Data Fig. 1). In addition, grade-2 neutropenia was noted 6–8 days after the second dose in 1 participant each in the 10-μg and 30-μg BNT162b1 groups. These two participants continue to be followed in the study, and no adverse events or clinical manifestations of neutropenia have been reported to date. None of the post-vaccination abnormalities observed were associated with clinical findings.

Immunogenicity

RBD-binding IgG concentrations and SARS-CoV-2-neutralizing titres were assessed at baseline, at 7 and 21 days after the first dose, at 7 days (day 28) and 14 days (day 35) after the second dose of BNT162b1. By 21 days after the first dose (for all three dose levels), geometric mean concentrations (GMCs) of RBD-binding IgG ranged from 534 to 1,778 U ml^{-1} (Fig. 4a). In comparison, a panel of 38 SARS-CoV-2 infection and/or COVID-19 convalescent sera drawn at least 14 days after a PCR-confirmed diagnosis from patients with COVID-19 (18–83 years

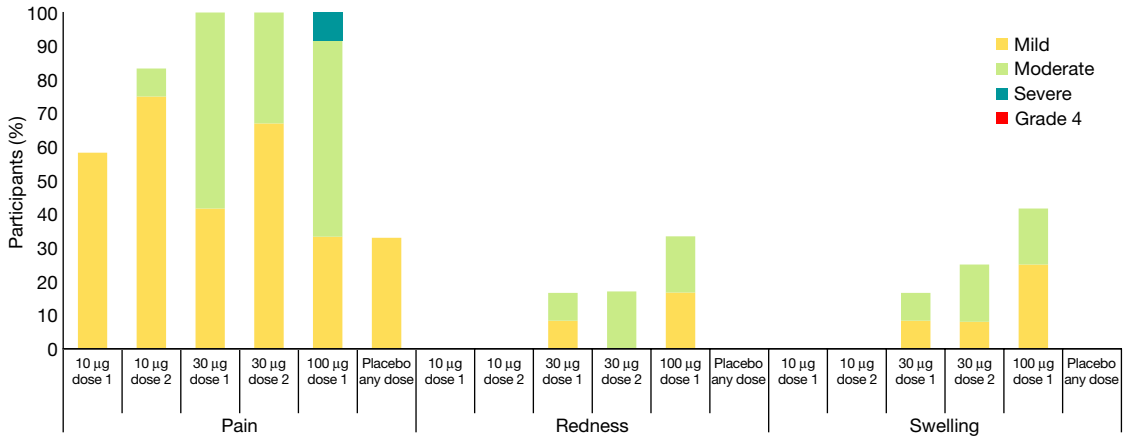

Fig. 2 | Local reactions reported within 7 days of vaccination for all dose levels. Solicited injection-site (local) reactions were: pain at injection site (mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; grade 4, emergency room visit or hospitalization) and redness and swelling (mild, 2.0–5.0 cm in diameter; moderate, >5.0–10.0 cm in diameter; severe, >10.0 cm in diameter; grade 4: necrosis or exfoliative dermatitis for redness, and necrosis for swelling). Data were collected with the use of electronic diaries for 7 days after each vaccination.

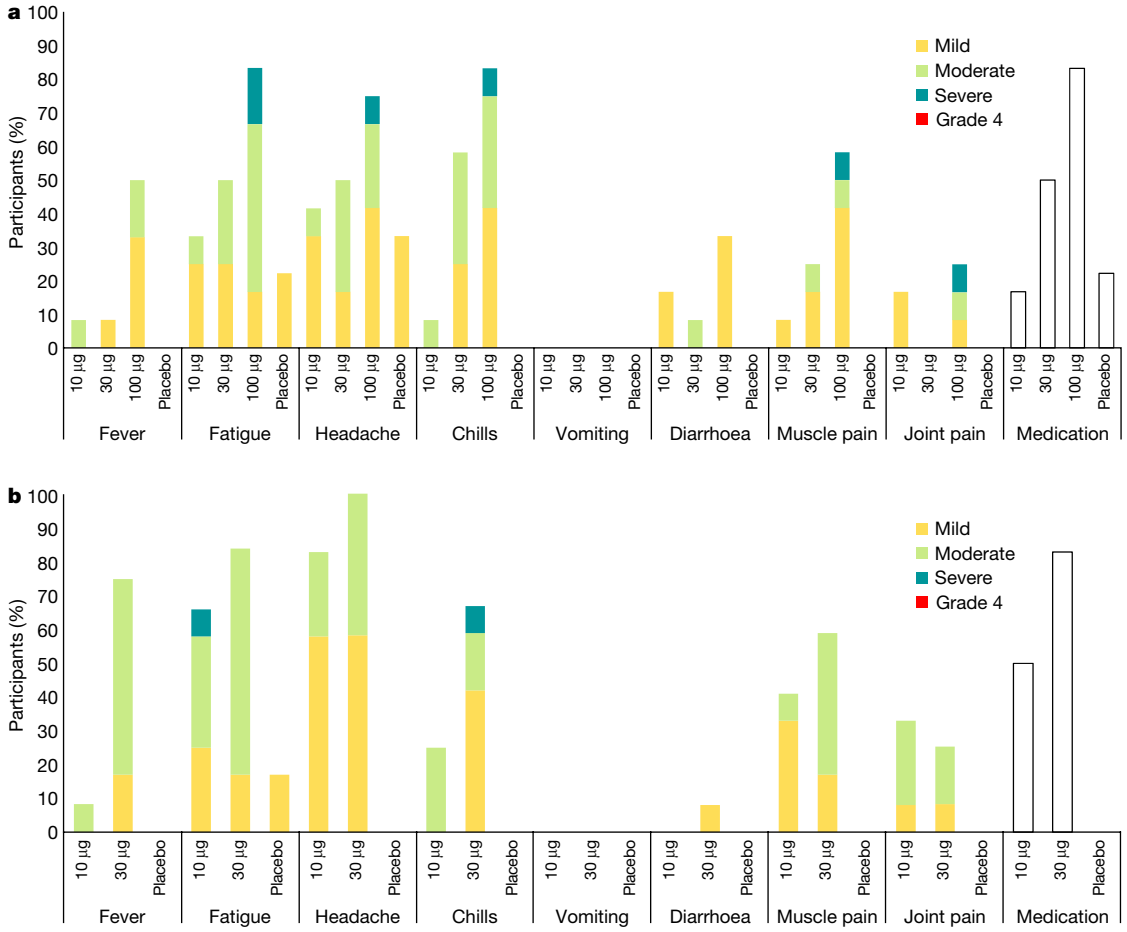

Fig. 3 | Systemic events and medication use reported within 7 days after vaccination. a, Systemic events and medication use reported within 7 days after vaccination 1 for all dose levels. **b**, Systemic events and medication use reported within 7 days after vaccination 2 for the 10-µg and 30-µg dose levels. Solicited systemic events were: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild, does not interfere with activity; moderate, some interference with activity; severe, prevents daily activity), vomiting (mild, 1–2 times in 24 h; moderate, >2 times in 24 h; severe, requires intravenous hydration), diarrhoea (mild, 2–3 loose stools in 24 h; moderate, 4–5 loose stools in 24 h; severe: 6 or more loose stools in 24 h); grade 4 for all events: emergency room visit or hospitalization; and fever (mild, 38.0–38.4 °C; moderate, 38.5–38.9 °C; severe, 39.0–40.0 °C; grade 4, >40.0 °C). Medication indicates the proportion of participants who reported the use of antipyretic or pain medication. Data were collected with the use of electronic diaries for 7 days after each vaccination.

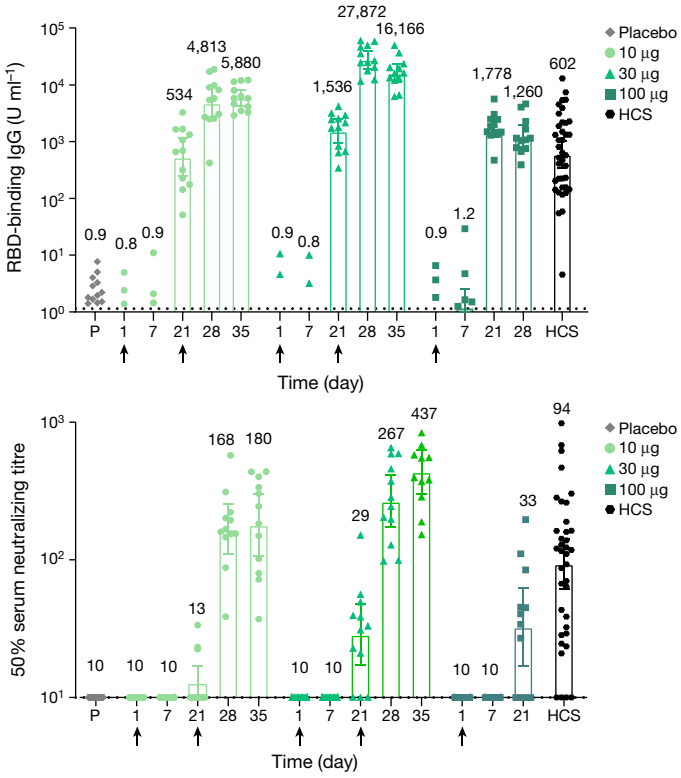

Fig. 4 | Immunogenicity of BNT162b1. Participants in groups of 15 were vaccinated with the indicated dose levels of BNT162b1 ($n = 12$) or with placebo ($n = 3$) on days 1 (all dose levels and placebo) and 21 (10-µg and 30-µg dose levels and placebo). Reponses in individuals who received the placebo for each of the dosing groups are combined. The 28- and 35-day blood samples were obtained 7 and 14 days after the second vaccination. Sera were obtained before vaccination (day 1), and 7, 21, 28 and 35 days after the first vaccination. Human COVID-19 convalescent sera (HCS, $n = 38$) were obtained at least 14 days after PCR-confirmed diagnosis and at a time when the donors were asymptomatic. **a**, GMCs of recombinant RBD-binding IgG. Because the measured antibody concentrations using the Luminex assay are obtained in arbitrary units, they cannot be directly translated into concentrations on a molar or mass basis. The lower limit of quantitation is 1.15. **b**, The 50% SARS-CoV-2-neutralizing GMTs. Each data point represents a serum sample, and each vertical bar represents a geometric mean with 95% confidence interval. The number above the bars are either the GMC (**a**) or GMT (**b**) for the group. Arrows indicate the timing of vaccination (blood was obtained before vaccination on the vaccination days).

of age) had an RBD-binding IgG GMC of 602 U ml^{-1}. (Additional information on the convalescent serum panel is included in the Methods.) By 7 days after the second dose (for the 10-µg and 30-µg dose levels), RBD-binding IgG GMCs had increased to 4,813 and to 27,872 U ml^{-1}, respectively. RBD-binding antibody concentrations among participants who received one dose of 100 µg BNT162b1 did not increase further at 21 days after the first vaccination. In the participants who received the 10-µg and 30-µg doses of BNT162b1, highly elevated RBD-binding antibody concentrations persisted to the last time point evaluated (day 35, 14 days after the second dose). These RBD-binding antibody concentrations were 5,880–16,166 U ml^{-1} compared to 602 U ml^{-1} in the panel of human convalescent sera.

For all doses, small increases in SARS-CoV-2-neutralizing geometric mean titres (GMTs) were observed 21 days after the first dose (Fig. 4b). Substantially greater serum neutralizing GMTs were achieved 7 days after the second 10-µg and 30-µg dose, reaching 168–267. Neutralizing GMTs further increased by 14 days after the second dose to 180 (10-µg dose level) and 437 (30-µg dose level), compared to 94 for the panel of human convalescent sera. The kinetics and durability of the neutralizing titres are being monitored.

Discussion

The RNA-based SARS-CoV-2 vaccine candidate BNT162b1, which was administered as 10-µg, 30-µg or 100-µg doses in healthy adults (18–55 years of age), exhibited a tolerability and safety profile consistent with those previously observed for mRNA-based vaccines[5]. A clear dose-level response in elicited neutralizing titres was observed after doses 1 and 2 in participants with a particularly steep dose response between the 10 µg and 30 µg dose levels.

On the basis of the tolerability profile of the first dose at 100 µg and the second dose at 30 µg, participants randomized to the 100-µg group did not receive a second vaccination. Reactogenicity was generally greater after the second dose in the other two dosing levels; however, symptoms were transient and resolved within a few days. Transient decreases in lymphocyte counts (grades 1–3) were observed within a few days after vaccination, and returned to baseline within 6–8 days in all participants. These laboratory abnormalities were not associated with clinical findings. RNA vaccines are known to induce type-I interferon, which has been associated with transient migration of lymphocytes into tissues[19–22].

Robust immunogenicity was observed after vaccination with BNT162b1. RBD-binding IgG concentrations were detected at 21 days after the first dose, and these were substantially increased 7 days after the second dose given at day 21. After the first dose, the RBD-binding IgG GMCs (10-µg dose) were similar to those observed in a panel of 38 convalescent human serum samples, obtained at least 14 days after a PCR-confirmed diagnosis of SARS-CoV-2 infection and/or COVID-19. After the first dose, GMCs were similar in the 30-µg and 100-µg groups and higher than those in the panel of human convalescent sera. After the second dose, with 10 µg or 30 µg BNT162b1, the RBD-binding IgG GMCs were around 8.0–50-fold that of the GMC of the convalescent serum panel.

The higher RBD-binding IgG GMC elicited by the vaccine relative to the GMC of the human convalescent serum panel may be attributed, in part, to antibodies that bind to epitopes that are exposed on the RNA-expressed RBD immunogen and the recombinant RBD target antigen of the binding assay but are buried and inaccessible to antibodies on the RBDs that are incorporated into the spikes of SARS-CoV-2 virions. Neutralization provides a measure of the vaccine-elicited antibody response that is more relevant to potential protection. Neutralization titres were measurable after a single vaccination at day 21 for all dose levels. At day 28 (7 days after the second dose), substantial SARS-CoV-2 neutralization titres were observed. The virus-neutralizing GMTs after the second dose of 10 µg and 30 µg were, respectively, 1.8-fold and 2.8-fold the GMT of the convalescent serum panel. By day 35 (14 days after the second dose)—despite a decrease in RBD-binding IgG titres since day 28—neutralizing GMTs continued to increase, to 1.9-fold and 4.6-fold the GMT of the convalescent panel for the 10 µg and 30 µg doses, respectively, which is consistent with affinity maturation.

Assuming that the neutralization titres that are induced by natural infection provide protection from COVID-19, comparing vaccine-induced SARS-CoV-2 neutralization titres to those from sera of convalescent humans provides a benchmark for the magnitude of the vaccine-elicited response and the potential of the vaccine to provide protection. Because the titre at which human neutralizing antibodies are protective remains unknown, these findings are not proof of vaccine efficacy. Efficacy will be determined in a pivotal phase III trial. Because the cohort that received the 100 µg dose level did not receive the booster dose, no data for immunogenicity after a second vaccination at this dose level are available; however, there were no substantial differences in immunogenicity between the 30-µg and 100-µg dose levels after the first dose. This observation suggests that a well-tolerated and immunogenic dose level may be between 10 µg and 30 µg for this vaccine candidate.

Our study had several limitations. Although we used convalescent sera as a comparator, the kind of immunity (T cells versus B cells or both) and level of immunity needed to protect from COVID-19 are unknown. Furthermore, this analysis of available data did not assess

immune responses or safety beyond 2 weeks after the second dose of vaccine. Both are important to inform the public health use of this vaccine. Follow-up will continue for all participants and will include collection of serious adverse events for 6 months and COVID-19 infection and multiple additional immunogenicity measurements for up to 2 years. Although our population of healthy adults up to 55 years of age is appropriate for a phase I/II study, it does not accurately reflect the population at highest risk for COVID-19. Adults who are 65 years of age and over have already been enrolled in this study and results will be reported as they become available. Later phases of this study will prioritize enrolment of more diverse populations, including those with chronic underlying health conditions and from racial and ethnic groups that are adversely affected by COVID-19[23].

The clinical testing of BNT162b1 described here has taken place in the context of a broader, ongoing COVID-19-vaccine-development program. That program includes the clinical testing of three additional vaccine candidates, including candidates that encode the full-length spike protein, and a parallel trial in Germany, in which additional immune responses, including neutralizing responses against variant strains and cell-mediated responses, are being assessed[24]. The resulting comparative data will allow us to address whether a full-length spike immunogen, which presents additional epitopes, is better able to elicit high virus-neutralizing titres that are robust to potential antigenic drift of SARS-CoV-2 than the relatively small RBD immunogen that is encoded by BNT162b1. The clinical findings for the BNT162b1 RNA-based vaccine candidate are encouraging and strongly support accelerated clinical development, including efficacy testing, and at-risk manufacturing to maximize the opportunity for the rapid production of a SARS-CoV-2 vaccine to prevent COVID-19.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2639-4.

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Methods

Study design

This study was conducted in healthy men and women (who were not pregnant) who were 18–55 years of age to assess the safety, tolerability and immunogenicity of ascending dose levels of various BNT162 mRNA vaccine candidates. In the part of the study reported here, assessment of three dose levels (10 μg, 30 μg or 100 μg) of the BNT162b1 candidate was conducted at two sites in the USA. This study used a sentinel cohort design with progression and dose escalation taking place after review of data from the sentinel cohort at each dose level. The study is registered at ClinicalTrials.gov (NCT04368728). The phase I portion of this study was observer-blinded at the site level. Investigators were blinded to participant-level study intervention assignment; but investigators were not blinded to group-level assignment for the dataset included in this Article.

Eligibility

Key exclusion criteria included individuals with known infection with human immunodeficiency virus, hepatitis C virus or hepatitis B virus; immunocompromised individuals and those with a history of autoimmune disease; and those with increased risk for severe COVID-19, previous clinical or microbiological diagnosis of COVID-19, receipt of medications intended to prevent COVID-19, previous vaccination with any coronavirus vaccine, a positive serological test for SARS-CoV-2 IgM and/or IgG at the screening visit, and a SARS-CoV-2 nucleic acid amplification test-positive nasal swab within 24 h before study vaccination.

The final protocol and informed consent document were approved by institutional review boards for each of the participating investigational centres. This study was conducted in compliance with all International Council for Harmonisation good clinical practice guidelines and the ethical principles of the Declaration of Helsinki. A signed and dated informed consent form was required before any study-specific activity was performed.

End points

In this report, results from the following study primary end points are presented: the proportion of participants who reported solicited local reactions, systemic events and use of antipyretic and/or pain medication within 7 days after vaccination, adverse events and serious adverse events (available up to around 45 days after dose 1), and the proportion of participants with clinical laboratory abnormalities 1 and 7 days after vaccination and grading shifts in laboratory assessments between baseline and 1 and 7 days after dose 1, and between dose 2 and 7 days after dose 2. Secondary end points included: SARS-CoV-2-neutralizing GMTs and SARS-CoV-2 RBD-binding IgG GMCs 7 and 21 days after dose 1, and 7 and 14 days after dose 2.

Procedures

Study participants were randomly assigned to a vaccine group using an interactive web-based response technology system with each group comprising 15 participants (12 active vaccine recipients and 3 placebo recipients). Participants received two 0.5-ml doses of either BNT162b1 or placebo, administered by intramuscular injection into the deltoid muscle.

BNT162b1 incorporates a good manufacturing practice-grade mRNA drug substance that encodes the trimerized SARS-CoV-2 spike glycoprotein RBD antigen. The coding sequence for the antigen has been deposited with GenBank (accession number, MN908947.3). The mRNA is formulated with lipids as the mRNA–lipid nanoparticle drug product. The vaccine was supplied as a buffered-liquid solution for intramuscular injection and was stored at −80 °C. The placebo was a sterile saline solution for injection (0.9% sodium chloride injection, in a 0.5-ml dose).

Safety assessments

Safety assessments included a 4-h observation after vaccination (for the first 5 participants vaccinated in each group), or a 30-min observation (for the remainder of participants) for immediate adverse events. The safety assessments also included self-reporting of solicited local reactions (redness, swelling and pain at the injection site), systemic events (fever, fatigue, headache, chills, vomiting, diarrhoea, muscle pain and joint pain), the use of antipyretic and/or pain medication in an electronic diary for 7 days after vaccination, and the reporting of unsolicited adverse events and serious adverse events after vaccination. Haematology and chemistry assessments were conducted at screening, 1 and 7 days after the first dose, and 7 days after the second dose.

There were protocol-specified safety stopping rules for all sentinel cohort participants. Both an internal review committee and an external data monitoring committee reviewed all safety data. No stopping rules were met before the publication of this report.

Human convalescent serum panel

The 38 human SARS-CoV-2 infection and/or COVID-19 convalescent sera were drawn from participants, who were 18–83 years of age, at least 14 days after PCR-confirmed diagnosis, and at a time when participants were asymptomatic. The mean age of the donors was 45 years of age. Neutralizing GMTs in subgroups of the donors were as follows: ≤55 years of age, 82 ($n = 29$); >55 years of age, 142 ($n = 9$); symptomatic infections, 90 ($n = 35$); asymptomatic infections, 156 ($n = 3$). The antibody titre for the one individual who was hospitalized was 618. The sera were obtained from Sanguine Biosciences, the MT Group and Pfizer Occupational Health and Wellness.

Immunogenicity assessments

For immunogenicity assessments, 50 ml of blood was collected before each study vaccination, at 7 and 21 days after the first dose, and at 7 and 14 days after the second dose. In the RBD-binding IgG assay, a recombinant SARS-CoV-2 RBD containing a C-terminal Avitag (Acro Biosystems, SPD-C82E9) and no foldon domain was bound to streptavidin-coated Luminex microspheres. In brief, 1.25×10^7 microspheres/ml were coated with streptavidin by 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride reaction. Recombinant RBD Avitag was coupled to streptavidin beads by incubating for 90 min at room temperature with shaking (35 rpm). Beads were blocked in 1% BSA buffer for 30 min at room temperature. Heat-inactivated serum from participants was diluted 1:500, 1:5,000 and 1:50,000 in assay buffer (PBS with 0.5% BSA, 0.05% Tween-20 and 0.02% sodium azide). Following a 16–20-h incubation at 2–8 °C with shaking (300 rpm), plates were washed three times in a solution containing 0.05% Tween-20. An R-phycoerythrin-conjugated goat anti-human polyclonal antibody (Jackson Labs) was then added to plates for 90 min at room temperature with shaking (300 RPM). Plates were then washed a final time in a solution containing 0.05% Tween-20. Data were captured as median fluorescent intensities using a Luminex reader and converted to U/ml antibody concentrations using a reference standard curve with arbitrary assigned concentrations of 100 U/ml and accounting for the serum dilution factor. The reference standard was composed of a pool of five COVID-19 convalescent serum samples (>14 days after PCR diagnosis). Three dilutions are used to increase the likelihood that at least one result for any sample will fall within the usable range of the standard curve. Assay results were reported in U/ml of IgG. The final assay results are expressed as the GMC of all sample dilutions that produced a valid assay result within the assay range.

The SARS-CoV-2 neutralization assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020) that had been rescued by reverse genetics and engineered by the insertion of an mNeonGreen gene into open-reading frame 7 of the viral genome[25]. This reporter virus generates similar plaque morphologies and indistinguishable growth curves from the wild-type virus. Viral master stocks (2×10^7

plaque-forming units per ml) used for the neutralization assay were grown in Vero E6 cells as previously described[25]. When testing patient convalescent serum specimens, the fluorescent neutralization assay produced comparable results as the conventional plaque reduction neutralization assay[26]. In brief, serial dilutions of heat-inactivated sera from participants were incubated with the reporter virus to yield an infection rate of approximately 10–30% of the Vero monolayer) for 1 h at 37 °C before inoculating Vero CCL81 cell monolayers (targeted to have 8,000–15,000 cells per well) in 96-well plates to enable the accurate quantification of infected cells. Total cell counts per well were enumerated by nuclear stain (Hoechst 33342) and fluorescent virally infected foci were detected 16–24 h after inoculation with a Cytation 7 Cell Imaging Multi-Mode Reader (BioTek) with Gen5 Image Prime v.3.09. Titres were calculated in GraphPad Prism v.8.4.2 by generating a four-parameter logistical fit of the percentage neutralization at each serial serum dilution. The 50% neutralization titre was reported as the interpolated reciprocal of the dilution that yielded a 50% reduction in fluorescent viral foci.

Statistical analysis

The sample size for the reported part of the study was not based on statistical hypothesis testing. The primary safety objective was evaluated by descriptive summary statistics for local reactions, systemic events, abnormal haematology and chemistry laboratory parameters, adverse events and serious adverse events after each vaccine dose for each vaccine group. The secondary immunogenicity objectives were descriptively summarized at the various time points. All participants with data available were included in the safety and immunogenicity analyses.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. These data are interim data from an ongoing study for which the database is not locked. Data have not yet been source-verified or subjected to standard quality check procedures that would occur at the time of database lock and may therefore be subject to change.

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Author contributions K.U.J., P.R.D., W.C.G., N.K., S.L., A.G., R.B., O.T. and U.Ş. were involved in the design of the overall study and strategy. K.N., M.J.M., E.E.W., R.F. and A.R.F. provided feedback on the study design. W.K., D.C., K.A.S., K.R.T., C.F.-G. and P.-Y.S. performed the immunological analyses. M.J.M., K.N., E.E.W., R.F., A.R.F., K.E.L. and V.R. collected data as study investigators. P.L. and K.K. developed the statistical design and oversaw the data analysis. J.A., K.U.J., P.R.D. and W.C.G. drafted the initial version of the manuscript. All authors reviewed and edited the manuscript and approved the final version.

Competing interests N.K., J.A., A.G., S.L., R.B., K.A.S., P.L., K.K., W.K., D.C., K.R.T., P.R.D., W.C.G. and K.U.J. are employees of Pfizer and may hold stock options. U.Ş. and Ö.T. are stock owners, management board members and employees at BioNTech and are inventors on patents and patent applications related to RNA technology. M.J.M., K.E.L., K.N., E.E.W., A.R.F., R.F. and V.R. received compensation from Pfizer for their role as study investigators. C.F.-G. and P.-Y.S. received compensation from Pfizer to perform the neutralization assay.

Additional information
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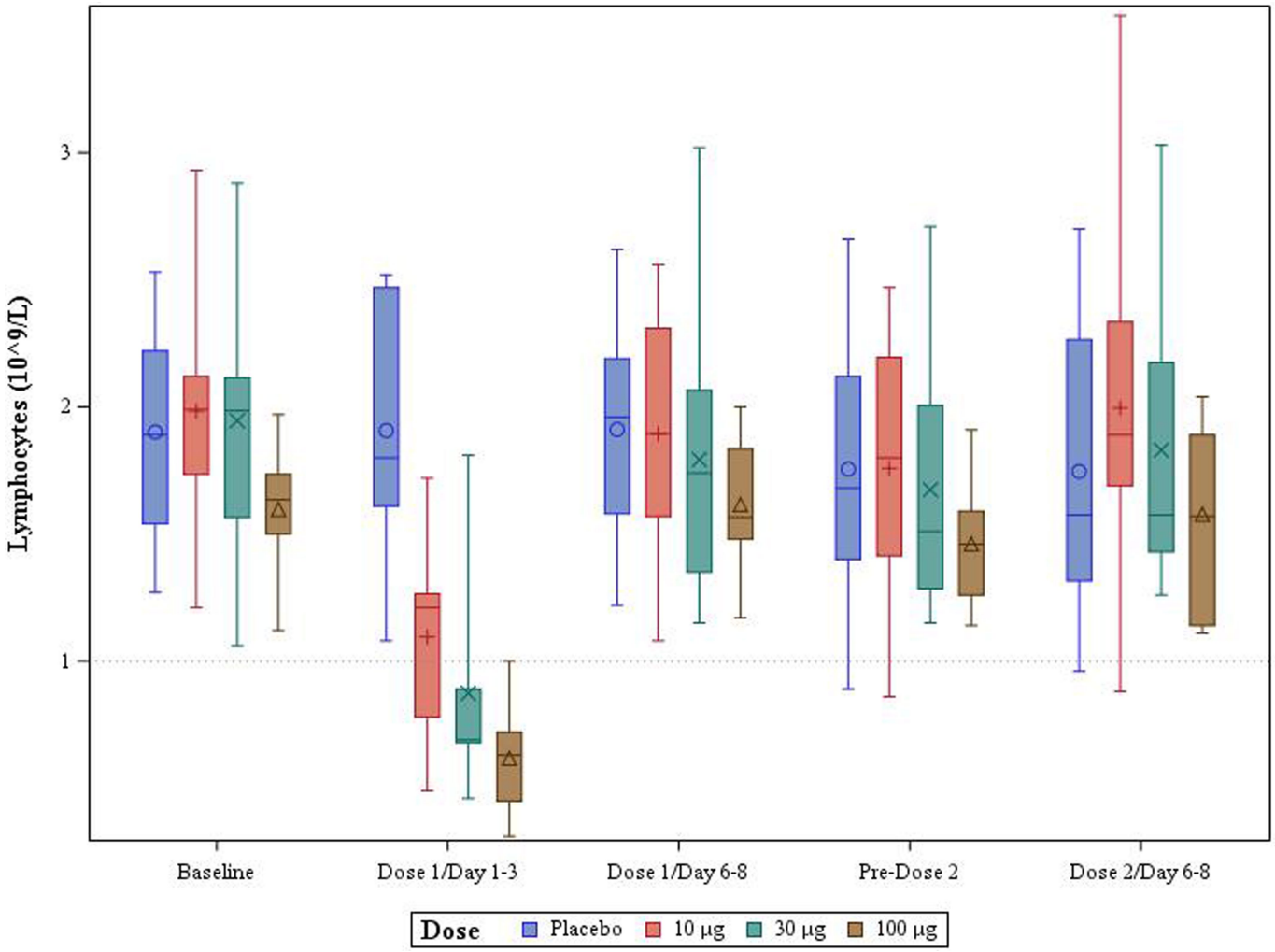

Extended Data Fig. 1 | Post vaccination changes in lymphocyte count over time. The following time points are shown: dose 1/day 1–3, around 1 day after dose 1; dose 1/day 6–8, around 7 days after dose 1; pre-dose 2, before dose 2; dose 2/day 6–8, around 7 days after dose 2. Symbols denote group means; circle, placebo; plus, 10 µg; cross, 30 µg; triangle, 100 µg. The box-and-whisker plots show the median (centre), first and third quartiles (lower and upper edges), and minimum and maximum values (lower and upper whiskers).

Extended Data Table 1 | Demographic characteristics

	10 µg (N=12) n (%)	30 µg (N=12) n (%)	100 µg (N=12) n (%)	Placebo (N=9) n (%)	Total (N=45) n (%)
Sex					
Male	7 (58.3)	6 (50.0)	5 (41.7)	5 (55.6)	23 (51.1)
Female	5 (41.7)	6 (50.0)	7 (58.3)	4 (44.4)	22 (48.9)
Race					
White	8 (66.7)	10 (83.3)	11 (91.7)	8 (88.9)	37 (82.2)
Black or African American	1 (8.3)	0	0	0	1 (2.2)
Asian	3 (25.0)	2 (16.7)	1 (8.3)	1 (11.1)	7 (15.6)
Ethnicity					
Hispanic/Latino	1 (8.3)	1 (8.3)	0	0	2 (4.4)
Non-Hispanic/non-Latino	11 (91.7)	10 (83.3)	12 (100.0)	9 (100.0)	42 (93.3)
Not reported	0	1 (8.3)	0	0	1 (2.2)
Age at vaccination (years)					
Mean (SD)	29.4 (6.39)	35.8 (9.96)	38.3 (9.34)	39.0 (11.16)	35.4 (9.71)
Median	26.5	33.5	38.0	41.0	33.0
Min, max	(24, 42)	(23, 52)	(25, 53)	(19, 54)	(19, 54)

N, the number of participants in the specified group or the total sample. This value is the denominator for the percentage calculations. *n*, the number of participants with the specified characteristic.

Extended Data Table 2 | Adverse events

	10 µg (N=12)	30 µg (N=12)	100 µg (N=12)	Placebo (N=9)
Adverse Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any event	6 (50.0)	6 (50.0)	7 (58.3)	1 (11.1)
Related	3 (25.0)	6 (50.0)	6 (50.0)	1 (11.1)
Severe	0	1 (8.3)	1 (8.3)	0
Life-threatening	0	0	0	0
Any serious adverse event	0	0	0	0
Related	0	0	0	0
Severe	0	0	0	0
Life-threatening	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0
Related	0	0	0	0
Severe	0	0	0	0
Life-threatening	0	0	0	0
Death	0	0	0	0

N, the number of participants in the specified group or the total sample. This value is the denominator for the percentage calculations. *n*, the number of participants who reported at least one occurrence of the specified adverse event category. For 'any event', *n* indicates the number of participants who reported at least one occurrence of any adverse event. Related, assessed by the investigator as related to the investigational product.

nature research

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Reporting Summary

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n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Inform (for data collected in the case report form) and electronic diary (Signant Health platform) for participant self reported reactogenicity
Data analysis	SAS 9.4

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical trials/trial data and results for more information

Field-specific reporting

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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size for this interim report was not based on statistical hypothesis testing. A total of 45 participants were enrolled in this part of the study. For the purposes of tolerability and dose escalation study a total of 15 participants (12 receiving vaccine and 3 receiving placebo) was deemed sufficient for a dosing finding phase study.
Data exclusions	All safety and immunogenicity data that were available at the time of the data snapshot were included in the interim report. No data were excluded from the analyses.
Replication	This is an interim report of an ongoing human clinical trial. There was no attempt at replication of study findings
Randomization	This is an randomized controlled trial. Study participants were randomly assigned to a vaccine group using an interactive web based response technology system with each group comprising 15 participants (12 active vaccine recipients and 3 placebo recipients).
Blinding	This is an observer blinded study which is investigator blinded but Sponsor unblinded during Stage 1 (the stage from which data in the manuscript are presented). Investigators were unblinded to group level data but not subject level data for the purposes of interpretation and summary of the results included in this interim report.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP seq
☒	☐ Flow cytometry
☒	☐ MRI based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Study participants were healthy men or women 18 55 years of age. Key exclusion criteria included individuals with known infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus; immunocompromised individuals and those with a history of autoimmune disease; those with increased risk for severe COVID 19; previous clinical or microbiological diagnosis of COVID 19; receipt of medications intended to prevent COVID 19; previous vaccination with any coronavirus vaccine; a positive serological test for SARS CoV 2 IgM and/or IgG at the screening visit; and a SARS CoV 2 NAAT positive nasal swab within 24 hours before study vaccination.
Recruitment	Study participants were recruited at the two individual sites and recruitment strategies were at the discretion of individual sites and could include identification of interested individuals from the sites local database or through advertising in the local community. Once recruited participants were screened for eligibility based on pre specified protocol criteria. Eligible participants were then randomized to vaccine or placebo in a blinded manner. These processes therefore did not led themselves to enrollment biases however participants who did not know about the study may have had less of an opportunity to participate.
Ethics oversight	The study protocol was approved by the western institutional review board for one site and by the Langone Health New York University Institutional IRB prior to enrollment of any participants

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov identifier: NCT04368728
Study protocol	Details of protocol elements can be accessed from clinicaltrials.gov
Data collection	Data were collected at screening (up to 14 days before vaccination) and for randomized participants at the investigative site at baseline, 1 day, 7 days and 21 days, after Dose 1, 7 days after dose 2 and up to 14 days after dose 2. Both safety and/or serum collection for immunogenicity assessments were collected for all stated time points. In addition, reactogenicity data were assessed through participant self reports via an electronic diary for 7 days after dose 1.
Outcomes	In this interim report, the following study primary endpoints are presented: the proportion of participants reporting prompted local reactions, systemic events, and use of antipyretic and/or pain medication within 7 days after vaccination, AEs and serious adverse events (SAEs) (available through up to ~45 days after Dose 1), and the proportion of participants with clinical laboratory abnormalities 1 and 7 days after vaccination and grading shifts in laboratory assessments between baseline and 1 and 7 days after Dose 1 and between Dose 2 and 7 days after Dose 2. Secondary endpoints included: SARS CoV 2 neutralizing geometric mean titers (GMTs); SARS CoV 2 RBD binding IgG geometric mean concentrations (GMCs) 7 and 21 days after Dose 1 and 7 and 14 days after Dose 2

ORIGINAL ARTICLE

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates

Edward E. Walsh, M.D., Robert W. Frenck, Jr., M.D., Ann R. Falsey, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., Kathleen Neuzil, M.D., Mark J. Mulligan, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Ping Li, Ph.D., Kenneth Koury, Ph.D., Warren Kalina, Ph.D., David Cooper, Ph.D., Camila Fontes-Garfias, B.Sc., Pei-Yong Shi, Ph.D., Özlem Türeci, M.D., Kristin R. Tompkins, B.Sc., Kirsten E. Lyke, M.D., Vanessa Raabe, M.D., Philip R. Dormitzer, M.D., Kathrin U. Jansen, Ph.D., Uğur Şahin, M.D., and William C. Gruber, M.D.

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and the resulting disease, coronavirus disease 2019 (Covid-19), have spread to millions of persons worldwide. Multiple vaccine candidates are under development, but no vaccine is currently available. Interim safety and immunogenicity data about the vaccine candidate BNT162b1 in younger adults have been reported previously from trials in Germany and the United States.

METHODS

In an ongoing, placebo-controlled, observer-blinded, dose-escalation, phase 1 trial conducted in the United States, we randomly assigned healthy adults 18 to 55 years of age and those 65 to 85 years of age to receive either placebo or one of two lipid nanoparticle–formulated, nucleoside-modified RNA vaccine candidates: BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor–binding domain; or BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation. The primary outcome was safety (e.g., local and systemic reactions and adverse events); immunogenicity was a secondary outcome. Trial groups were defined according to vaccine candidate, age of the participants, and vaccine dose level (10 μg, 20 μg, 30 μg, and 100 μg). In all groups but one, participants received two doses, with a 21-day interval between doses; in one group (100 μg of BNT162b1), participants received one dose.

RESULTS

A total of 195 participants underwent randomization. In each of 13 groups of 15 participants, 12 participants received vaccine and 3 received placebo. BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults. In both younger and older adults, the two vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titers, which were similar to or higher than the geometric mean titer of a panel of SARS-CoV-2 convalescent serum samples.

CONCLUSIONS

The safety and immunogenicity data from this U.S. phase 1 trial of two vaccine candidates in younger and older adults, added to earlier interim safety and immunogenicity data regarding BNT162b1 in younger adults from trials in Germany and the United States, support the selection of BNT162b2 for advancement to a pivotal phase 2–3 safety and efficacy evaluation. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

From the University of Rochester and Rochester General Hospital, Rochester (E.E.W., A.R.F.), Vaccine Research and Development, Pfizer, Pearl River (J.A., A.G., K.A.S., K.K., W.K., D.C., K.R.T., P.R.D., K.U.J., W.C.G.), and New York University Langone Vaccine Center and Grossman School of Medicine, New York (M.J.M., V.R.) — all in New York; Cincinnati Children's Hospital, Cincinnati (R.W.F.); Vaccine Research and Development, Pfizer, Hurley, United Kingdom (N.K., S.L., R.B.); the University of Maryland School of Medicine, Center for Vaccine Development and Global Health, Baltimore (K.N., K.E.L.); Vaccine Research and Development, Pfizer, Collegeville, PA (P.L.); the University of Texas Medical Branch, Galveston (C.F.-G., P.-Y.S.); and BioNTech, Mainz, Germany (Ö.T., U.Ş.). Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

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Since the first cases of coronavirus disease 2019 (Covid-19) in Wuhan, China, in December 2019, pandemic illness has spread to millions of persons worldwide. An increased risk of severe disease and death has been noted among the elderly and among persons with preexisting medical conditions. No Covid-19 vaccines are currently available, and they are urgently needed to combat escalating cases and deaths worldwide.[1]

In response, BioNTech and Pfizer launched a coordinated program to compare four RNA-based Covid-19 pandemic vaccine candidates in umbrella-type clinical studies conducted in Germany (BNT162-01) and the United States (C4591001). The program was designed to support the selection of a single vaccine candidate and dose level for a pivotal international safety and efficacy trial. On the basis of initial clinical-trial results in Germany,[2] two lipid nanoparticle–formulated,[3] nucleoside-modified RNA (modRNA)[4] vaccine candidates against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were evaluated in the phase 1 portion of the trial in the United States.[5] One of these candidates, BNT162b1, encodes the SARS-CoV-2 receptor–binding domain, trimerized by the addition of a T4 fibritin foldon domain to increase its immunogenicity through multivalent display.[6-8] The other candidate, BNT162b2, encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation[9] and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact.[10]

Previous articles have described the assessment of BNT162b1, at multiple dose levels, in healthy adults 18 to 55 years of age.[2,5] These studies indicated that dose levels of BNT162b1 that elicited an acceptable level of reactogenicity also efficiently elicited titers that were as high as those in a panel of SARS-CoV-2 human convalescent serum samples and that were broadly neutralizing across a panel of 17 SARS-CoV-2 pseudoviruses representing a diversity of circulating strains. BNT162b1 also elicited CD4+ type 1 helper T (Th1) cell responses and strong interferon-γ–producing and interleukin-2–producing CD8+ cytotoxic T-cell responses. This ability to elicit both humoral and cell-mediated antiviral mechanisms makes BNT162b1 a promising vaccine candidate.

Here, we report the full set of safety and immunogenicity data from the phase 1 portion of an ongoing randomized, placebo-controlled, observer-blinded, dose-escalation trial in the United States that was used to select the final vaccine candidate, as well as the comparison of the safety and immunogenicity of both vaccine candidates and additional phase 1 data that have been collected since candidate selection. These data include evaluation of the 10-μg, 20-μg, and 30-μg dose levels of BNT162b1 and BNT162b2 in adults 18 to 55 years of age and adults 65 to 85 years of age.

METHODS

TRIAL OBJECTIVES, PARTICIPANTS, AND OVERSIGHT

We assessed the safety and immunogenicity of three dose levels of BNT162b1 and BNT162b2. Healthy adults 18 to 55 years of age or 65 to 85 years of age were eligible for inclusion. Key exclusion criteria were known infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus; an immunocompromised condition; a history of autoimmune disease; a previous clinical or microbiologic diagnosis of Covid-19; the receipt of medications intended to prevent Covid-19; any previous coronavirus vaccination; positive test for SARS-CoV-2 IgM or IgG at the screening visit; and positive nasal-swab results on a SARS-CoV-2 nucleic acid amplification test within 24 hours before the receipt of trial vaccine or placebo.

BioNTech was the regulatory sponsor of the trial. Pfizer was responsible for the trial design; for the collection, analysis, and interpretation of the data; and for the writing of the report. The corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit the manuscript for publication. All the trial data were available to all the authors.

TRIAL PROCEDURES

Using an interactive Web-based response technology system, we randomly assigned trial participants to groups defined according to the vaccine candidate, dose level, and age range. Groups of participants 18 to 55 years of age and 65 to 85 years of age were to receive doses of 10 μg, 20 μg, or 30 μg of BNT162b1 or BNT162b2 (or placebo) on a two-dose schedule; one group of participants

18 to 55 years of age was assigned to receive 100-μg doses of BNT162b1 or placebo. All the participants were assigned to receive two 0.5-ml injections of active vaccine (BNT162b1 or BNT162b2) or placebo into the deltoid, administered 21 days apart.

The first five participants in each new dose level or age group (with a randomization ratio of 4:1 for active vaccine:placebo) were observed for 4 hours after the injection to identify immediate adverse events. All the other participants were observed for 30 minutes. Blood samples were obtained for safety and immunogenicity assessments.

SAFETY

The primary end points in phase 1 of this trial were solicited local reactions (i.e., specific local reactions as prompted by and recorded in an electronic diary), systemic events, and use of antipyretic or pain medication within 7 days after the receipt of vaccine or placebo, as prompted by and recorded in an electronic diary; unsolicited adverse events and serious adverse events (i.e., those reported by the participants, without electronic-diary prompts), assessed from the receipt of the first dose through 1 month and 6 months, respectively, after the receipt of the second dose; clinical laboratory abnormalities, assessed 1 day and 7 days after the receipt of vaccine or placebo; and grading shifts in laboratory assessments between baseline and 1 day and 7 days after the first dose and between 2 days and 7 days after the second dose. Protocol-specified safety stopping rules were in effect for all the participants in the phase 1 portion of the trial. The full protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. An internal review committee and an external data and safety monitoring committee reviewed all safety data.

IMMUNOGENICITY

Immunogenicity assessments (SARS-CoV-2 serum neutralization assay and receptor-binding domain [RBD]–binding or S1-binding IgG direct Luminex immunoassays) were conducted before the administration of vaccine or placebo, at 7 days and 21 days after the first dose, and at 7 days (i.e., day 28) and 14 days (i.e., day 35) after the second dose. The neutralization assay, which also generated previously described virus-neutralization data from trials of the BNT162 candidates,[2,5] used a previously described strain of SARS-CoV-2 (USA_WA1/2020) that had been generated by reverse genetics and engineered by the insertion of an mNeonGreen gene into open reading frame 7 of the viral genome.[11,12] The 50% neutralization titers and 90% neutralization titers were reported as the interpolated reciprocal of the dilutions yielding 50% and 90% reductions, respectively, in fluorescent viral foci. Any serologic values below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation. Available serologic results were included in the analysis.

Immunogenicity data from a human convalescent serum panel were included as a benchmark. A total of 38 serum samples were obtained from donors 18 to 83 years of age (median age, 42.5 years) who had recovered from SARS-CoV-2 infection or Covid-19; samples were obtained at least 14 days after a polymerase chain reaction–confirmed diagnosis and after symptom resolution. Neutralizing geometric mean titers (GMTs) in subgroups of the donors were as follows: 90, among 35 donors with symptomatic infections; 156, among 3 donors with asymptomatic infection; and 618, in 1 donor who was hospitalized. Each serum sample in the panel was from a different donor. Thus, most of the serum samples were obtained from persons with moderate Covid-19 who had not been hospitalized. The serum samples were obtained from Sanguine Biosciences, the MT Group, and Pfizer Occupational Health and Wellness.

STATISTICAL ANALYSIS

We report descriptive results of safety and immunogenicity analyses, and the sample size was not based on statistical hypothesis testing. Results of the safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after the administration of vaccine or placebo, according to terms in the *Medical Dictionary for Regulatory Activities*, version 23.0, for each vaccine group. Summary statistics are provided for abnormal laboratory values and grading shifts. Given the small number of participants in each group, the trial was not powered for formal statistical comparisons between dose levels or between age groups.

Immunogenicity analyses of SARS-CoV-2 serum neutralizing titers, S1-binding IgG and RBD-binding IgG concentrations, GMTs, and geometric

mean concentrations (GMCs) were computed along with associated 95% confidence intervals. The GMTs and GMCs were calculated as the mean of the assay results after the logarithmic transformation was made; we then exponentiated the mean to express results on the original scale. Two-sided 95% confidence intervals were obtained by performing logarithmic transformations of titers or concentrations, calculating the 95% confidence interval with reference to Student's t-distribution, and then exponentiating the limits of the confidence intervals.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF THE PARTICIPANTS

Between May 4, 2020, and June 22, 2020, a total of 332 healthy adults (men and nonpregnant women) underwent screening at four sites in the United States (two sites per vaccine candidate). A total of 195 participants were randomly assigned to 13 groups comprising 15 participants each; in each group, 12 participants received vaccine and 3 received placebo (Fig. 1). In all groups

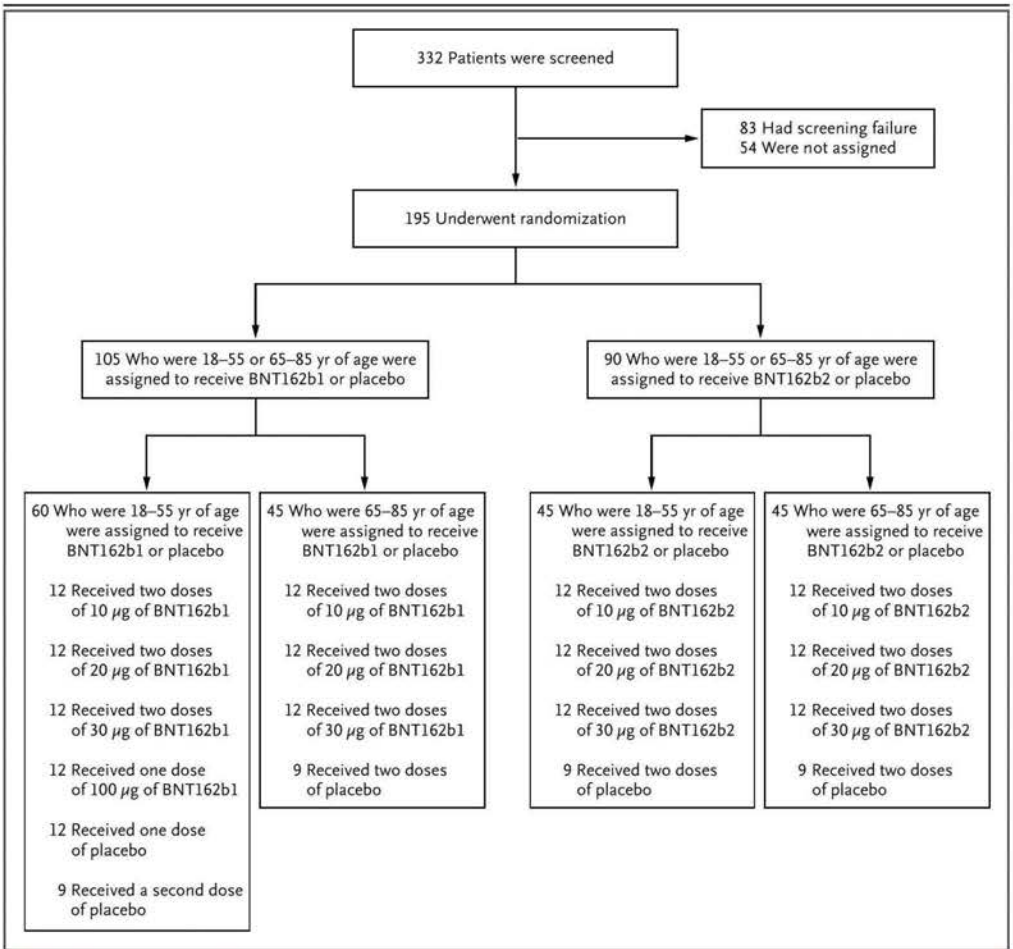

Figure 1. Screening and Randomization of the Participants.

The 54 participants who were not assigned to a trial group were screened but did not undergo randomization because trial enrollment had closed. All the participants received two doses of the vaccine (BNT162b1 or BNT162b2) or placebo, except for the participants who were assigned to receive 100 μg of BNT162b1 or placebo, who received one dose.

Table 1. Demographic Characteristics of the Participants, According to Vaccine Candidate and Age Group.*

Variable	Participants 18–55 Years of Age						Participants 65–85 Years of Age				
	10 μg	20 μg	30 μg	100 μg	Placebo	Total	10 μg	20 μg	30 μg	Placebo	Total
BNT162b1											
No. of participants	12	12	12	12	12	60	12	12	12	9	45
Sex — no. (%)											
Male	7 (58)	9 (75)	6 (50)	5 (42)	7 (58)	34 (57)	4 (33)	4 (33)	4 (33)	1 (11)	13 (29)
Female	5 (42)	3 (25)	6 (50)	7 (58)	5 (42)	26 (43)	8 (67)	8 (67)	8 (67)	8 (89)	32 (71)
Race — no. (%)†											
White	8 (67)	11 (92)	10 (83)	11 (92)	11 (92)	51 (85)	12 (100)	11 (92)	10 (83)	9 (100)	42 (93)
Black	1 (8)	1 (8)	0	0	0	2 (3)	0	1 (8)	0	0	1 (2)
Asian	3 (25)	0	2 (17)	1 (8)	1 (8)	7 (12)	0	0	2 (17)	0	2 (4)
Hispanic ethnic group — no. (%)†	1 (8)	0	1 (8)	0	0	2 (3)	0	0	0	1 (11)	1 (2)
Age — yr‡											
Mean	29.4±6.4	44.8±8.3	35.8±10.0	38.3±9.3	36.3±11.3	36.9±10.2	69.7±5.4	70.6±4.9	69.9±3.6	68.2±3.0	69.7±4.3
Median (range)	26.5 (24–42)	49.0 (30–54)	33.5 (23–52)	38.0 (25–53)	35.0 (19–54)	35.0 (19–54)	68.5 (65–82)	69.0 (65–81)	69.0 (65–77)	68.0 (65–73)	69.0 (65–82)
BNT162b2											
No. of participants	12	12	12	0	9	45	12	12	12	9	45
Sex — no. (%)											
Male	5 (42)	6 (50)	3 (25)	—	5 (56)	19 (42)	2 (17)	5 (42)	6 (50)	4 (44)	17 (38)
Female	7 (58)	6 (50)	9 (75)	—	4 (44)	26 (58)	10 (83)	7 (58)	6 (50)	5 (56)	28 (62)
Race — no. (%)†											
White	11 (92)	10 (83)	9 (75)	—	9 (100)	39 (87)	12 (100)	12 (100)	12 (100)	9 (100)	45 (100)
Black	0	2 (17)	1 (8)	—	0	3 (7)	0	0	0	0	0
Asian	1 (8)	0	2 (17)	—	0	3 (7)	0	0	0	0	0
Hispanic ethnic group — no. (%)†	1 (8)	1 (8)	0	—	0	2 (4)	0	0	0	0	0
Age — yr‡											
Mean	36.8±12.2	37.6±10.1	37.3±9.8	—	34.4±13.2	36.7±11.0	68.0±2.9	71.0±5.8	68.5±2.8	70.0±3.8	69.3±4.1
Median (range)	37.0 (21–53)	38.0 (23–53)	36.5 (23–54)	—	30.0 (19–53)	37.0 (19–54)	67.0 (65–73)	68.5 (65–81)	68.0 (65–74)	69.0 (65–77)	68.0 (65–81)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participant.
‡ The age of the participants was the age at the time of the injection.

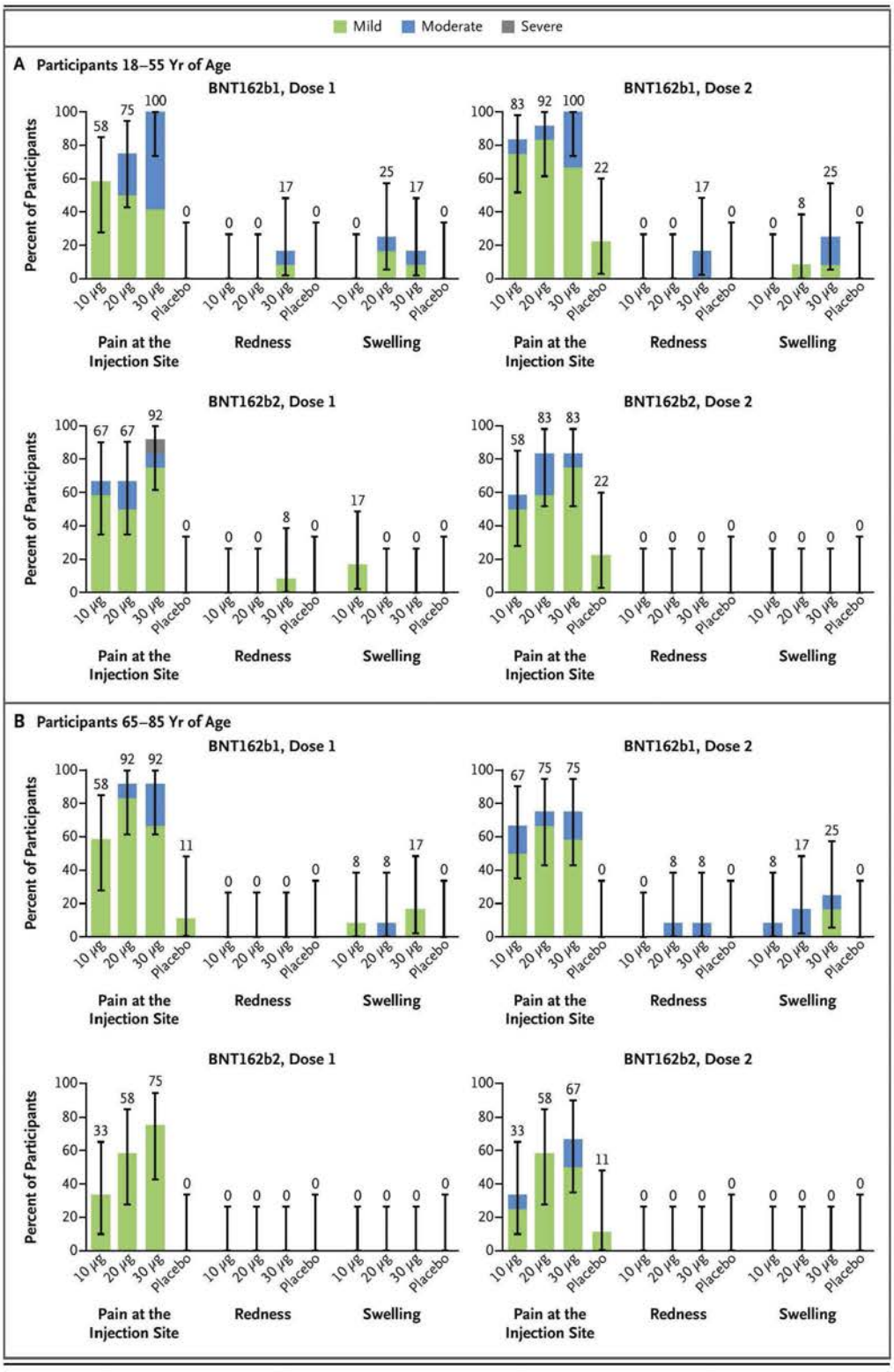

Figure 2 (facing page). Local Reactions Reported within 7 Days after the Administration of Vaccine or Placebo, According to Age Group.

Panel A shows local reactions in participants 18 to 55 years of age, and Panel B those in participants 65 to 85 years of age. Injection-site (local) reactions were recorded in electronic diaries for 7 days after each injection. Pain at the injection site was graded as mild (does not interfere with activity), moderate (interferes with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). Redness and swelling were graded as mild (2.0 to 5.0 cm in diameter), moderate (>5.0 to 10.0 cm in diameter), severe (>10.0 cm in diameter), or grade 4 (necrosis or exfoliative dermatitis for redness and necrosis for swelling). I bars represent 95% confidence intervals. The numbers above the I bars show the overall percentage of the participants in each group who reported the specified local reaction. No participant who received either vaccine candidate reported a grade 4 local reaction.

but one, all the participants who underwent randomization received the assigned two doses of vaccine or placebo. Participants 18 to 55 years of age who had been assigned to receive 100 μg of BNT162b1 or placebo received one dose; the second dose was not administered because of reactogenicity in the participants who received active vaccine.[5]

The majority of participants were White (67 to 100%) and non-Hispanic (89 to 100%) (Table 1). More older women than older men participated. The median age among the younger participants was 35 years in the BNT162b1 group and 37 years in the BNT162b2 group; the median age among the older participants was 69 years and 68 years, respectively.

SAFETY

Local Reactions

Participants 18 to 55 years of age who received 10 μg, 20 μg, or 30 μg of BNT162b1 reported mild-to-moderate local reactions, primarily pain at the injection site, within 7 days after an injection; the local reactions were more frequent after the second dose.[2,5] BNT162b1 elicited local reactions in similar proportions of the participants in the younger age group and in the older age group. Among the older participants, mild-to-moderate injection-site pain was reported by 92% after the first dose and by 75% after the second dose (Fig. 2). A similar pattern was observed after vaccination with BNT162b2. No older participant who received BNT162b2 reported redness or swelling. No participant who received either BNT162 vaccine candidate reported a grade 4 local reaction.

Systemic Events

Participants 18 to 55 years of age who received 10 μg, 20 μg, or 30 μg of BNT162b1 frequently had mild-to-moderate fever and chills, with 75% of the participants reporting a temperature of 38.0°C or higher after the second 30-μg dose (Fig. 3; and Fig. S1 in the Supplementary Appendix, available at NEJM.org).[5] In participants 65 to 85 years of age who received BNT162b1, systemic events were milder than in the younger participants, although many older participants reported fatigue and headache after the first or second dose, and 33% reported a temperature of 38°C or higher after the second dose, including one older participant who reported a fever of 38.9 to 40.0°C (Fig. 3 and Fig. S2). As was observed with local reactions, systemic events were dose-dependent (greater after the second dose than after the first dose) and transient. Symptoms generally peaked by day 2 after vaccination and resolved by day 7.

Systemic events in response to BNT162b2 were milder than those in response to BNT162b1 (Fig. 3 and Figs. S1 and S2). For example, 17% of the participants 18 to 55 years of age and 8% of those 65 to 85 years of age reported fever (≥38.0 to 38.9°C) after the second dose of 30 μg of BNT162b2. Severe systemic events (fatigue, headache, chills, muscle pain, and joint pain) were reported in small numbers of younger recipients of BNT162b2, but no severe systemic events were reported by older recipients of this vaccine candidate. No participant who received either BNT162 vaccine candidate reported a grade 4 systemic event. After the first dose, systemic events that were reported by participants 65 to 85 years of age who received BNT162b2 were similar to those reported by participants who received placebo.

In both age groups and for both vaccine candidates, the use of antipyretic or pain medication increased with increasing dose level and with the number of doses administered. Fewer BNT162b2 recipients than BNT162b1 recipients reported using antipyretic or pain medication.

Adverse Events and Shifts in Laboratory Values

Through 1 month after the receipt of the second dose, adverse events that were considered by the

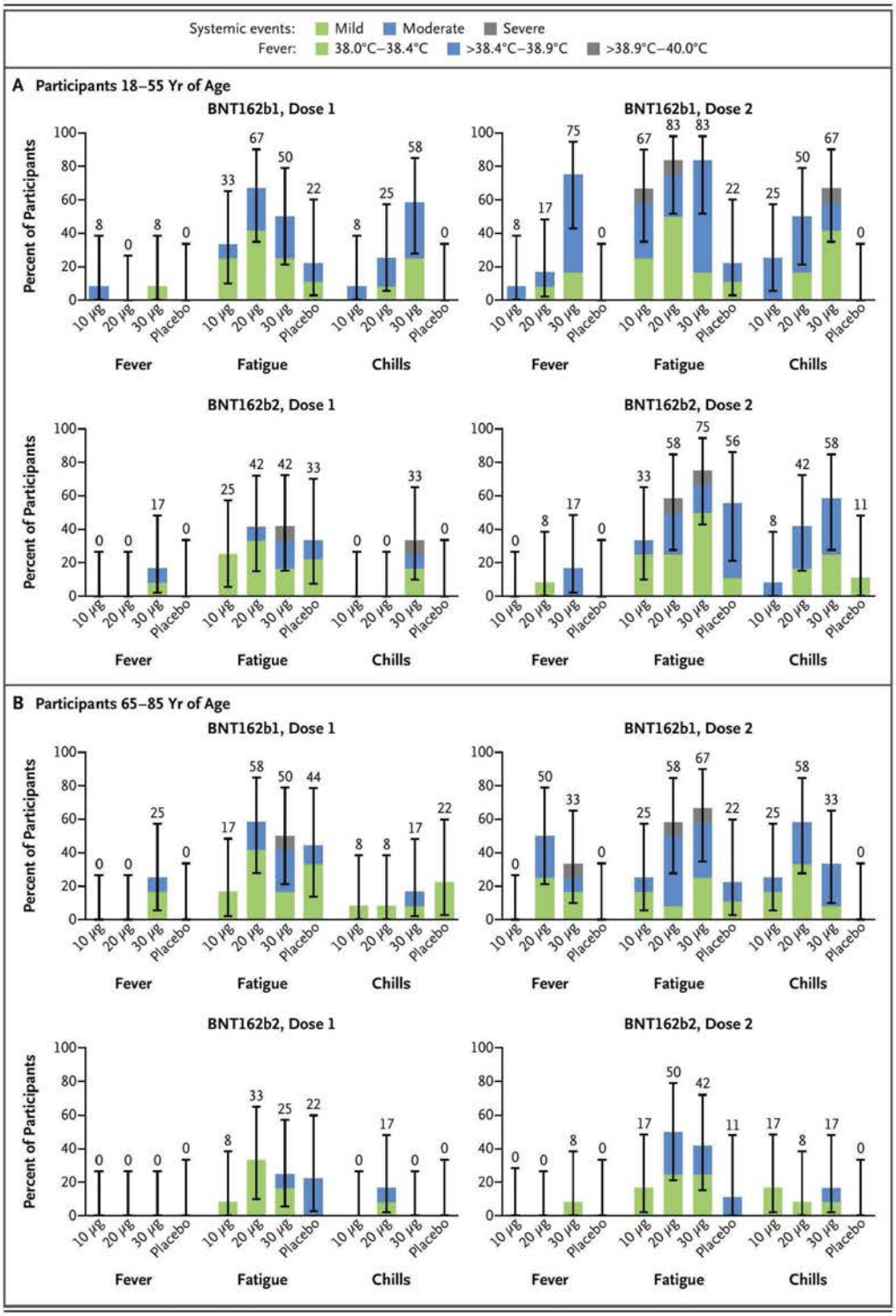

Figure 3 (facing page). Selected Systemic Events Reported within 7 Days after the Administration of Vaccine or Placebo, According to Age Group.

Panel A shows systemic reactions in participants 18 to 55 years of age, and Panel B those in participants 65 to 85 years of age. Data on fever, chills, and fatigue are reported here. (Data on headache, vomiting, diarrhea, muscle pain, and joint pain are reported in Fig. S1.) Data on systemic events were recorded in electronic diaries for 7 days after each injection. The fever scale is shown in the key. Chills and fatigue were graded as being mild (does not interfere with activity), moderate (interferes somewhat with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). I bars represent 95% confidence intervals. The numbers above the I bars show the overall percentage of participants in each group who reported the specified systemic event. No participant who received either vaccine candidate reported a grade 4 systemic event or a temperature higher than 40.0°C.

investigators to be related to vaccine or placebo were reported by 50% of the participants 18 to 55 years of age who received 30 μg of BNT162b1, as compared with 8% of those who received placebo.[5] Adverse events that were considered to be related to vaccine were reported by 17% of the participants 65 to 85 years of age who received 30 μg of BNT162b1 and by 25% of the participants 18 to 55 years of age who received 30 μg of BNT162b2. No participant 65 to 85 years of age who received 30 μg of BNT162b2 reported a related adverse event (Table S1).

No serious adverse events were reported, and no stopping rules were met as of the time of this report. The largest changes from baseline in laboratory values were transient decreases in lymphocyte counts, which resolved within 1 week after vaccination (Fig. S3) and which were not associated with clinical manifestations.

IMMUNOGENICITY

The serologic responses elicited by BNT162b1 and BNT162b2 were similar (Fig. 4). Two serum samples, both from the group of participants 18 to 55 years of age who received 30 μg of BNT162b2, were obtained outside the specified time windows (one each at day 28 and day 35) and thus were excluded from the reported immunogenicity analysis. Antigen-binding IgG and virus-neutralizing responses to vaccination with 10 μg to 30 μg of BNT162b1 or BNT162b2 were boosted by the second dose in both the younger adults[2,5] and the older adults. Both vaccines elicited generally lower antigen-binding IgG and virus-neutralizing responses in participants 65 to 85 years of age than in those 18 to 55 years of age. Higher doses appeared to elicit somewhat higher antibody responses.

The highest neutralization titers were measured in samples obtained on day 28 (i.e., 7 days after the second dose) or on day 35 (i.e., 14 days after the second dose). Similar trends were observed for the 50% and 90% neutralizing titers (Fig. S4). The 50% neutralizing GMTs for the two vaccine candidates at the 30-μg dose level on day 28 or day 35 ranged from 1.7 to 4.6 times the GMT of the convalescent serum panel among participants 18 to 55 years of age and from 1.1 to 2.2 times the GMT of the convalescent serum panel among those 65 to 85 years of age. With 10 to 12 valid results per assay from samples that could be evaluated for each group at each time point, pair-wise comparisons are subject to error and have no clear interpretation.

DISCUSSION

Previously reported data from vaccination with 10 μg or 30 μg of BNT162b1 in adults 18 to 55 years of age suggested that it could be a promising Covid-19 vaccine candidate.[2,5] Consistent with our strategy to evaluate several RNA vaccine candidates and make a data-driven decision to advance the candidate with the best safety and immunogenicity profile, we compared clinical data obtained after vaccination with BNT162b1,[2,5] which encodes the RBD, with data obtained after vaccination with BNT162b2, which encodes the full-length spike. The data presented here include those that guided our decision to advance BNT162b2 at the 30-μg dose level to the phase 2–3, international trial to evaluate its safety and efficacy in participants 18 to 85 years of age.

The primary consideration driving this decision was the milder systemic reactogenicity profile of BNT162b2, particularly in older adults, in the context of the similar antibody responses elicited by the two candidate vaccines. Short-lived decreases in postvaccination lymphocyte counts had no associated clinical effect, were observed

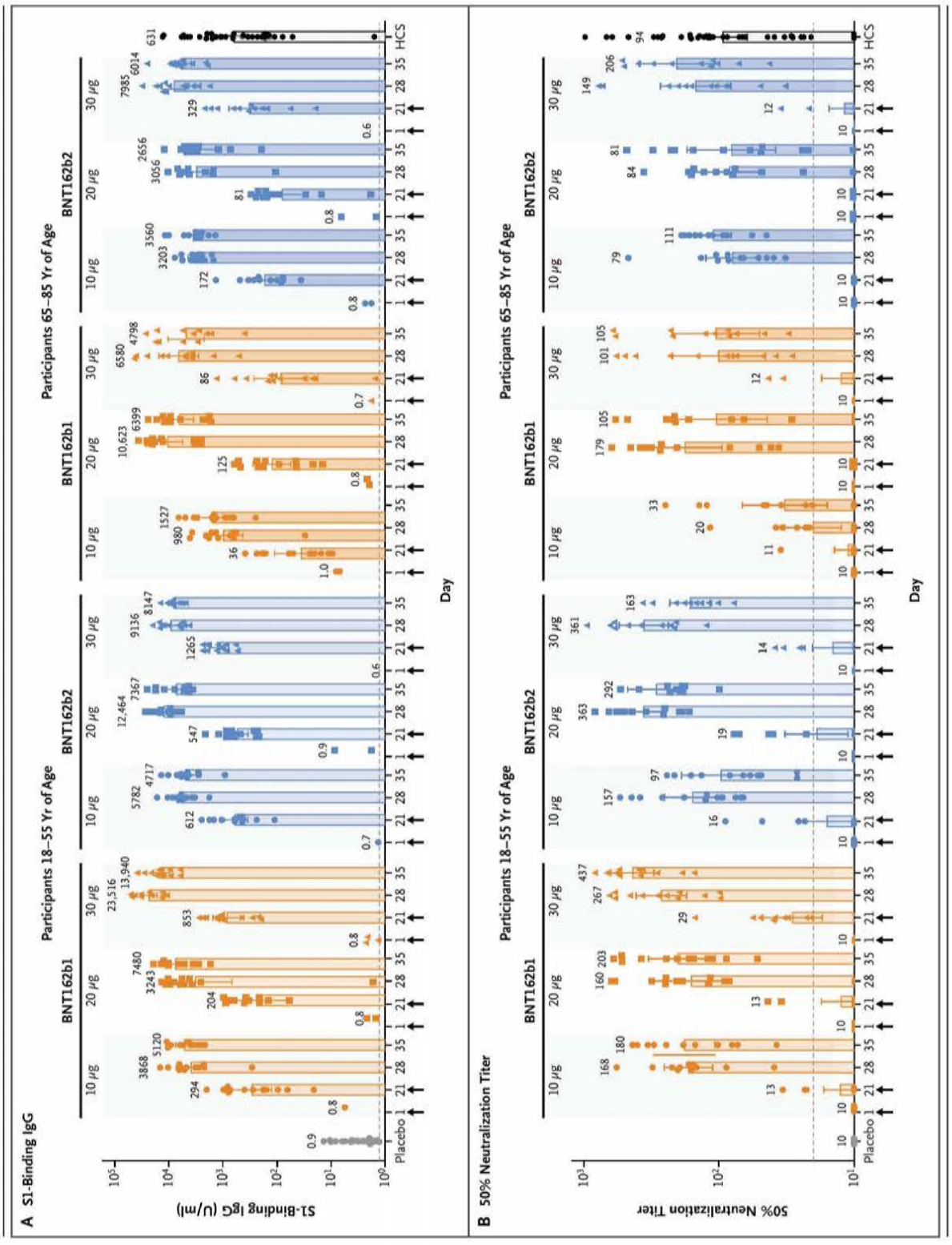

Figure 4 (facing page). Immunogenicity of BNT162b1 and BNT162b2.

Participants in groups of 15 received an injection with the indicated dose levels of one of either of the BNT162 vaccine candidates (12 participants) or placebo (3 participants) on days 1 and 21. Arrows indicate days of vaccination. Responses in the placebo recipients in each of the dose-level groups are combined. Serum samples were obtained before injection (on day 1) and on days 21, 28, and 35 after the first dose. The blood samples obtained on days 28 and 35 are those obtained 7 days and 14 days, respectively, after the second dose. Human coronavirus disease 2019 (Covid-19) or SARS-CoV-2 infection convalescent serum (HCS) samples were obtained from 38 donors at least 14 days after polymerase chain reaction–confirmed diagnosis and at a time when the donors were asymptomatic. Panel A shows the geometric mean concentrations of recombinant S1-binding IgG (lower limit of quantitation, 1.267; dashed line), and Panel B the 50% SARS-CoV-2–neutralizing geometric mean titers (lower limit of quantitation, 20; dashed line). On days that vaccine or placebo was administered, samples were obtained before the injection. Each data point represents a serum sample, and the top of each vertical bar represents the geometric mean with the 95% confidence interval (I bar). Data points associated with placebo, HCS samples, or the 10-μg dose of vaccine are shown as circles, those for the 20-μg dose as squares, and those for the 30-μg dose as triangles. The numbers above the bars show the geometric mean concentration or geometric mean titer in the group. All the vaccine groups had 12 valid results from samples that could be evaluated at each time point except for the following: among participants who received BNT162b2, 11 results from day 28 in younger participants who received 30 μg, 10 results from day 35 in younger participants who received 30 μg, and 11 results from day 35 in older participants who received 10 μg.

across the age groups, and probably reflect a temporary redistribution of lymphocytes from the bloodstream to lymphoid tissues as a functional response to immune stimulation by the vaccine.[13-16] The immune response and toxicity profile at the selected, relatively low, 30-μg dose level indicate that the BNT162b2 modRNA vaccine candidate has a favorable balance of reactogenicity and immunogenicity.[17,18]

The composition of the lipid nanoparticles, the formulation components, or the sequence selection for the vaccine RNA could influence the side-effect profile. The reason for the lower reactogenicity of BNT162b2 than of BNT162b1 is not certain, given that the two vaccine candidates share the same modRNA platform, RNA production and purification processes, and formulation of lipid nanoparticles. They differ in the nucleotide sequences that encode the vaccine antigens and in the overall size of the RNA constructs, which results in a number of RNA molecules in 30 μg of BNT162b1 that is approximately 5 times as high as that in 30 μg of BNT162b2. The nucleotide composition of RNA has been reported to affect its immune stimulatory activity and reactogenicity profile, and this is a possible explanation for the differences in these vaccine candidates.[19]

The immune responses elicited by BNT162b1 and BNT162b2 were similar. As has been observed with other vaccines and as is probably associated with immunosenescence,[20,21] the immunogenicity of the two vaccine candidates decreased with age, eliciting lower overall humoral responses in adults 65 to 85 years of age than in those 18 to 55 years of age. Nevertheless, at 7 days and 14 days after the second dose, the 50% and 90% neutralizing GMTs that were elicited by 30 μg of BNT162b2 in older adults exceeded those of the convalescent serum panel. Antibody responses in both younger and older adults showed a clear benefit of a second dose.

This trial and interim report have several limitations. First, the relative importance of humoral and cellular immunity with regard to protection from Covid-19 has not yet been fully characterized. Although strong cell-mediated immune responses (Th1-biased CD4+ and CD8+) elicited by BNT162b1 have been observed and reported in the German trial,[2] the cellular immune responses elicited by BNT162b2 are still being studied. Second, although the serum neutralizing responses that were elicited by the vaccine candidates relative to those elicited by natural infection are highly encouraging, the degree of protection against Covid-19 provided by this or any other benchmark is unknown. Third, the phase 1 portion of this trial tested many hypotheses and was not powered to make formal statistical comparisons. Fourth, the human convalescent serum panels that have been used by different vaccine developers are not standardized among laboratories, and each represents a unique distribution of donor characteristics and times of collection. Therefore, the serum panel that we used does not provide a well-controlled benchmark for comparisons of the serologic responses elicited by these two BNT162 vaccine candidates with those elicited by other Covid-19 vaccine candi-

dates. Finally, the participants in this early-stage clinical trial were healthy and had limited racial and ethnic diversity as compared with the general population.

Many of the limitations cited above are being addressed in the international, phase 2–3 portion of this trial. In this later, pivotal part of the trial, we are assessing the safety and efficacy of two doses of 30 μg of BNT162b2 in up to 44,000 participants (randomly assigned in a 1:1 ratio to receive vaccine or placebo) from diverse backgrounds, including persons with stable chronic underlying health conditions, persons at increased risk owing to occupational exposure, and persons from racial and ethnic backgrounds at higher risk for severe Covid-19.[22] We are conducting outreach to recruit trial participants from many backgrounds and are using U.S. Census data to locate trial sites in diverse communities.

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Disclosure forms provide by the authors are available with the full text of the article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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A Quick Take is available at NEJM.org

Coronavirus disease 2019 (COVID-19) has affected tens of millions of people globally[1] since it was declared a pandemic by the World Health Organization on March 11, 2020.[2] Older adults, persons with certain coexisting conditions, and front-line workers are at highest risk for Covid-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 in other populations, including younger adults.[3] Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which has had devastating medical, economic, and social consequences.

We previously reported phase 1 safety and immunogenicity results from clinical trials of the vaccine candidate BNT162b2,[4] a lipid nanoparticle–formulated,[5] nucleoside-modified RNA (modRNA)[6] encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation.[7] Findings from studies conducted in the United States and Germany among healthy men and women showed that two 30-μg doses of BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.[8] The 50% neutralizing geometric mean titers elicited by 30 μg of BNT162b2 in older and younger adults exceeded the geometric mean titer measured in a human convalescent serum panel, despite a lower neutralizing response in older adults than in younger adults. In addition, the reactogenicity profile of BNT162b2 represented mainly short-term local (i.e., injection site) and systemic responses. These findings supported progression of the BNT162b2 vaccine candidate into phase 3.

Here, we report safety and efficacy findings from the phase 2/3 part of a global phase 1/2/3 trial evaluating the safety, immunogenicity, and efficacy of 30 μg of BNT162b2 in preventing Covid-19 in persons 16 years of age or older. This data set and these trial results are the basis for an application for emergency use authorization.[9] Collection of phase 2/3 data on vaccine immunogenicity and the durability of the immune response to immunization is ongoing, and those data are not reported here.

Methods

Trial Objectives, Participants and Oversight

We assessed the safety and efficacy of two 30-μg doses of BNT162b2, administered intramuscularly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript. BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data.

Trial Procedures

With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 μg of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.

Safety

The primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in this report. In this report, safety

data are reported for all participants who provided informed consent and received at least one dose of vaccine or placebo. Per protocol, safety results for participants infected with HIV (196 patients) will be analyzed separately and are not included here.

During the phase 2/3 portion of the study, a stopping rule for the theoretical concern of vaccine-enhanced disease was to be triggered if the one-sided probability of observing the same or a more unfavorable adverse severe case split (a split with a greater proportion of severe cases in vaccine recipients) was 5% or less, given the same true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-COV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Details are provided in the protocol.

An explanation of the various denominator values for use in assessing the results of the trial is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. In brief, the safety population includes persons 16 years of age or older; a total of 43,448 participants constituted the population of enrolled persons injected with the vaccine or placebo. The main safety subset as defined by the FDA, with a median of 2 months of follow-up as of October 9, 2020, consisted of 37,706 persons, and the reactogenicity subset consisted of 8183 persons. The modified intention-to-treat (mITT) efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases). The number of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%.

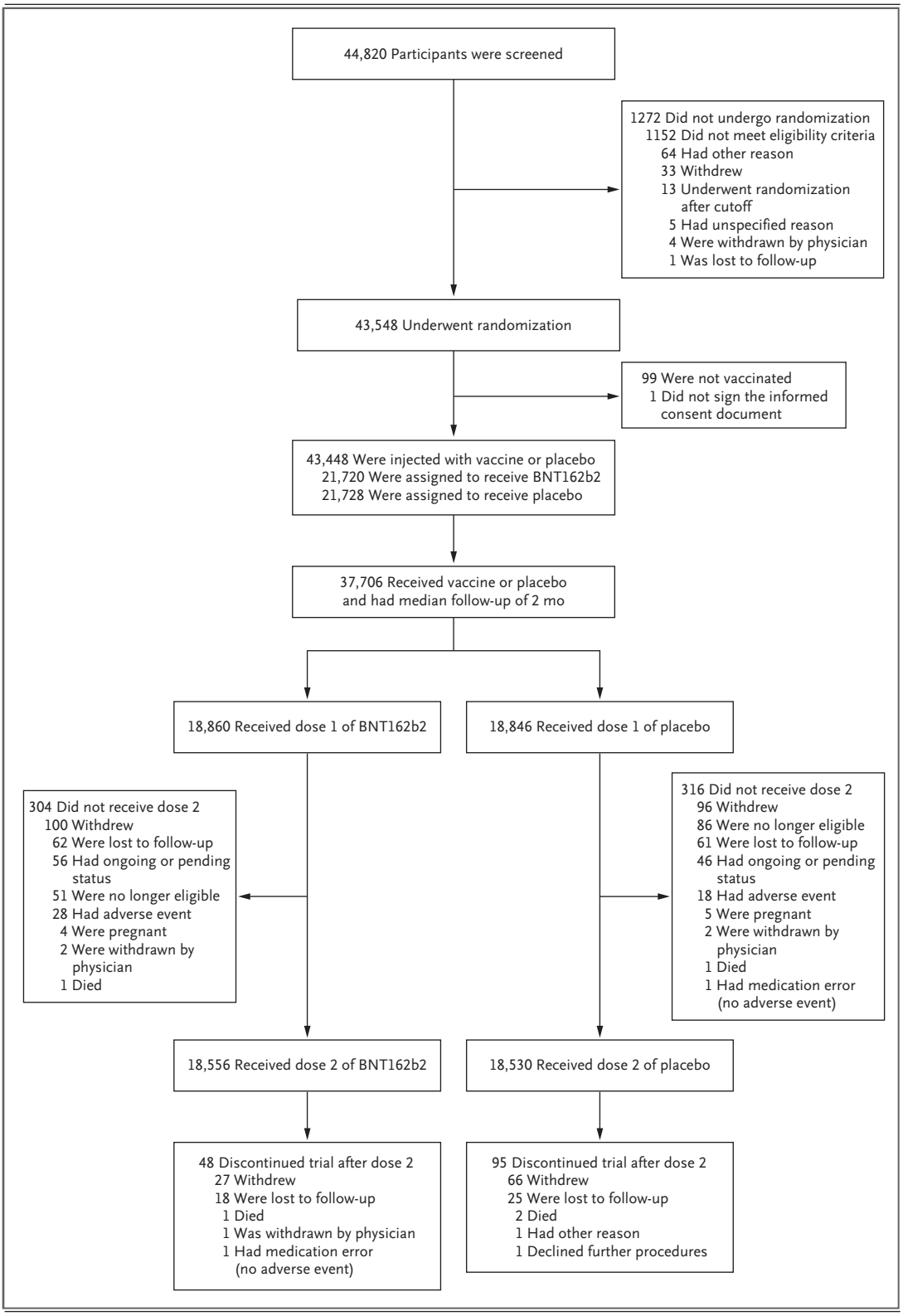


Figure 1 (facing page). Enrollment and Randomization.
The diagram represents all enrolled participants through November 14, 2020. The safety subset (those with a median of 2 months of follow-up, in accordance with application requirements for Emergency Use Authorization) is based on an October 9, 2020, data cutoff date. The further procedures that one participant in the placebo group declined after dose 2 (lower right corner of the diagram) were those involving collection of blood and nasal swab samples.

Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

RESULTS

PARTICIPANTS

Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of

Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

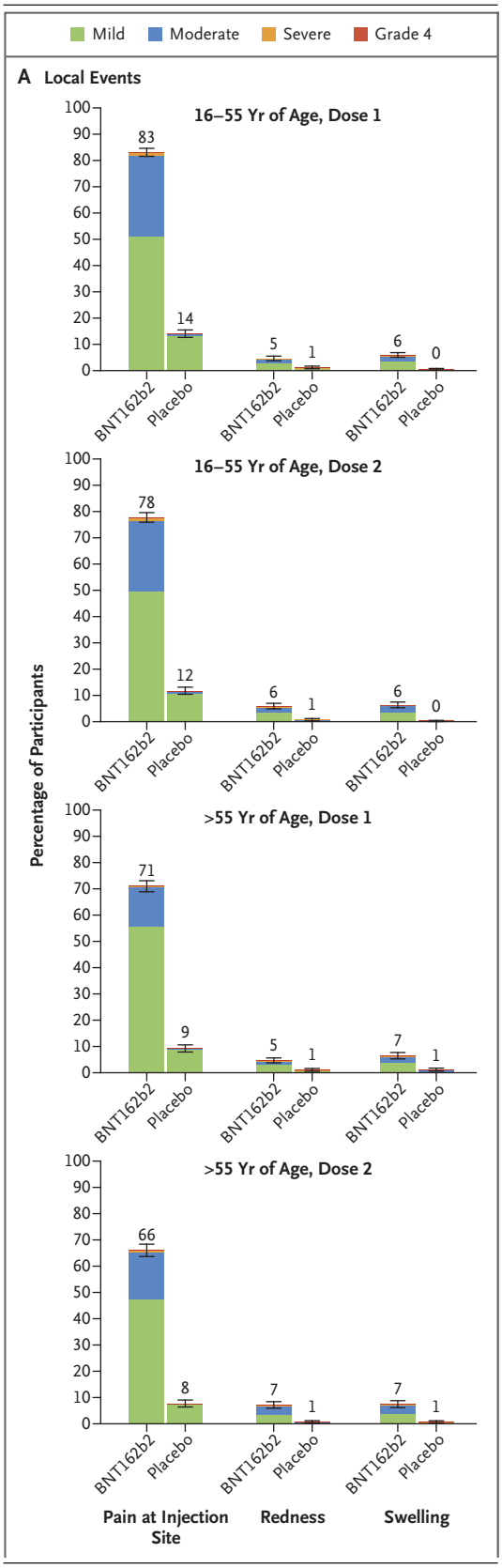


Figure 2. Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.

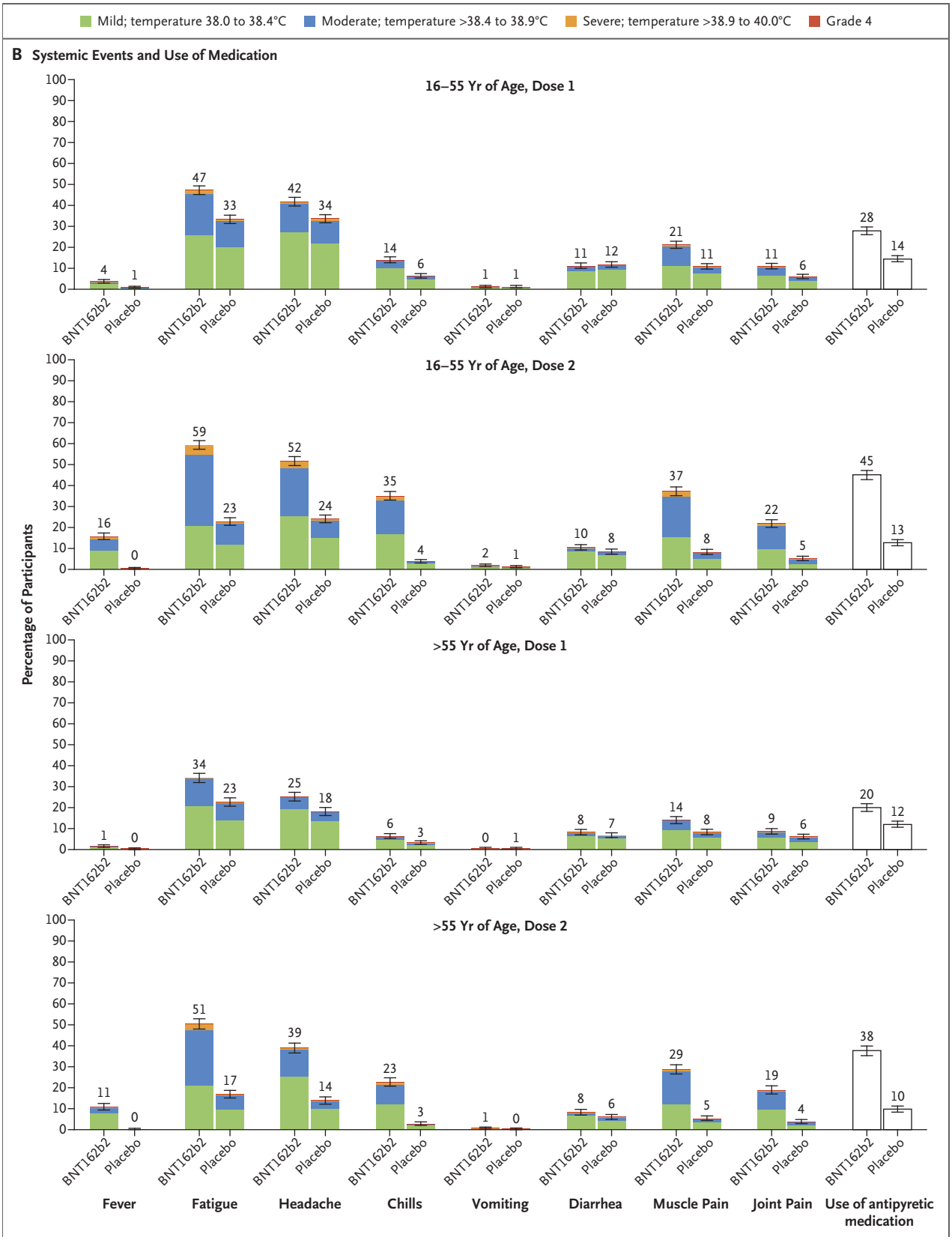
Data on local and systemic reactions and use of medication were collected with electronic diaries from participants in the reactogenicity subset (8,183 participants) for 7 days after each vaccination. Solicited injection-site (local) reactions are shown in Panel A. Pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and grade 4, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Systemic events and medication use are shown in Panel B. Fever categories are designated in the key; medication use was not graded. Additional scales were as follows: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); grade 4 for all events indicated an emergency department visit or hospitalization. I bars represent 95% confidence intervals, and numbers above the I bars are the percentage of participants who reported the specified reaction.

43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo (Fig. 1). At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

SAFETY

Local Reactogenicity

The reactogenicity subset included 8183 participants. Overall, BNT162b2 recipients reported more local reactions than placebo recipients. Among BNT162b2 recipients, mild-to-moderate pain at



the injection site within 7 days after an injection was the most commonly reported local reaction, with less than 1% of participants across all age groups reporting severe pain (Fig. 2). Pain was reported less frequently among participants older than 55 years of age (71% reported pain after the first dose; 66% after the second dose) than among younger participants (83% after the first dose; 78% after the second dose). A noticeably lower percentage of participants reported injection-site redness or swelling. The proportion of participants reporting local reactions did not increase after the second dose (Fig. 2A), and no participant reported a grade 4 local reaction. In general, local reactions were mostly mild-to-moderate in severity and resolved within 1 to 2 days.

Systemic Reactogenicity

Systemic events were reported more often by younger vaccine recipients (16 to 55 years of age) than by older vaccine recipients (more than 55 years of age) in the reactogenicity subset and more often after dose 2 than dose 1 (Fig. 2B). The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older recipients). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose.

Fever (temperature, ≥38°C) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients reported fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Two participants each in the vaccine and placebo groups reported temperatures above 40.0°C. Younger vaccine recipients were more likely to use antipyretic or pain medication (28% after dose 1; 45% after dose 2) than older vaccine recipients (20% after dose 1; 38% after dose 2), and placebo recipients were less likely (10 to 14%) than vaccine recipients to use the medications, regardless of age or dose. Systemic events including fever and chills were observed with the first 1 to 2 days after vaccination and resolved shortly thereafter.

Daily use of the electronic diary ranged from 90 to 93% for each day after the first dose and from 75 to 83% for each day after the second dose. No difference was noted between the BNT162b2 group and the placebo group.

ADVERSE EVENTS

Adverse event analyses are provided for all enrolled 43,252 participants, with variable follow-up time after dose 1 (Table S3). More BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). This distribution largely reflects the inclusion of transient reactogenicity events, which were reported as adverse events more commonly by vaccine recipients than by placebo recipients. Sixty-four vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) reported lymphadenopathy. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Two BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered by the investigators to be related to the vaccine or placebo. No Covid-19–associated deaths were observed. No stopping rules were met during the reporting period. Safety monitoring will continue for 2 years after administration of the second dose of vaccine.

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Ta-

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

ble 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

DISCUSSION

A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19. The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%. These results met our prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum FDA criteria for authorization.[9] Although the study was not powered to definitively assess efficacy by subgroup, the point estimates of efficacy for subgroups based on age, sex, race, ethnicity, body-mass index, or the presence of an underlying condition associated with a high risk of Covid-19 complications are also high. For all analyzed subgroups in which more than 10 cases of Covid-19 occurred, the lower limit of the 95% confidence interval for efficacy was more than 30%.

The cumulative incidence of Covid-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incuba-

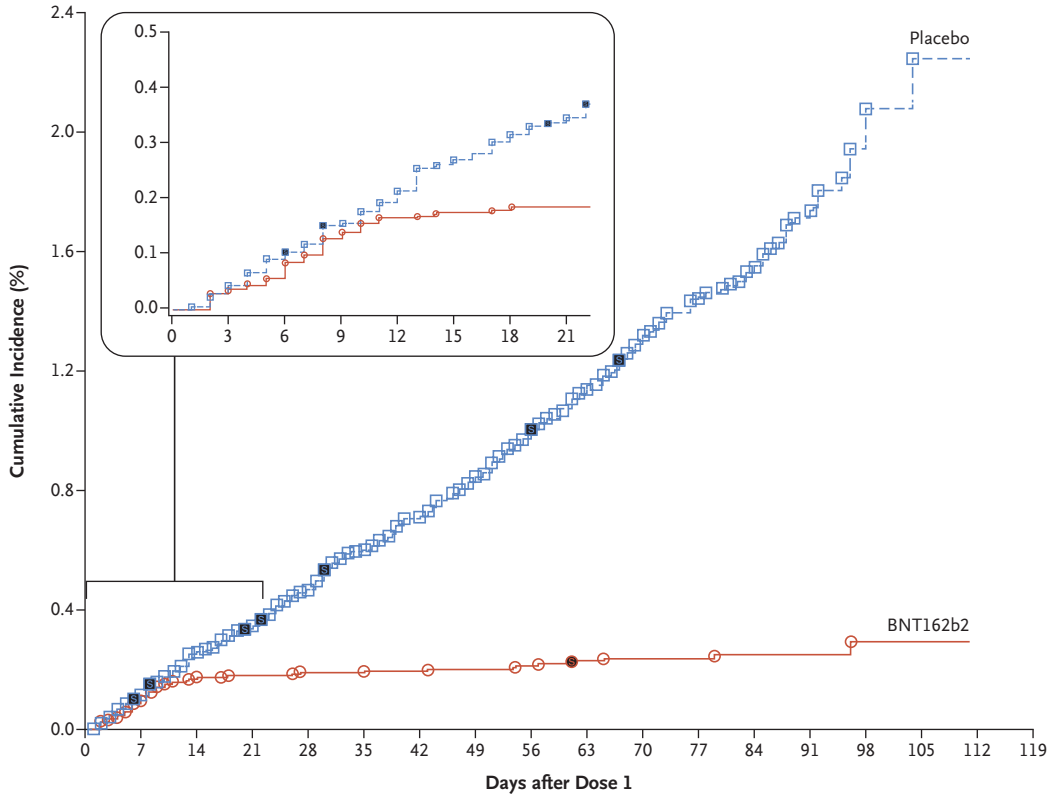
Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI)†
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group‡					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
† The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.
‡ Race or ethnic group was reported by the participants. "All others" included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.

tion period of 5 days,[10] indicating the early onset of a partially protective effect of immunization. The study was not designed to assess the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficacy against Covid-19 was 52%, and in the first 7 days after dose 2, it was 91%, reaching full efficacy against disease with onset at least 7 days after dose 2. Of the 10 cases of severe Covid-19 that were observed after the first dose, only 1 occurred in the vaccine group. This finding is consistent with overall high efficacy against all Covid-19 cases. The severe case split provides preliminary evidence of vaccine-mediated protection against severe disease, alleviating many of the theoretical concerns over vaccine-mediated disease enhancement.[11]

The favorable safety profile observed during phase 1 testing of BNT162b2[4,8] was confirmed in the phase 2/3 portion of the trial. As in phase 1, reactogenicity was generally mild or moderate, and reactions were less common and milder in older adults than in younger adults. Systemic reactogenicity was more common and severe after the second dose than after the first dose, although local reactogenicity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of some vaccines recommended for older adults.[12] This rate of severe fatigue is also lower than that observed in recipients of another approved viral vaccine for older adults.[13] Overall, reactogenicity events were transient and resolved within a couple



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Shown is the cumulative incidence of Covid-19 after the first dose (modified intention-to-treat population). Each symbol represents Covid-19 cases starting on a given day; filled symbols represent severe Covid-19 cases. Some symbols represent more than one case, owing to overlapping dates. The inset shows the same data on an enlarged y axis, through 21 days. Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from the first dose to the end of the surveillance period. The confidence interval (CI) for vaccine efficacy (VE) is derived according to the Clopper–Pearson method.

of days after onset. Lymphadenopathy, which generally resolved within 10 days, is likely to have resulted from a robust vaccine-elicited immune response. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively).

This trial and its preliminary report have several limitations. With approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both

the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later. Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establishment of a correlate of protection has not been feasible at the time of this report.

This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women. Safety and immune response data from this trial after immunization of adolescents 12 to 15 years of age will be reported subsequently, and additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups, such as immunocompromised persons. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage. The current cold storage requirement may be alleviated by ongoing stability studies and formulation optimization, which may also be described in subsequent reports.

The data presented in this report have significance beyond the performance of this vaccine candidate. The results demonstrate that Covid-19 can be prevented by immunization, provide proof of concept that RNA-based vaccines are a promising new approach for protecting humans against infectious diseases, and demonstrate the speed with which an RNA-based vaccine can be developed with a sufficient investment of resources. The development of BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative. This rigorous demonstration of safety and efficacy less than 11 months later provides a practical demonstration that RNA-based vaccines, which require only viral genetic sequence information to initiate development, are a major new tool to combat pandemics and other infectious disease outbreaks. The continuous phase 1/2/3 trial design may provide a model to reduce the protracted development timelines that have delayed the availability of vaccines against other infectious diseases of medical importance. In the context of the current, still expanding pandemic, the BNT162b2 vaccine, if approved, can contribute, together with other public health measures, to reducing the devastating loss of health, life, and economic and social well-being that has resulted from the global spread of Covid-19.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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BRIEF COMMUNICATION

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Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera

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We engineered three severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses containing key spike mutations from the newly emerged United Kingdom (UK) and South African (SA) variants: N501Y from UK and SA; 69/70-deletion + N501Y + D614G from UK; and E484K + N501Y + D614G from SA. Neutralization geometric mean titers (GMTs) of 20 BTN162b2 vaccine-elicited human sera against the three mutant viruses were 0.81- to 1.46-fold of the GMTs against parental virus, indicating small effects of these mutations on neutralization by sera elicited by two BNT162b2 doses.

We previously reported that BNT162b2, a nucleoside-modified RNA vaccine that encodes the SARS-CoV-2 full-length, prefusion-stabilized spike glycoprotein, elicited dose-dependent SARS-CoV-2-neutralizing GMTs that were similar to or higher than the GMT of a panel of SARS-CoV-2 convalescent human serum samples[1]. We subsequently reported that, in a randomized, placebo-controlled trial of approximately 44,000 participants 16 years of age or older, a two-dose regimen of BNT162b2 conferred 95% protection against Coronavirus Disease 2019 (COVID-19)[2].

Since the previously reported studies were conducted, rapidly spreading variants of SARS-CoV-2 have arisen in the UK, SA and other regions[3,4]. These variants have multiple mutations in their spike glycoproteins, which are key targets of virus-neutralizing antibodies. The emerged spike mutations have raised concerns of vaccine efficacy against these new strains. The goal of this study was to examine the effect of several key spike mutations from the UK and SA strains on BNT162b2 vaccine-elicited neutralization.

Using an infectious complementary DNA (cDNA) clone of SARS-CoV-2 (ref. [5]), we engineered three spike mutant viruses on the genetic background of clinical strain USA-WA1/2020 (Supplementary Fig. 1). 1) Mutant N501Y virus contains the N501Y mutation that is shared by both the UK and SA variants. This mutation is located in the viral receptor-binding domain (RBD) for cell entry, increases binding to the angiotensin-converting enzyme 2 receptor and enables the virus to expand its host range to infect mice[5,6]. 2) Mutant Δ69/70 + N501Y + D614G virus contains two additional changes present in the UK variants: amino acid 69 and 70 deletion (Δ69/70) and D614G substitution. Amino acids 69 and 70 are located in the N-terminal domain of the spike S1 fragment; deletion of these residues might allosterically change S1 conformation[6]. The D614G mutation is dominant in circulating strains around the world[7,8]. 3) Mutant E484K + N501Y + D614G virus additionally contains the E484K substitution, which is also located in the viral RBD. The E484K substitution alone confers resistance to several monoclonal antibodies[9,10]. Compared to the wild-type (WT) USA-WA1/2020 strain, the three mutant viruses showed similar plaque morphologies on Vero E6 cells (Supplementary Fig. 2).

We tested a panel of human sera from 20 participants in the previously reported clinical trial[1,2], drawn 2 or 4 weeks after immunization with two 30-μg doses of BNT162b2 spaced 3 weeks apart (Supplementary Fig. 3). All neutralization assays were done with the same 20 sera samples, with the two experiments (as described in the Fig. 1 legend) done at different times. Each serum was tested for neutralization of WT USA-WA1/2020 strain and the three mutant viruses by a 50% plaque-reduction neutralization assay ($PRNT_{50}$; Supplementary Tables 1 and 2). All sera showed equivalent neutralization titers between the WT and mutant viruses, with differences of four-fold or less (Fig. 1). Notably, ten out of the 20 sera had neutralization titers against mutant Δ69/70 + N501Y + D614G virus that were twice their titers against the WT virus (Fig. 1b), whereas six out of the 20 sera had neutralization titers against mutant E484K + N501Y + D614G virus that were half their titers against the WT virus (Fig. 1c). The ratios of the neutralization GMTs of the sera against the N501Y, Δ69/70 + N501Y + D614G and E484K + N501Y + D614G viruses to their GMTs against the USA-WA1/2020 virus were 1.46, 1.41 and 0.81, respectively (Supplementary Fig. 4).

Consistent with other recent reports of the neutralization of SARS-CoV-2 variants or corresponding pseudoviruses by convalescent or post-immunization sera[11,12], the neutralization GMT of the serum panel against the virus with three mutations from the SA variant (E484K + N501Y + D614G) was slightly lower than the neutralization GMTs against the N501Y virus or the virus with three mutations from the UK variant (Δ69/70 + N501Y + D614G). However, the magnitude of the differences in neutralization GMTs against any of the mutant viruses in this study was small (0.81- to 1.41-fold), as compared to the greater than four-fold differences in

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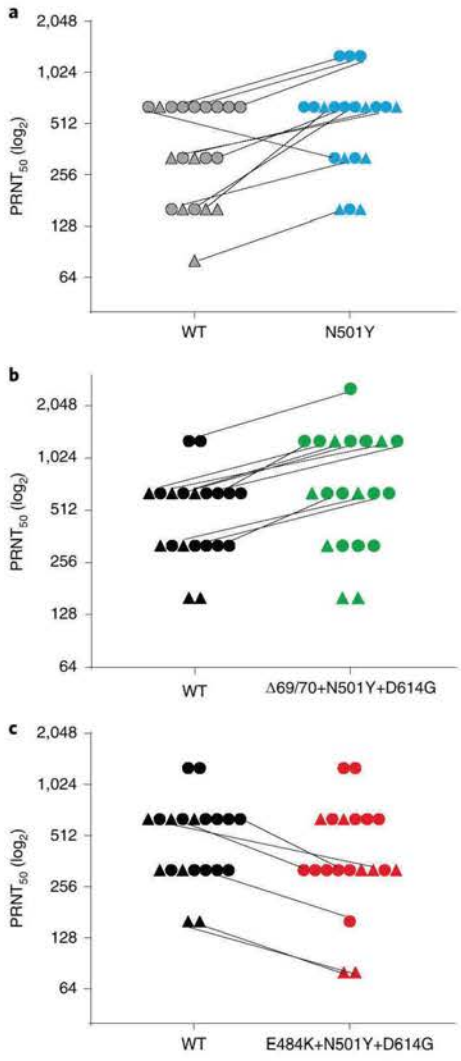

Fig. 1 | $PRNT_{50}$s of 20 BNT162b2-vaccinated human sera against WT and mutant SARS-CoV-2. a, WT (USA-WA1/2020) and mutant N501Y. **b**, WT and Δ69/70 + N501Y + D614G. **c**, WT and E484K + N501Y + D614G. Seven (triangles) and 13 (circles) sera were drawn 2 and 4 weeks after the second dose of vaccination, respectively. Sera with different $PRNT_{50}$s against WT and mutant viruses are connected by lines. Results in **a** were from one experiment; results in **b** and **c** were from another set of experiments. Each data point is the average of duplicate assay results.

hemagglutination-inhibition titers that have been used to signal potential need for a strain change in influenza vaccines[13].

A limitation of the current study is that the engineered viruses do not include the full set of spike mutations found in the UK or SA variants[3,4]. Nevertheless, preserved neutralization of N501Y, Δ69/70 + N501Y + D614G and E484K + N501Y + D614G viruses by BNT162b2 vaccine-elicited human sera is consistent with preserved neutralization of a panel of 15 pseudoviruses bearing spikes with other single mutations found in circulating SARS-CoV-2 strains[14]. The emergence of the common mutation N501Y from different geographical regions, as well as the previously emerged globally dominant D614G mutation, suggest that these mutations might improve viral fitness, as recently demonstrated for the increased viral transmission by the D614G mutation in animal models[7,15]. The biological functions of N501Y and the other mutations (such as Δ69/70 and E484K) remain to be defined for viral replication, pathogenesis and/or transmission in animal models. A second limitation of the study is that no serological correlate of protection against COVID-19 has been defined. Therefore, predictions about vaccine efficacy based on neutralization titers require assumptions about the levels of neutralization and roles of humoral and cell-mediated immunity in vaccine-mediated protection. Clinical data are needed for firm conclusions about vaccine effectiveness against variant viruses.

The ongoing evolution of SARS-CoV-2 necessitates continuous monitoring of the significance of changes for vaccine efficacy. This surveillance should be accompanied by preparations for the possibility that future mutations might necessitate changes to vaccine strains. The serological criteria for strain changes of influenza vaccine have been well accepted[16]. For COVID-19, such vaccine updates would be facilitated by the flexibility of messenger RNA-based vaccine technology.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01270-4.

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Methods

Construction of isogenic viruses. Three recombinant SARS-CoV-2 mutants (N501Y, Δ69/70-N501Y + D614G and E484K + N501Y + D614G in spike protein) were prepared on the genetic background of an infectious cDNA clone derived from clinical strain WA1 (2019-nCoV/USA_WA1/2020)[5] by following the polymerase chain reaction-based mutagenesis protocol as reported previously[7]. The full-length infectious cDNAs were in vitro ligated and used as templates to transcribe full-length viral RNA. Mutant viruses (P0) were recovered on day 2 from Vero E6 cells after electroporation of the in vitro RNA transcripts. P1 viruses were harvested as stocks by passaging the P0 virus once on Vero E6 cells. The titers of P1 viruses were determined by plaque assay on Vero E6 cells. The genome sequences of the P1 viruses were validated by Sanger sequencing. The detailed protocol was recently reported[17].

Serum specimens and neutralization assay. Serum samples were collected from BNT162b2 vaccinees participating in the phase 1 portion of the ongoing phase 1/2/3 clinical trial (ClinicalTrials.gov identifier: NCT04368728). The protocol and informed consent were approved by institutional review boards for each of the investigational centers participating in the study. The study was conducted in compliance with all International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki.

The immunization and serum collection regimens are illustrated schematically in Supplementary Fig. 3. A conventional (non-fluorescent) plaque-reduction neutralization assay was performed to quantify the serum-mediated virus suppression as previously reported[18]. Briefly, each serum was two-fold serially diluted in culture medium, with the first dilution of 1:40 (dilution range of 1:40 to 1:1280). The diluted sera were incubated with 100 plaque-forming units of WT or mutant viruses at 37 °C for 1 h, after which the serum–virus mixtures were inoculated onto Vero E6 cell monolayer in six-well plates. After 1 h of infection at 37 °C, 2 ml of 2% SeaPlaque agar (Lonza) in DMEM containing 2% FBS and 1% penicillin–streptomycin was added to the cells. After 2 d of incubation, 2 ml of 2% SeaPlaque agar in DMEM containing 2% FBS, 1% penicillin–streptomycin and 0.01% neutral red (Sigma-Aldrich) were added on top of the first layer. After another 16 h of incubation at 37 °C, plaque numbers were counted. The minimal serum dilution that inhibits 50% of plaque counts is defined as the $PRNT_{50}$. Each serum was tested in duplicates. The $PRNT_{50}$ assay was performed at the Biosafety Level-3 facility with the approval from the Institutional Biosafety Committee at the University of Texas Medical Branch.

Statistics. No statistical analysis was performed in the study.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Author contributions

Conceptualization: X.X., V.D.M., S.C.W. and P.-Y.S.; Methodology: X.X., Y.L., J.L., J.Z., C.R.F.G., H.X. and P.-Y.S; Investigation: X.X., Y.L., J.L., J.Z., C.R.F.G., H.X., K.A.S., D.C., P.R.D. and P.-Y.S; Resources: M.C., D.C., P.R.D. and P.-Y.S; Data curation: X.X., Y.L., J.L., J.Z., C.R.F.G. and P.-Y.S; Writing-original draft: X.X. and P.-Y.S; Writing-review and editing: X.X., P.R.D. and P.-Y.S.; Supervision: X.X., M.C., D.C., P.R.D. and P.-Y.S.; Funding acquisition: P.-Y.S.

Competing interests

The authors declare competing interests. X.X., V.D.M. and P.-Y.S. have filed a patent on the reverse genetic system. K.A.S., M.C., D.C. and P.R.D. are employees of Pfizer and might hold stock options. X.X., J.Z., C.R.F.G., H.X. and P.-Y.S. received compensation from Pfizer to perform the neutralization assay.

Additional information

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☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No code and software used for the data collection
Data analysis	Graphpad Prism 9

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample size calculation was performed. Based on the availability, 20 samples were collected from BNT162b2 vaccinees participating in the phase 1 portion of the ongoing phase 1/2/3 clinical trial (ClinicalTrials.gov identifier: NCT04368728). Those 20 samples had been tested as neutralizing positive against WT SARS-CoV-2 using the method according to the reference (Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020.).
Data exclusions	No data was excluded in the study.
Replication	Each human serum sample was analyzed in duplication. The averaged results from the duplication were reported in this study.
Randomization	No randomization was performed. All samples were analyzed for the neutralizing activities against WT SARS-CoV-2 and variants in the same experimental settings.
Blinding	Patient information was blinded in the study. Those 20 samples had been tested as neutralizing positive against WT SARS-CoV-2 using the method according to the reference (Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020.).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Vero E6 cells (ATCC® CRL-1586) were obtained from ATCC
Authentication	ATCC have comprehensively performed authentication on cell lines.
Mycoplasma contamination	All cell lines were tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	not applicable

Human research participants

Policy information about studies involving human research participants

Population characteristics	Only serum samples were used in this study. Please refer to the ClinicalTrials.gov identifier: NCT04368728 for the population characterisistics.

Recruitment	Only serum samples were used in this study. Please refer to the ClinicalTrials.gov identifier: NCT04368728 for the patient recruitment requirment.
Ethics oversight	The protocol and informed consent were approved by institutional review boards for each of the investigational centers participating in the study. The study was conducted in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the ethical principles of the Declaration of Helsinki.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

CORRESPONDENCE

Neutralizing Activity of BNT162b2-Elicited Serum

TO THE EDITOR: BNT162b2 is a nucleoside-modified RNA vaccine expressing the full-length prefusion spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a randomized, placebo-controlled clinical trial involving approximately 44,000 participants, immunization conferred 95% efficacy against coronavirus disease 2019 (Covid-19).[1]

New, highly transmissible SARS-CoV-2 variants that were first detected in the United Kingdom (B.1.1.7 lineage), South Africa (B.1.351 lineage), and Brazil (P.1 lineage) with mutations in the *S* gene are spreading globally. To analyze effects on neutralization elicited by BNT162b2, we engineered *S* mutations from each of the three new lineages into USA-WA1/2020, a relatively early isolate of the virus from January 2020 (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We thereby produced three recombinant viruses representing each of these lineages and two additional ones in which we engineered subsets of mutations of the B.1.351 lineage. Thus, the first recombinant virus had all the mutations found in the *S* gene in the B.1.1.7 lineage (B.1.1.7-spike), the second had all the mutations found in the *S* gene in the P.1 lineage (P.1-spike), the third had all the mutations found in the *S* gene in the B.1.351 lineage (B.1.351-spike), the fourth had an N-terminal domain deletion found in the B.1.351 lineage and the globally dominant D614G substitution (B.1.351-Δ242-244+D614G), and the fifth had the three mutations from the B.1.351 lineage affecting amino acids in the receptor-binding site (K417N, E484K, and N501Y) and a D614G substitution (B.1.351-RBD+D614G). The mutant amino acid residues in the B.1.351-RBD+D614G recombinant virus are also among those in the P.1 lineage virus, although in the P.1 lineage virus, K417 is mutated to threonine rather than asparagine. All the mutant viruses yielded infectious viral titers exceeding 10^7 plaque-forming units per milliliter. The B.1.1.7-spike and B.1.351-spike viruses formed plaques that were smaller than those formed by the other viruses (Fig. S2).

We performed 50% plaque reduction neutralization testing ($PRNT_{50}$) using 20 serum samples that had been obtained from 15 participants in the pivotal trial[1,2] 2 or 4 weeks after the administration of the second dose of 30 μg of BNT162b2 (which occurred 3 weeks after the first immunization) (Fig. S3). All the serum samples efficiently neutralized USA-WA1/2020 and all the viruses with variant spikes. Almost all of them did so at titers higher than 1:40. Geometric mean neutralizing titers against USA-WA1/2020, B.1.1.7-spike, P.1-spike, B.1.351-spike, B.1.351-Δ242-244+D614G, and B.1.351-RBD+D614G viruses were 532, 663, 437, 194, 485, and 331, respectively (Fig. 1 and Table S1). Thus, as compared with neutralization of USA-WA1/2020, neutralization of B.1.1.7-spike and P.1-spike viruses was roughly equivalent, and neutralization of B.1.351-spike virus was robust but lower. Our data are also consistent with lower neutralization titers against the virus with the full set of B.1.351-spike mutations than against virus with either subset of mutations. Our findings also suggest that mutations that result in amino acid substitutions K417N, E484K, and N501Y in the receptor-binding site have a greater effect on neutralization than the 242–244 deletion affecting the N-terminal domain of the spike protein.

Limitations of the study include the potential for mutations to alter neutralization by affecting spike function rather than antigenicity. Therefore, each neutralization assay with a different target virus is unique, and comparisons between neutralization titers from different assays should be interpreted with caution. Neutralizing activity against the B.1.351 lineage virus was robust at a geometric mean titer that was much higher than that obtained after one dose of BNT162b2, when strong efficacy was already observed in the C4591001 efficacy trial.[1-3] T-cell immunity may also be involved in protection,[4] and BNT162b2

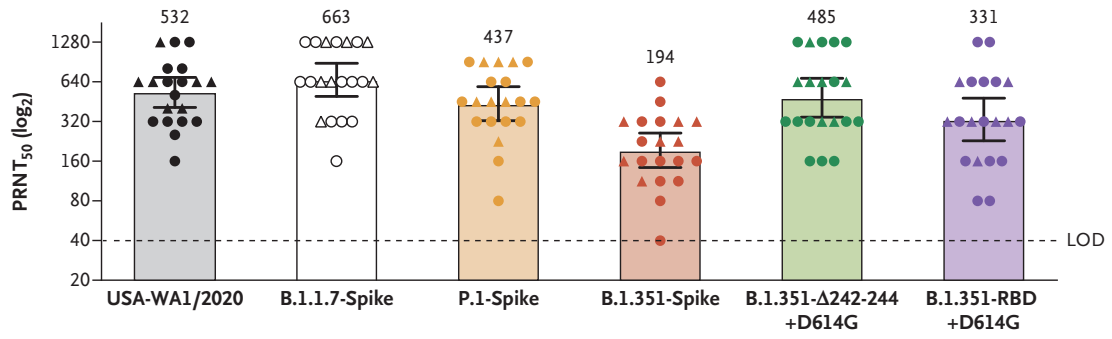

Figure 1. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

Shown are the results of 50% plaque reduction neutralization testing ($PRNT_{50}$) with the use of 20 samples obtained from 15 trial participants 2 weeks (circles) or 4 weeks (triangles) after the administration of the second dose of the BNT162b2 vaccine. The mutant viruses were obtained by engineering the full set of mutations in the B.1.1.7, P.1., or B.1.351 lineage or subsets of the *S* gene mutations in the B.1.351 lineage (B.1.351-Δ242-244+D614G and B.1.351-RBD+D614G) into USA-WA1/2020. Each data point represents the geometric mean $PRNT_{50}$ obtained with a serum sample against the indicated virus, including data from repeat experiments, as detailed in Table S1 in the Supplementary Appendix. The data for USA-WA1/2020 are from three experiments; for B.1.1.7-spike, B.1.351-Δ242-244+D614G, and B.1.351-RBD-D614G viruses from one experiment each; and for P.1-spike and B.1.351-spike viruses from two experiments each. In each experiment, the neutralization titer was determined in duplicate assays, and the geometric mean was taken. The heights of bars and the numbers over the bars indicate geometric mean titers. The I bars indicate 95% confidence intervals. Statistical analysis was performed with the use of the Wilcoxon signed-rank test. The statistical significance of the difference between geometric mean titers in the USA-WA1/2020 neutralization assay and in each variant virus neutralization assay with the same serum samples are as follows: P=0.02 for B.1.1.7-spike; P=0.06 for P.1-spike; P<0.001 for B.1.351-spike; P=0.99 for B.1.351-Δ242-244+D614G; and P=0.005 for B.1.351-RBD+D614G. LOD denotes limit of detection.

immunization elicits CD8+ T-cell responses that recognize multiple variants.[5] Ultimately, conclusions about vaccine-mediated protection that are extrapolated from neutralization or T-cell data must be validated by real-world evidence collected in regions where the SARS-CoV-2 variants are circulating.

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ORIGINAL ARTICLE

Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents

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ABSTRACT

BACKGROUND

Until very recently, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and socialization, and contribute to herd immunity.

METHODS

In this ongoing multinational, placebo-controlled, observer-blinded trial, we randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 μg of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, ≥7 days after dose 2) in the 12-to-15-year-old cohort were assessed.

RESULTS

Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100).

CONCLUSIONS

The BNT162b2 vaccine in 12-to-15-year-old recipients had a favorable safety profile, produced a greater immune response than in young adults, and was highly effective against Covid-19. (Funded by BioNTech and Pfizer; C4591001 ClinicalTrials.gov number, NCT04368728.)

From Cincinnati Children's Hospital, Cincinnati (R.W.F.); Kaiser Permanente Vaccine Study Center, Oakland (N.P.K.), and the California Research Foundation, San Diego (D.M.B.) — both in California; Vaccine Research and Development, Pfizer, Hurley, United Kingdom (N.K., S.L., R.B.); Vaccine Research and Development, Pfizer, Pearl River (A.G., J.A., K.A.S., K.K., W.V.K., D.C., P.R.D., K.U.J., W.C.G.), and SUNY Upstate Medical University, Syracuse (S.J.T.) — both in New York; Vaccine Research and Development (J.L.P., H.M., X.X.) and Worldwide Safety, Safety Surveillance and Risk Management (S.M.), Pfizer, Collegeville, PA; Duke Human Vaccine Institute, Durham, NC (E.B.W.); Senders Pediatrics, South Euclid, OH (S.S.); Clinical Research Professionals, Chesterfield, MO (T.J.); BioNTech, Mainz, Germany (Ö.T., U.Ş.); and Worldwide Safety, Safety Surveillance and Risk Management, Pfizer, Groton, CT (D.B.T.). Address reprint requests to Dr. Gurtman at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at alejandra.gurtman@pfizer.com.

*The members of C4591001 Clinical Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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As of May 21, 2021, the coronavirus disease 2019 (Covid-19) pandemic has caused more than 165 million infections across all ages globally, as well as more than 3.4 million deaths.[1] BNT162b2 (Pfizer–BioNTech) is a Covid-19 vaccine containing nucleoside-modified messenger RNA encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein.[2] In healthy adults, two 30-μg doses of BNT162b2 elicited high neutralizing titers and robust, antigen-specific CD4+ and CD8+ T-cell responses against SARS-CoV-2.[3,4] In the phase 2–3 part of an ongoing global, phase 1–2–3 randomized, controlled trial involving participants 16 years of age or older, BNT162b2 had a favorable safety profile characterized by transient mild-to-moderate injection-site pain, fatigue, and headache and was 95% effective in preventing Covid-19 from 7 days after dose 2.[5] On the basis of these findings, BNT162b2 received emergency use authorization from the Food and Drug Administration on December 11, 2020, for Covid-19 prevention in persons 16 years of age or older.[6] On May 10, 2021, the emergency use authorization was expanded to include persons 12 years of age or older on the basis of data presented in this report.[7] Other vaccines against SARS-CoV-2 are authorized for emergency use[1,8-10]; however, BNT162b2 is the only one currently authorized for use in persons younger than 16 years of age.

Although children and adolescents generally have milder Covid-19 than adults, severe illness can occur in this population, especially in those with underlying medical conditions.[11] Adolescents may play an important role in SARS-CoV-2 transmission.[12,13] Thus, their vaccination may prevent disease and contribute to herd immunity. Furthermore, with immunization of older persons, younger persons account for an increased proportion of Covid-19 infections.[14,15] The pandemic has interrupted the education and social development of students and has simultaneously burdened caregivers.[16-18] Safe, efficacious vaccines for younger populations are therefore paramount.

METHODS

OBJECTIVES, PARTICIPANTS, AND OVERSIGHT

We conducted a randomized, placebo-controlled, observer-blinded, phase 3 trial as part of a phase 1–2–3 trial assessing BNT162b2 safety, immunogenicity, and efficacy in healthy persons 12 years of age or older. This report presents findings from 12-to-15-year-old participants enrolled in the United States, including descriptive comparisons of safety between participants in that age cohort and those who were 16 to 25 years of age and an evaluation of the noninferiority of immunogenicity in the 12-to-15-year-old cohort to that in the 16-to-25-year-old cohort. Data were collected through the cutoff date of March 13, 2021.

Eligible participants were healthy or had stable preexisting disease (including hepatitis B, hepatitis C, or human immunodeficiency virus infection). Persons with a previous clinical or virologic Covid-19 diagnosis or SARS-CoV-2 infection, previous coronavirus vaccination, diagnosis of an immunocompromising or immunodeficiency disorder, or treatment with immunosuppressive therapy (including cytotoxic agents and systemic glucocorticoids) were excluded.

The ethical conduct of the trial is summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. Additional details of the trial are provided in the protocol, available at NEJM.org. Pfizer was responsible for the trial design and conduct, data collection, data analysis, data interpretation, and writing of the manuscript that was submitted. Both Pfizer and BioNTech manufactured the vaccine and placebo. BioNTech was the regulatory sponsor of the trial and contributed to data interpretation and writing of the manuscript. All data were available to the authors, who vouch for their accuracy and completeness and for the adherence of the trial to the protocol.

PROCEDURES

Randomization was conducted with the use of an interactive Web-based response system. Participants were assigned in a 1:1 ratio to receive two intramuscular injections of 30 μg of BNT162b2 or placebo (saline) 21 days apart. For evaluation of immediate vaccine-associated reactions, participants were observed in the clinic for 30 minutes after vaccination.

SAFETY

Safety objectives included the assessment of local or systemic reactogenicity events, which were recorded by the participants in an electronic diary (e-diary) for 7 days after each dose. Unsolicited adverse events (i.e., those reported by the partici-

pant without e-diary prompting) and serious adverse events were also recorded from receipt of the first dose through 1 month and 6 months after dose 2, respectively.

IMMUNOGENICITY

Immunogenicity assessments (SARS-CoV-2 serum neutralization assay and receptor-binding domain [RBD]–binding or S1-binding IgG direct Luminex immunoassays) were performed before vaccination and 1 month after dose 2, as described previously.[3] The immunogenicity objective was to show noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants. Noninferiority was assessed among participants who had no evidence of previous SARS-CoV-2 infection with the use of the two-sided 95% confidence interval for the geometric mean ratio of SARS-CoV-2 50% neutralizing titers in 12-to-15-year-old participants as compared with 16-to-25-year-old participants 1 month after dose 2. BNT162b2 immunogenicity was evaluated in participants with and those without serologic or virologic evidence of previous SARS-CoV-2 infection. Corresponding end points were the geometric mean SARS-CoV-2 neutralizing titers at baseline (i.e., immediately before receipt of the first injection) and 1 month after dose 2 and geometric mean fold rises (GMFRs) in titers from baseline to 1 month after dose 2.

EFFICACY

The efficacy of BNT162b2 against confirmed Covid-19 with an onset 7 or more days after dose 2 was summarized in participants who did not have evidence of previous SARS-CoV-2 infection, as well as in all vaccinated participants. Surveillance for potential Covid-19 cases was undertaken throughout the trial; if acute respiratory illness developed in a participant, the participant was tested for SARS-CoV-2. Methods for identifying SARS-CoV-2 infections and Covid-19 diagnoses are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

The safety population included all participants who received at least one dose of BNT162b2 or placebo. The reactogenicity subset included all 12-to-15-year-old participants and a subset of 16-to-25-year-old participants (those who received an e-diary to record reactogenicity events). Safety end points are presented descriptively as counts, percentages, and associated Clopper–Pearson two-sided 95% confidence intervals, with adverse events and serious adverse events described according to terms in the *Medical Dictionary for Regulatory Activities*, version 23.1, for each group.

Immunogenicity was assessed in a random subset of participants in each age cohort with the use of a simple random-sample selection procedure. For immunogenicity assessments, all participants in both age cohorts were from U.S. sites. The dose 2 immunogenicity population that could be evaluated included participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window (19 to 42 days after dose 1), had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was assessed on the basis of the geometric mean ratio of SARS-CoV-2 50% neutralizing titers. A sample of 225 BNT162b2 recipients who could be evaluated (or 280 BNT162b2 recipients overall) in each age cohort was estimated to provide 90.8% power for declaring noninferiority (defined as a lower limit of the 95% confidence interval for the geometric mean ratio of >0.67). A testing laboratory supply limitation of the qualified viral lot used for assay validation and clinical testing resulted in the trial having fewer participants than anticipated for the immunogenicity analyses. Calculations of the geometric mean ratios, geometric mean titers, and GMFRs are described in the Supplementary Appendix.

Although the formal evaluation of efficacy was to be based on the overall results obtained across all age cohorts, the statistical analysis plan specified that descriptive efficacy summaries would be provided for each age cohort (the stratification factor). The efficacy analysis for the 12-to-15-year-old cohort was planned as a descriptive analysis because the number of cases that would occur in the age subgroups was unknown. The efficacy population that could be evaluated included all eligible 12-to-15-year-old participants who underwent randomization and

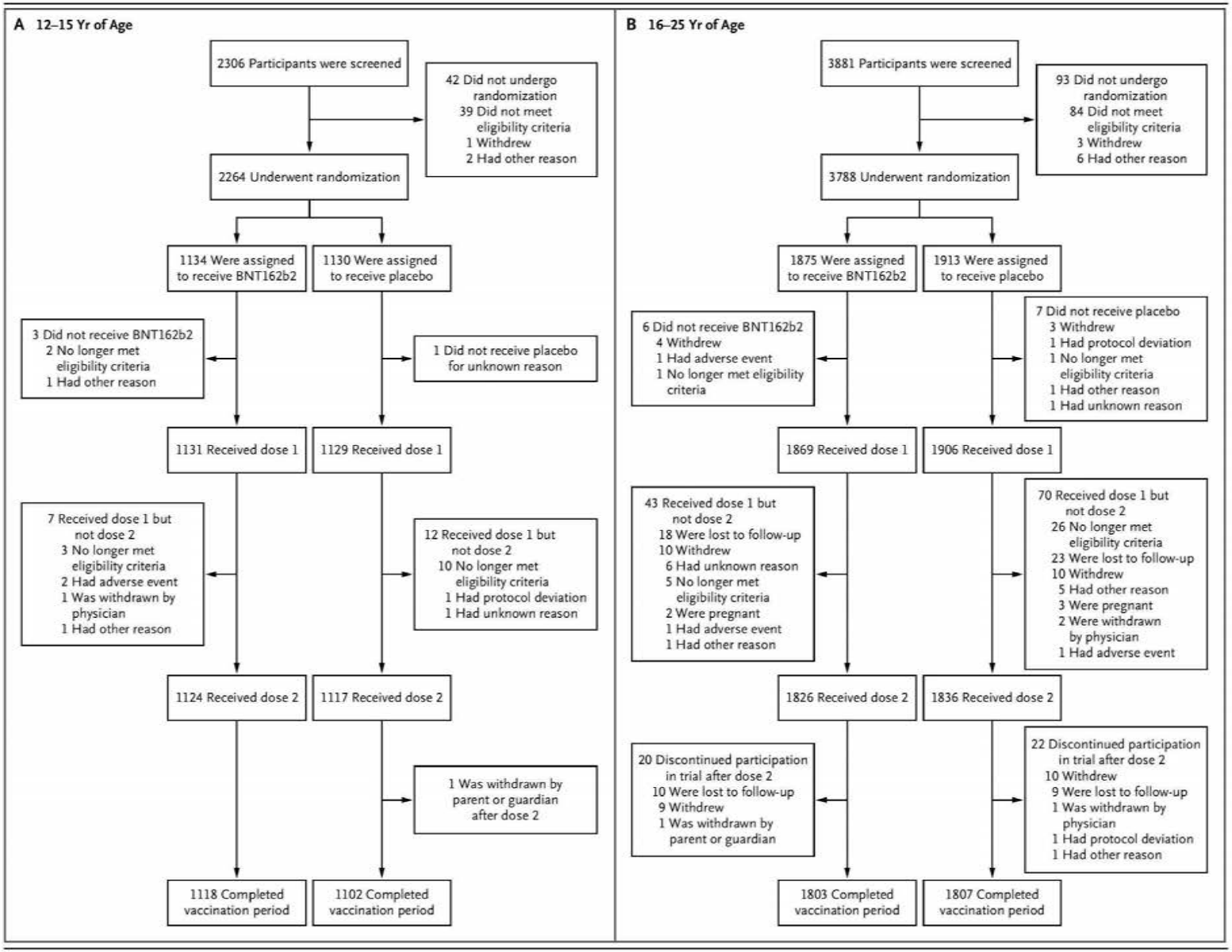

Figure 1 (facing page). Screening, Randomization, and Vaccine and Placebo Administration.

Participants who received dose 1 but not dose 2 could continue to be evaluated for safety. Participants were considered to have completed the vaccination period if they had completed the follow-up visit 1 month after dose 2 as of the data-cutoff date. As of the data-cutoff date, some participants had not yet completed their 1-month follow-up visit after dose 2. Some participants became eligible for a vaccine according to local or national recommendations before the 1-month follow-up visit after dose 2. These participants could choose to be made aware of their randomly assigned injection, and those who had received placebo could then choose to receive BNT162b2. Participants who had originally received placebo and chose to receive BNT162b2 as part of the trial would then follow a different visit schedule.

received two doses of BNT162b2 or placebo, received dose 2 within the prespecified window (19 to 42 days after dose 1), and had no major protocol deviations. The all-available efficacy population included all participants who received one or two doses. Vaccine efficacy was defined as $100 \times (1 - \text{IRR})$, where IRR is the ratio of the rate of a first confirmed Covid-19 illness in the BNT162b2 group to the corresponding rate in the placebo group. Two-sided Clopper–Pearson 95% confidence intervals were calculated (not adjusted for multiple comparisons). Because the number of participants who reported symptoms but were missing a valid polymerase-chain-reaction test result was small, data for these participants were not imputed in the analysis.

RESULTS

PARTICIPANTS

Between October 15, 2020, and January 12, 2021, a total of 2306 adolescents 12 to 15 years of age were screened for inclusion, and 2264 underwent randomization across 29 U.S. sites; 2260 participants received injections, with 1131 receiving BNT162b2 and 1129 receiving placebo (Fig. 1). More than 97% of the BNT162b2 recipients received dose 2. In the reactogenicity subset, all the 12-to-15-year-old participants were from the United States and the 16-to-25-year-old participants were recruited globally (Table 1). Although documented previous Covid-19 was an exclusion criterion, approximately 5% of the participants were SARS-CoV-2–positive at baseline, possibly because of previous asymptomatic infection. In the immunogenicity subset, all the participants in both age cohorts were from the United States. Among the 2260 participants who were 12 to 15 years of age, 51% were male, 86% were White, and 12% were Hispanic or Latinx. Overall, 1308 participants (58%) had at least 2 months of follow-up after their second vaccine dose. The trial populations are summarized in Table S1 in the Supplementary Appendix.

SAFETY

Reactogenicity

In both age cohorts, BNT162b2 recipients reported more local and systemic events than placebo recipients (Fig. 2). Local and systemic events were generally mild to moderate in severity, reported at similar frequencies in both age cohorts, and typically resolved within 1 or 2 days. In both age cohorts, injection-site pain was the most common local reaction. Severe injection-site pain after any BNT162b2 dose was reported in 1.5% of 12-to-15-year-old participants and in 3.4% of 16-to-25-year-old participants; no severe pain was reported after placebo administration.

In both age cohorts, headache and fatigue were the most frequently reported systemic events. After BNT162b2 injection, severe headache and severe fatigue were reported in a lower percentage of 12-to-15-year-old participants than of 16-to-25-year-old participants. Fever (oral body temperature, ≥38°C) occurred after dose 2 of BNT162b2 in 20% of 12-to-15-year-old recipients and in 17% of 16-to-25-year-old recipients. The use of antipyretic agents was slightly more frequent among BNT162b2 recipients who were 12 to 15 years of age than among those who were 16 to 25 years of age (37% vs. 32% after dose 1, and 51% vs. 46% after dose 2). Fever with a temperature higher than 40°C occurred in 1 (0.1%) of the 12-to-15-year-old participants 1 day after BNT162b2 dose 1. In general, systemic events were reported more often after BNT162b2 dose 2 than after dose 1. No differences in reactogenicity were noted between participants who were SARS-CoV-2–positive at baseline and those who were SARS-CoV-2–negative at baseline (Fig. S1).

Adverse Events

Among 12-to-15-year-old participants, adverse events occurring from dose 1 through 1 month after dose 2 were reported by 6% of BNT162b2

Table 1. Demographic Characteristics of the Participants.*

Characteristic	BNT162b2		Placebo	
	12–15 Yr (N=1131)	16–25 Yr (N=537)	12–15 Yr (N=1129)	16–25 Yr (N=561)
Male sex — no. (%)	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)
Race or ethnic group — no. (%)†				
White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Black or African American	52 (4.6)	47 (8.8)	57 (5.0)	50 (8.9)
American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Hispanic or Latinx ethnic group — no. (%)†				
Hispanic or Latinx	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Non-Hispanic or non-Latinx	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Country — no. (%)				
Argentina	0	20 (3.7)	0	28 (5.0)
Brazil	0	24 (4.5)	0	19 (3.4)
Germany	0	11 (2.0)	0	20 (3.6)
South Africa	0	34 (6.3)	0	45 (8.0)
Turkey	0	12 (2.2)	0	15 (2.7)
United States	1131 (100)	436 (81.2)	1129 (100)	434 (77.4)
Age at vaccination — yr				
Mean	13.6±1.11	19.4±3.26	13.6±1.11	19.6±3.33
Median (range)	14.0 (12–15)	18.0 (16–25)	14.0 (12–15)	19.0 (16–25)
Baseline SARS-CoV-2 status — no. (%)‡				
Positive	46 (4.1)	30 (5.6)	47 (4.2)	34 (6.1)
Negative	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)

* Plus–minus values are means ±SD. Results are for the reactogenicity subset of the safety population, which included all participants in the 12-to-15-year-old cohort and a subset of participants in the 16-to-25-year-old cohort. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the participants.

‡ A positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status required a positive N-binding antibody result at vaccination visit 1, a positive nucleic acid amplification test (NAAT) result at vaccination visit 1, or a medical history of coronavirus disease 2019 (Covid-19).

and placebo recipients; slightly more BNT162b2 recipients than placebo recipients reported related adverse events (3% vs. 2%) (Table S2). Among 16-to-25-year-old BNT162b2 recipients, 11% reported any adverse event and 6% had vaccine-related adverse events. Among BNT162b2 recipients, severe adverse events were reported in 0.6% of those who were 12 to 15 years of age and in 1.7% of those who were 16 to 25 years of age.

One BNT162b2 recipient in the 12-to-15-year-

old cohort discontinued vaccination because of a vaccine-related adverse event: a temperature greater than 40°C (described above) in a 14-year-old boy who was SARS-CoV-2–negative at baseline, had no reported medical history, and had no other symptoms. He received BNT162b2 dose 1 and had fever (temperature, 40.4°C) 1 day after vaccination, which resolved 2 days later. The participant did not receive dose 2 but remained in the trial for safety follow-up. One BNT162b2 recipient in the 16-to-25-year-old cohort discontinued vaccination because of severe vaccine-related injection-site pain and headache, both of which were reported 1 day after dose 1 and resolved within 1 day. Lymphadenopathy was reported in 9 of 1131 BNT162b2 recipients (0.8%) and in 2 of 1129 placebo recipients (0.2%) who were 12 to 15 years of age, as compared with in 1 of 536 BNT162b2 recipients (0.2%) and in no placebo recipients who were 16 to 25 years of age. Appendicitis was reported in 2 participants: 1 BNT162b2 recipient in the 16-to-25-year-old cohort and 1 placebo recipient in the 12-to-15-year-old cohort. No thromboses or hypersensitivity adverse events or vaccine-related anaphylaxis was seen. Few participants in any cohort (≤0.4% through 1 month after dose 2) had serious adverse events, and none were considered by the investigators to have been vaccine-related. No deaths were reported.

IMMUNOGENICITY

The immune response to BNT162b2 in 12-to-15-year-old adolescents was noninferior to that observed in 16-to-25-year-old young adults. The geometric mean ratio of the BNT162b2 neutralizing geometric mean titer in 12-to-15-year-old participants to that in 16-to-25-year-old participants 1 month after dose 2 was 1.76 (95% confidence interval [CI], 1.47 to 2.10) (Table 2), which met the noninferiority criterion (i.e., a lower boundary of the two-sided 95% confidence interval of >0.67). The lower boundary of the two-sided 95% confidence interval for the geometric mean ratio was greater than 1, indicating a greater response in adolescents than in young adults.

Among all participants regardless of serologic evidence of previous SARS-CoV-2 infection, the serum-neutralizing geometric mean titer 1 month after BNT162b2 dose 2 was 1283.0 in the 12-to-15-year-old cohort and 730.8 in the 16-to-25-year-old cohort (Fig. S2). The corresponding geometric mean titers at 1 month among placebo recipients were 15.1 and 10.7. Substantial increases in the 50% neutralizing titer from baseline were observed, with GMFRs from baseline to 1 month after dose 2 of 118.3 among 12-to-15-year-old participants and 71.2 among 16-to-25-year-old participants. The corresponding GMFRs among placebo recipients were 1.4 and 1.1.

EFFICACY

Among the 1983 participants in the 12-to-15-year-old cohort who could be evaluated and did not have evidence of previous SARS-CoV-2 infection, no cases of Covid-19 with an onset of 7 or more days after dose 2 were observed among BNT162b2 recipients and 16 cases were observed among placebo recipients, which corresponded to an observed vaccine efficacy of 100% (95% CI, 75.3 to 100) (Table 3). Similarly, in the group that included all 2229 participants in the 12-to-15-year-old cohort who could be evaluated, regardless of whether they had evidence of previous SARS-CoV-2 infection, vaccine efficacy from 7 days after dose 2 was 100% (95% CI, 78.1 to 100), with no Covid-19 cases observed among BNT162b2 recipients and 18 cases observed among placebo recipients. After dose 1 and before dose 2, there were 3 Covid-19 cases noted (within 11 days after dose 1) among BNT162b2 recipients, as compared with 12 cases among placebo recipients (vaccine efficacy, 75%; 95% CI, 7.6 to 95.5) (Table S3). No cases of severe Covid-19 were observed in this age cohort.

DISCUSSION

A two-dose regimen of 30 μg of BNT162b2 administered 21 days apart to adolescents 12 to 15 years of age was safe and immunogenic and resulted in an observed vaccine efficacy of 100% against Covid-19 from 7 days after dose 2. BNT162b2 elicited a high immune response in adults,[3] which translated to a 95% vaccine efficacy among participants in the phase 2–3 trial who were 16 years of age or older.[5] Noninferiority of immunogenicity in 12-to-15-year-old adolescents, as shown in our trial, was initially planned as the primary assessment of vaccine effectiveness through "immunobridging," an approach in which the effectiveness of a vaccine is inferred from immunogenicity data. The efficacy analysis was descriptive because a sufficient number of Covid-19 cases was not anticipated. However,

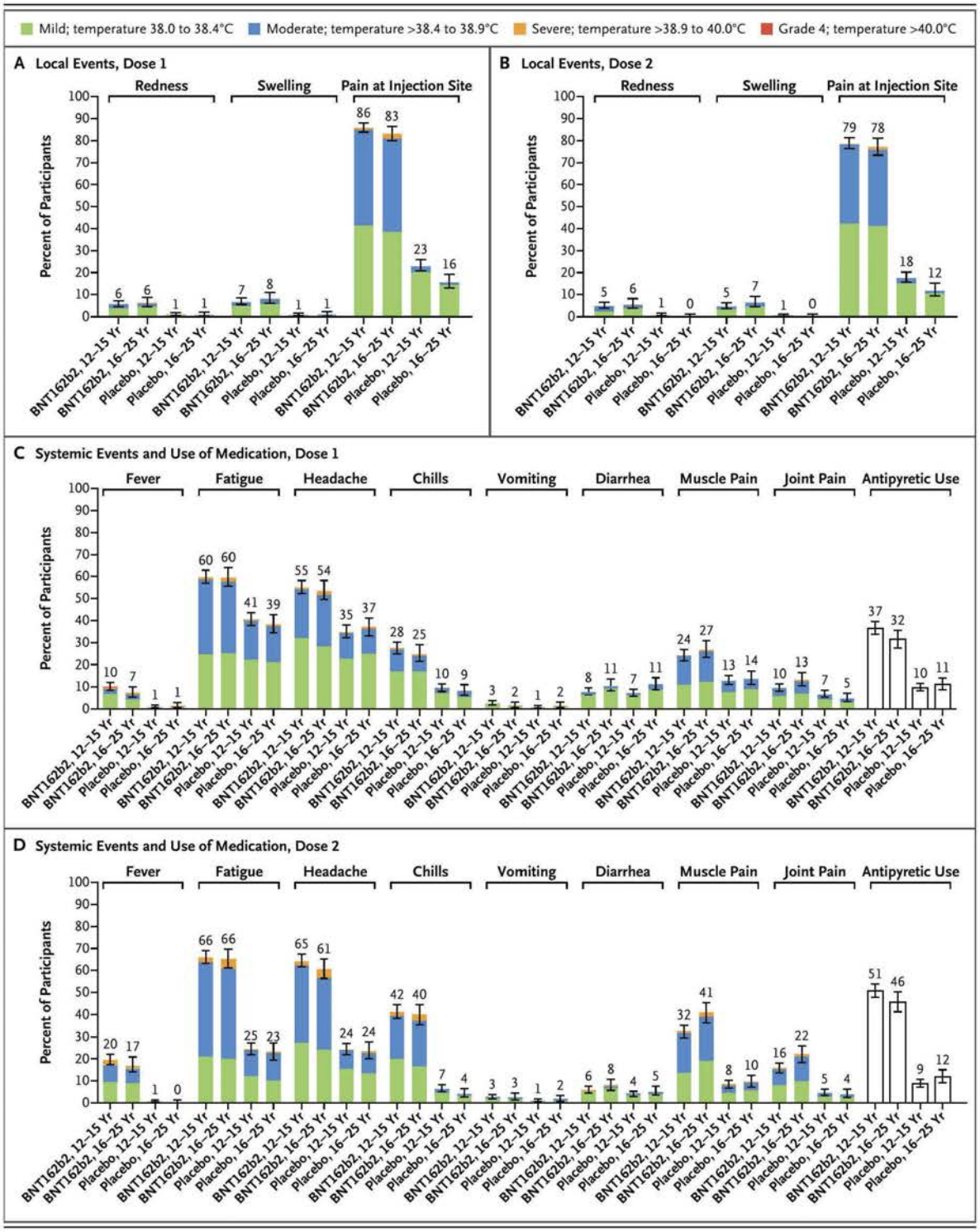

Figure 2 (facing page). Local Reactions and Systemic Events Reported within 7 Days after Administration of BNT162b2 or Placebo.

The results shown are for the reactogenicity subset of the safety population, which included all participants in the 12-to-15-year-old cohort and the subset of participants in the 16-to-25-year-old cohort who had electronic diary data available. Pain at the injection site was graded as mild (does not interfere with activity), moderate (interferes with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). Redness and swelling were graded as mild (>2.0 to 5.0 cm in diameter), moderate (>5.0 to 10.0 cm in diameter), severe (>10.0 cm in diameter), or grade 4 (necrosis or exfoliative dermatitis for redness and necrosis for swelling). Fever categories are designated in the key. Fatigue, headache, chills, new or worsened muscle pain, and new or worsened joint pain were graded as mild (does not interfere with activity), moderate (some interference with activity), or severe (prevents daily routine activity). Vomiting was graded as mild (one or two times in 24 hours), moderate (more than two times in 24 hours), or severe (requires intravenous hydration), and diarrhea as mild (two or three loose stools in 24 hours), moderate (four or five loose stools in 24 hours), or severe (six or more loose stools in 24 hours). Grade 4 for all systemic events indicated an emergency department visit or hospitalization. I bars indicate 95% confidence intervals. The numbers above the I bars are the overall percentages of the participants in each group who reported the specified local reaction or systemic event. No participant had a grade 4 local reaction. With regard to systemic events, there was one incident of fever with a temperature higher than 40°C in a 12-to-15-year-old participant after dose 1 of BNT162b2.

given the number of cases and the precision of vaccine efficacy estimates, the vaccine efficacy in this trial provides a high level of certainty about the efficacy results. The lower limit of the 95% confidence interval for vaccine efficacy, which was greater than 75%, provides substantial evidence of efficacy in this age group and is consistent with the high efficacy previously reported in participants 16 years of age or older.[5] Although BNT162b2 is a two-dose regimen, early protection after a single dose has been reported in clinical trials and on the basis of real-world data.[5,19,20] It is reassuring that early protection is also observed in this age group, given the important public health implications for pandemic control.

Evaluation of BNT162b2 in younger adolescents was undertaken for several reasons. The incidence of Covid-19 is reported to be higher among 12-to-17-year-old adolescents than among younger children.[21] In addition, children, especially from low-income families, have been negatively affected by the lack of in-person learning during the pandemic.[17,18] Therefore, a demonstration of efficacy and safety in 12-to-15-year-old adolescents is important in order to expand the emergency use authorization to include children 12 years of age or older and make a critical step toward achieving herd immunity. Finally, the favorable safety and side-effect profile and high efficacy, along with the acceptable risk-to-benefit ratio in ado-

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.*

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

* Results are for the subset of participants in the dose 2 immunogenicity population that could be evaluated (i.e., participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window, had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations) who had no evidence of previous SARS-CoV-2 infection. Participants without evidence of previous infection were those who had no serologic or virologic evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit up to 1 month after dose 2.

† Geometric mean titers and two-sided 95% confidence intervals were calculated by exponentiating the mean logarithm of the titers and the corresponding confidence intervals (based on the Student's t distribution). Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation.

‡ The geometric mean ratio and two-sided 95% confidence intervals were calculated by exponentiating the mean difference of the logarithms of the titers (the 12-to-15-year-old cohort minus the 16-to-25-year-old cohort) and the corresponding confidence intervals (based on the Student's t distribution). The noninferiority criterion was met, since the lower boundary of the two-sided confidence interval for the geometric mean ratio was greater than 0.67.

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.*

Efficacy End Point†	BNT162b2		Placebo		% Vaccine Efficacy (95% CI)‡
	No. of Participants with Event/ Total No.§	Surveillance Time (No. at Risk)¶	No. of Participants with Event/ Total No.§	Surveillance Time (No. at Risk)¶	
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	0.154 (1001)	16/978	0.147 (972)	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	0.170 (1109)	18/1110	0.163 (1094)	100 (78.1–100)

* Results are for the efficacy population that could be evaluated, which included all eligible 12-to-15-year-old participants who received two doses of BNT162b2 or placebo as randomly assigned, with dose 2 received within the prespecified window, and had no major protocol deviations.

† Participants without evidence of previous infection were those who had no serologic or virologic evidence of past SARS-CoV-2 infection before 7 days after dose 2 (i.e., N-binding antibody testing [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit before 7 days after dose 2.

‡ The 95% confidence interval for vaccine efficacy was derived on the basis of the Clopper–Pearson method with adjustment for surveillance time.

§ The number of participants with a first occurrence of Covid-19 at 7 or more days after dose 2 and the total number of participants with data are shown.

¶ Total surveillance time in 1000 person-years for the given end point across all participants within each group of participants who were at risk for the end point is shown. The period for Covid-19 case accrual was from 7 days after dose 2 to the end of the surveillance period.

lescents, now justify vaccine evaluation in younger age groups.[22]

The favorable safety profile of BNT162b2, which was seen in adults in the pivotal trial and through ongoing pharmacovigilance after vaccine introduction, was also observed in 12-to-15-year-old recipients.[5,23] Adherence was high, with more than 97% of BNT162b2 recipients receiving dose 2. As previously reported for vaccine recipients 16 years of age or older, systemic events in 12-to-15-year-old BNT162b2 recipients were reported more often after dose 2 than after dose 1.[5] Antipyretic use after both doses was slightly higher in the 12-to-15-year-old cohort than in the 16-to-25-year-old cohort. This favorable safety profile is important, because a precedent exists for vaccines being increasingly reactogenic when administered to younger people. In the small percentage of participants who were SARS-CoV-2–positive at baseline, no differences in reactogenicity from those who were SARS-CoV-2–negative at baseline were noted, which supports immunization without screening for evidence of previous SARS-CoV-2 infection.

These results have several implications. Vaccination of adolescents is likely to confer the direct benefit of preventing disease along with indirect benefits, including community protection.[24] Although children generally have a lower burden of symptomatic Covid-19 than adults, schools, youth sports, and other community gatherings may represent important sources of ongoing outbreaks and transmission, despite high rates of adult immunization.[13,14,25] Vaccination of adolescents will allow them to reintegrate into society and resume in-person learning safely, which are especially important outcomes given the severe mental health effects of the Covid-19 pandemic on this group.[18,22,26] Recent real-world data suggest that BNT162b2 prevents asymptomatic infection.[19,27] Given the observed immunogenicity and efficacy, it is likely that vaccination will also prevent asymptomatic infection in children, thereby broadening community protection.

This analysis has some limitations. The efficacy analysis was prespecified as descriptive because an accurate sample size to assess vaccine efficacy could not be calculated before the start of the trial, given uncertainties about the incidence of SARS-CoV-2 infection. Therefore, the primary basis for the establishment of efficacy in 12-to-15-year-old adolescents was a neutralizing antibody response that was found to be noninferior to that in vaccine recipients 16 years

of age or older, for whom efficacy had been shown.[5] This report includes safety data through 1 month of follow-up after dose 2 for some participants. Data on longer-term safety and the duration of efficacy and antibody responses in children are not yet available.

Although racial and ethnic diversity was lower among the 12-to-15-year-old participants than among those who were 16 years of age or older, vaccine efficacy in the latter age cohort is consistent among racial and ethnic subgroups,[5] and a similar pattern is likely in the younger cohort. All 12-to-15-year-old participants in this trial were enrolled at U.S. sites, whereas the 16-to-25-year-old participants were recruited globally. In the immunogenicity subset, however, all participants in both age cohorts were from the United States. The testing laboratory supply limitation resulted in fewer than anticipated participants in the immunogenicity analyses; however, even with the smaller sample size and lower power, the trial still established noninferiority of the immune response. Although some participants received other vaccinations during the trial period, we did not formally examine concomitant vaccination with BNT162b2 and other vaccines received during adolescence. These results do not determine whether BNT162b2 vaccination prevents asymptomatic infection or transmission of SARS-CoV-2; asymptomatic surveillance is ongoing in this age group.

Given the safety, immune response, and efficacy of the BNT162b2 vaccine in adolescents 12 to 15 years of age reported in this analysis, studies are ongoing to evaluate these measures in younger children and in other special populations, such as pregnant women.

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ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months

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ABSTRACT

BACKGROUND

BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine encoding a prefusion-stabilized, membrane-anchored severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike protein. BNT162b2 is highly efficacious against coronavirus disease 2019 (Covid-19) and is currently approved, conditionally approved, or authorized for emergency use worldwide. At the time of initial authorization, data beyond 2 months after vaccination were unavailable.

METHODS

In an ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy trial, we randomly assigned 44,165 participants 16 years of age or older and 2264 participants 12 to 15 years of age to receive two 30-μg doses, at 21 days apart, of BNT162b2 or placebo. The trial end points were vaccine efficacy against laboratory-confirmed Covid-19 and safety, which were both evaluated through 6 months after vaccination.

RESULTS

BNT162b2 continued to be safe and have an acceptable adverse-event profile. Few participants had adverse events leading to withdrawal from the trial. Vaccine efficacy against Covid-19 was 91.3% (95% confidence interval [CI], 89.0 to 93.2) through 6 months of follow-up among the participants without evidence of previous SARS-CoV-2 infection who could be evaluated. There was a gradual decline in vaccine efficacy. Vaccine efficacy of 86 to 100% was seen across countries and in populations with diverse ages, sexes, race or ethnic groups, and risk factors for Covid-19 among participants without evidence of previous infection with SARS-CoV-2. Vaccine efficacy against severe disease was 96.7% (95% CI, 80.3 to 99.9). In South Africa, where the SARS-CoV-2 variant of concern B.1.351 (or beta) was predominant, a vaccine efficacy of 100% (95% CI, 53.5 to 100) was observed.

CONCLUSIONS

Through 6 months of follow-up and despite a gradual decline in vaccine efficacy, BNT162b2 had a favorable safety profile and was highly efficacious in preventing Covid-19. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A list of the investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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The coronavirus disease 2019 (COVID-19) pandemic continues, with recent estimates of more than 187 million cases diagnosed and more than 4 million deaths.[1] Vaccines are currently available by means of full approval, conditional marketing approval, and emergency use authorization pathways.[2-5] BNT162b2 is a lipid nanoparticle–formulated,[6] nucleoside-modified RNA[7] encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike glycoprotein in a prefusion stabilized conformation.[8] To date, more than 1 billion doses of BNT162b2 have been distributed.

We previously reported safety and efficacy data obtained through a median of 2 months of postimmunization follow-up from a global phase 1–2–3 trial of BNT162b2 involving persons 16 years of age or older. Vaccine efficacy against Covid-19 was 95%. BNT162b2 had a favorable safety profile in diverse populations.[9] These data formed the basis for BNT162b2 emergency or conditional authorizations globally.[10] Safety, efficacy, and immunogenicity data from participants 12 to 15 years of age in this trial have been reported.[11] Here, we report safety and efficacy findings from a prespecified analysis of the phase 2–3 portion of the trial through approximately 6 months of follow-up. These additional data contributed to the full approval of BNT162b2 in the United States.

Methods

Objectives, Participants, and Oversight

This randomized, placebo-controlled, observer-blinded, phase 1–2–3 trial assessed the safety, efficacy, and immunogenicity of the BNT162b2 vaccine in adolescents and adults. The current report of the findings from the phase 2–3 portion of the trial focuses on safety assessments among participants 16 years of age or older and prespecified assessments of vaccine efficacy among participants 12 years of age or older through 6 months of follow-up after immunization. Because the enrollment of participants 12 to 15 years of age began on October 15, 2020, 6-month postimmunization data are currently unavailable for this age cohort. Shorter-duration safety, immunogenicity, and efficacy data for participants 12 to 15 years of age are reported separately[11]; however, data for this cohort are included in the analyses of vaccine efficacy in the overall population (all participants ≥12 years of age) reported here.

Participants who were healthy or had stable chronic medical conditions were eligible. An active immunocompromising condition or recent immunosuppressive therapy was an exclusion criterion. Participants with a history of Covid-19 were excluded, although evidence of current or previous SARS-CoV-2 infection on laboratory testing of trial-obtained samples was not an exclusion criterion. Trial-related responsibilities and ethical conduct are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol contains additional details of the trial and is available at NEJM.org. The first draft of the manuscript was written by the fourth author. The authors had the opportunity to review the data included in this article and confirm the accuracy of the data presented through the specified data cutoff date. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Procedures

The participants were randomly assigned in a 1:1 ratio to receive two 30-μg intramuscular injections, 21 days apart, of BNT162b2 (0.3 ml volume per dose) or saline placebo. Randomization was performed with an interactive Web-based system. Starting in December 2020, after BNT162b2 became available under emergency or conditional use authorizations, participants 16 years of age or older who became eligible for Covid-19 vaccination according to national or local recommendations were given the option to learn their trial assignment. Those who had been randomly assigned to receive placebo were offered BNT162b2. After unblinding of the group assignments, participants were followed in an open-label trial period.

Safety

Safety end points included solicited, prespecified local reactions, systemic events, and antipyretic or pain medication use during the first 7 days after receipt of each vaccine or placebo dose, which were recorded in an electronic diary; unsolicited adverse events after receipt of the first dose through 1 month after the second dose; and serious adverse events after receipt of the first dose through 1 and 6 months after the second dose

was received. Safety data are presented for the blinded follow-up and open-label periods.

EFFICACY

BNT162b2 efficacy against laboratory-confirmed Covid-19 with an onset of 7 days or more after the second dose was assessed and summarized descriptively in participants without serologic or virologic evidence of SARS-CoV-2 infection within 7 days after the second dose and in participants with or without evidence of previous infection. Efficacy against severe Covid-19 was also assessed. Lineages of SARS-CoV-2 detected in midturbinate specimens are reported here for Covid-19 cases that occurred 7 days or more after the second dose in South African participants without evidence of previous infection. Methods for determining SARS-CoV-2 lineages and case definitions for confirmed and severe cases of Covid-19 are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

The analysis populations are summarized in Table S1 in the Supplementary Appendix. Safety analyses included participants 16 years of age or older without known human immunodeficiency virus (HIV) infection who provided informed consent and received at least one BNT162b2 or placebo dose. The results of the safety analyses, which are descriptive and not based on formal hypothesis testing, are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for adverse events, according to terms in the *Medical Dictionary for Regulatory Activities*, version 23.1, and reactogenicity events for each trial group. Safety data that were reported up to March 13, 2021, are summarized here. The 95% confidence intervals in this report were not adjusted for multiplicity.

The analysis of vaccine efficacy during the blinded period of the trial included all participants 12 years of age or older without known HIV infection who received at least one BNT162b2 or placebo dose. Vaccine efficacy was calculated as $100 \times (1-\text{IRR})$, where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. Descriptive analyses of vaccine efficacy were performed and associated 95% confidence intervals were calculated with the use of the Clopper–Pearson method, with adjustment for surveillance time, which accounts for potential differential follow-up between the two trial groups. As described in the statistical analysis plan, available with the protocol, hypothesis-testing analyses were performed with the use of a Bayesian approach, and the descriptive analyses presented here were performed with a frequentist approach for clarity of communication. Because the percentage of participants who reported symptoms but were missing a valid polymerase-chain-reaction test result was small and slightly higher in the placebo group, data for these participants were not imputed in the analysis.

The previously reported primary efficacy objective was achieved on the basis of an analysis of 170 accrued cases of Covid-19 that could be evaluated (data cutoff date, November 14, 2020).[9] The current report provides updated efficacy analyses that were performed with data from cases that had accrued up to March 13, 2021.

RESULTS

PARTICIPANTS

Between July 27, 2020, and October 29, 2020, a total of 45,441 participants 16 years of age or older underwent screening, and 44,165 underwent randomization at 152 sites (130 sites in the United States, 1 site in Argentina, 2 sites in Brazil, 4 sites in South Africa, 6 sites in Germany, and 9 sites in Turkey) in the phase 2–3 portion of the trial. Of these participants, 44,060 received at least one dose of BNT162b2 (22,030 participants) or placebo (22,030), and 98% (21,759 in the BNT162b2 group and 21,650 in the placebo group) received the second dose (Fig. 1). During the blinded period of the trial, 51% of the participants in each group had 4 to less than 6 months of follow-up after the second dose; 8% of the participants in the BNT162b2 group and 6% of those in the placebo group had 6 months of follow-up or more after the second dose. During the combined blinded and open-label periods, 55% of the participants in the BNT162b2 group had 6 months of follow-up or more after the second dose. A total of 49% of the participants were female, 82% were White, 10% were Black, and 26% were Hispanic or Latinx; the median age was 51 years. A total of 34% of the participants had a body-mass index (the weight in kilograms divided by the square of the height in meters) of

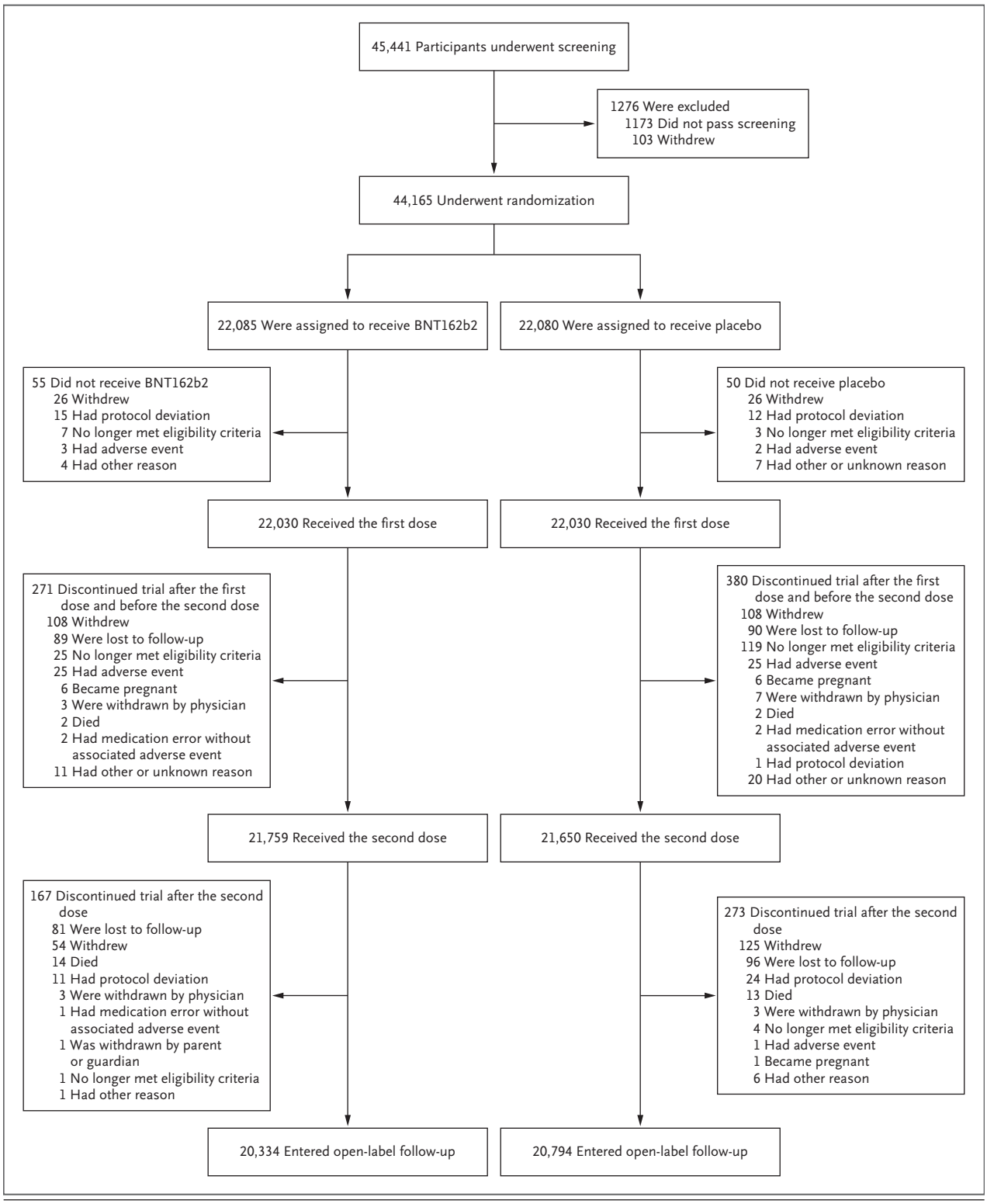


Figure 1 (facing page). Screening, Randomization, and Follow-up.

The diagram represents all enrolled participants 16 years of age or older through the data cutoff date (March 13, 2021). The diagram includes two deaths that occurred after the second dose in human immunodeficiency virus (HIV)–infected participants (one in the BNT162b2 group and one in the placebo group; these deaths were not reported in the Results section of this article because the analysis of HIV-infected participants is being conducted separately). Information on the screening, randomization, and follow-up of the participants 12 to 15 years of age has been reported previously.[11]

30.0 or more, 21% had at least one underlying medical condition, and 3% had baseline evidence of a previous or current SARS-CoV-2 infection (Table 1 and Table S2).

Between October 15, 2020, and January 12, 2021, a total of 2306 participants 12 to 15 years of age underwent screening, and 2264 underwent randomization at 29 U.S. sites. Of these participants, 2260 received at least one dose of BNT162b2 (1131 participants) or placebo (1129), and 99% (1124 in the BNT162b2 group and 1117 in the placebo group) received the second dose.[11] Among participants who received at least one dose of BNT162b2 or placebo, 58% had at least 2 months of follow-up after the second dose, 49% were female, 86% were White, 5% were Black, and 12% were Hispanic or Latinx. Full details of the demographic characteristics of the participants have been reported previously.[11]

SAFETY

Reactogenicity

The subgroup that was evaluated for reactogenicity in the current report, in which reactions were reported in an electronic diary, included 9839 participants 16 years of age or older. In this subgroup, 8183 participants had been included in the previous analysis, and 1656 were enrolled after the data cutoff for that analysis.[9] The reactogenicity profile of BNT162b2 in this expanded subgroup did not differ substantially from that described previously.[9] This subgroup included 364 participants who had evidence of previous SARS-CoV-2 infection, 9426 who did not have evidence, and 49 who lacked the data needed to determine previous infection status.

More participants in the BNT162b2 group than in the placebo group reported local reactions, the most common of which was mild-to-moderate pain at the injection site (Fig. S1A). Local reactions were reported with similar frequency among the participants with or without evidence of previous SARS-CoV-2 infection, and the reactions were of similar severity. No local reactions of grade 4 (according to the guidelines of the Center for Biologics Evaluation and Research[12]) were reported.

More participants in the BNT162b2 group than in the placebo group reported systemic events, the most common of which was fatigue (Fig. S1B). Systemic events were mostly mild to moderate in severity, but there were occasional severe events. Systemic reactogenicity was similar among those with or without evidence of previous SARS-CoV-2 infection, although BNT162b2 recipients with evidence of previous infection reported systemic events more often after receipt of the first dose, and those without evidence reported systemic events more often after receipt of the second dose. For example, 12% of recipients with evidence of previous SARS-CoV-2 infection and 3% of those without evidence reported fever after receipt of the first dose; 8% of those with evidence of previous infection and 15% of those without evidence reported fever after the second dose. The highest temperature reported was a transient fever of higher than 40.0°C on day 2 after the second dose in a BNT162b2 recipient without evidence of previous infection.

Adverse Events

Analyses of adverse events during the blinded period included 43,847 participants 16 years of age or older (Table S3). Reactogenicity events among the participants who were not in the reactogenicity subgroup were reported as adverse events, which resulted in imbalances between the BNT162b2 group and the placebo group with respect to adverse events (30% vs. 14%), related adverse events (24% vs. 6%), and severe adverse events (1.2% vs. 0.7%). New adverse events attributable to BNT162b2 that were not previously

Table 1. Demographic Characteristics of the Participants at Baseline.*

Characteristic	BNT162b2 (N = 22,026)	Placebo (N = 22,021)	Total (N = 44,047)
Sex — no. (%)			
Male	11,322 (51.4)	11,098 (50.4)	22,420 (50.9)
Female	10,704 (48.6)	10,923 (49.6)	21,627 (49.1)
Race or ethnic group — no. (%)†			
White	18,056 (82.0)	18,064 (82.0)	36,120 (82.0)
Black or African American	2,098 (9.5)	2,118 (9.6)	4,216 (9.6)
Asian	952 (4.3)	942 (4.3)	1,894 (4.3)
American Indian or Alaska Native	221 (1.0)	217 (1.0)	438 (1.0)
Native Hawaiian or other Pacific Islander	58 (0.3)	32 (0.1)	90 (0.2)
Multiracial	550 (2.5)	533 (2.4)	1,083 (2.5)
Not reported	91 (0.4)	115 (0.5)	206 (0.5)
Ethnicity†			
Hispanic or Latinx	5,704 (25.9)	5,695 (25.9)	11,399 (25.9)
Not reported	111 (0.5)	114 (0.5)	225 (0.5)
Country — no. (%)			
Argentina	2,883 (13.1)	2,881 (13.1)	5,764 (13.1)
Brazil	1,452 (6.6)	1,448 (6.6)	2,900 (6.6)
Germany	249 (1.1)	250 (1.1)	499 (1.1)
South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Turkey	249 (1.1)	249 (1.1)	498 (1.1)
United States	16,792 (76.2)	16,794 (76.3)	33,586 (76.3)
Age group at vaccination — no. (%)			
16–55 yr	13,069 (59.3)	13,095 (59.5)	26,164 (59.4)
>55 yr	8,957 (40.7)	8,926 (40.5)	17,883 (40.6)
Age at vaccination — yr			
Median	51.0	51.0	51.0
Range	16–89	16–91	16–91
SARS-CoV-2 status — no. (%)‡			
Positive	689 (3.1)	716 (3.3)	1,405 (3.2)
Negative	21,185 (96.2)	21,180 (96.2)	42,365 (96.2)
Missing data	152 (0.7)	125 (0.6)	277 (0.6)
Body-mass index — no. (%)§			
≥30.0: obese	7,543 (34.2)	7,629 (34.6)	15,172 (34.4)
Missing data	7 (<1)	6 (<1)	13 (<1)

* Data are summarized for participants 16 years of age or older in the safety population. The demographic characteristics of participants 12 to 15 years of age were reported previously.[11] Percentages may not total 100 because of rounding. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.
† Race and ethnicity were reported by the participants. The categories shown are those that were used to collect the data.
‡ Positive status was defined as a positive N-binding antibody result or a positive nucleic acid amplification test (NAAT) result at visit 1 or medical history of coronavirus disease 2019 (Covid-19). Negative status was defined as a negative N-binding antibody result or a negative NAAT result at visit 1 and no medical history of Covid-19.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Vaccine Efficacy against Covid-19 from 7 Days after Receipt of the Second Dose during the Blinded, Placebo-Controlled Follow-up Period.*

Efficacy End Point	BNT162b2			Placebo			Vaccine Efficacy (95% CI)‡
	No. of Cases	Surveillance Time†	No. at Risk	No. of Cases	Surveillance Time†	No. at Risk	
		1000 person-yr			*1000 person-yr*		*percent*
		(N=20,998)			**(N=21,096)**		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants without evidence of previous infection	77	6.247	20,712	850	6.003	20,713	91.3 (89.0–93.2)
		(N=22,166)			**(N=22,320)**		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants with or without evidence of previous infection	81	6.509	21,642	873	6.274	21,689	91.1 (88.8–93.0)

* This analysis included participants who had no serologic or virologic evidence (within 7 days after receipt of the second dose) of previous SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] test at visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at visits 1 and 2) and had a negative NAAT at any unscheduled visit up to 7 days after receipt of the second dose.

† The surveillance time is the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from 7 days after the second dose to the end of the surveillance period.

‡ Vaccine efficacy was calculated as 100×(1−IRR), where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

identified in earlier reports included decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis. Few participants had serious adverse events or adverse events that led to trial withdrawal. No new serious adverse events were considered by the investigators to be related to BNT162b2 after the data cutoff date of the previous report.[9]

During the combined blinded and open-label periods, cumulative safety data during follow-up were available through 6 months after the second dose for 12,006 participants who were originally randomly assigned to the BNT162b2 group. No new safety signals relative to the previous report were observed during the longer follow-up period in the current report, which included open-label observation of the original BNT162b2 recipients and placebo recipients who received BNT162b2 after unblinding.[9]

During the blinded, placebo-controlled period, 15 participants in the BNT162b2 group and 14 in the placebo group died; during the open-label period, 3 participants in the BNT162b2 group and 2 in the original placebo group who received BNT162b2 after unblinding died. None of these deaths were considered to be related to BNT162b2 by the investigators. Causes of death were balanced between BNT162b2 and placebo groups (Table S4).

Safety monitoring will continue according to the protocol for 2 years after the second dose for participants who originally received BNT162b2 and for 18 months after the second BNT162b2 dose for placebo recipients who received BNT162b2 after unblinding.

EFFICACY

Among 42,094 participants 12 years of age or older who could be evaluated and had no evidence of previous SARS-CoV-2 infection, Covid-19 with an onset of 7 days or more after the second dose was observed in 77 vaccine recipients and in 850 placebo recipients up to the data cutoff date (March 13, 2021), corresponding to a vaccine efficacy of 91.3% (95% confidence interval [CI], 89.0 to 93.2) (Table 2). Among 44,486 participants

with or without evidence of previous infection who could be evaluated, cases of Covid-19 were observed in 81 vaccine recipients and in 873 placebo recipients, corresponding to a vaccine efficacy of 91.1% (95% CI, 88.8 to 93.0).

Among the participants with evidence of previous SARS-CoV-2 infection based on a positive baseline N-binding antibody test, Covid-19 was observed in 2 vaccine recipients after the first dose and in 7 placebo recipients. Among the participants with evidence of previous SARS-CoV-2 infection based on a positive nucleic acid amplification test at baseline, cases of Covid-19 were observed in 10 vaccine recipients and in 9 placebo recipients (Table S5). Covid-19 was less common among the placebo recipients with positive N-binding antibodies at trial entry (7 of 542 participants, for an incidence of 1.3%) than among those without evidence of infection at trial entry (1015 of 21,521, for an incidence of 4.7%); these findings indicate that previous infection conferred approximately 72.6% protection.

Among the participants with or without evidence of previous infection, cases of Covid-19 were observed in 46 vaccine recipients and in 110 placebo recipients from receipt of the first dose up to receipt of the second dose, corresponding to a vaccine efficacy of 58.4% (95% CI, 40.8 to 71.2) (Fig. 2). During the interval from the approximate start of observed protection at 11 days after receipt of the first dose up to receipt of the second dose, vaccine efficacy increased to 91.7% (95% CI, 79.6 to 97.4). From its peak after the second dose, observed vaccine efficacy declined. From 7 days to less than 2 months after the second dose, vaccine efficacy was 96.2% (95% CI, 93.3 to 98.1); from 2 months to less than 4 months after the second dose, vaccine efficacy was 90.1% (95% CI, 86.6 to 92.9); and from 4 months after the second dose to the data cutoff date, vaccine efficacy was 83.7% (95% CI, 74.7 to 89.9).

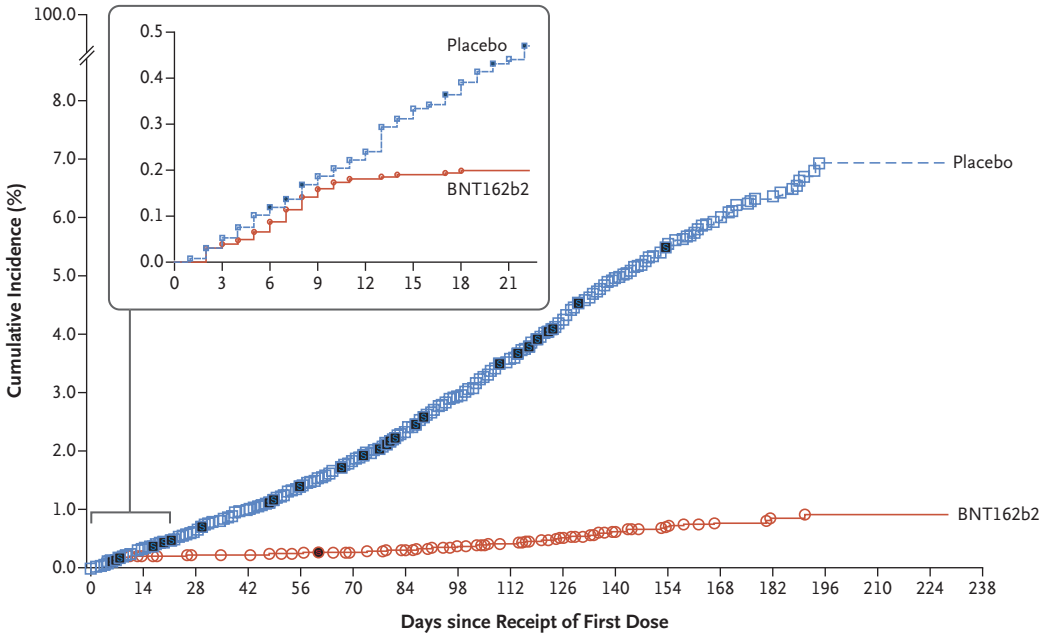
Severe Covid-19, as defined by the Food and Drug Administration,[13] with an onset after receipt of the first dose occurred in 31 participants, of whom 30 were placebo recipients; this finding corresponds with a vaccine efficacy of 96.7% (95% CI, 80.3 to 99.9) against severe Covid-19 (Fig. 2 and Table S6). Although the trial was not powered to definitively assess efficacy according to subgroup, supplemental analyses indicated that vaccine efficacy after the second dose in subgroups defined according to age, sex, race, ethnic group, presence or absence of coexisting medical conditions, and country was generally consistent with that observed in the overall population (Table 3 and Table S7).

Given the concern about the SARS-CoV-2 B.1.351 (or beta) variant, which appears to be neutralized less efficiently by BNT162b2-immune sera than many other lineages,[14] whole-viral-genome sequencing was performed on midturbinate samples from Covid-19 cases observed in South Africa, where this lineage was prevalent. Nine cases of Covid-19 were observed in South African participants without evidence of previous SARS-CoV-2 infection, all of whom were placebo recipients; this finding corresponds with a vaccine efficacy of 100% (95% CI, 53.5 to 100) (Table 3). Midturbinate specimens from 8 of 9 cases contained sufficient viral RNA for whole-genome sequencing. All viral genomes were the beta variant (Global Initiative on Sharing All Influenza Data accession codes are provided in the Supplementary Appendix).

DISCUSSION

In this update to the preliminary safety and efficacy report of two 30-μg doses, at 21 days apart, of BNT162b2, 91.1% vaccine efficacy against Covid-19 was observed from 7 days to 6 months after the second dose in participants 12 years of age or older. Vaccine efficacy against severe disease with an onset after receipt of the first dose was approximately 97%. This finding, combined with the totality of available evidence, including real-world effectiveness data,[15-18] alleviates theoretical concerns over potential enhancement of vaccine-mediated disease.[19]

The benefit of BNT162b2 immunization started approximately 11 days after receipt of the first dose, with 91.7% vaccine efficacy from 11 days after receipt of the first dose up to receipt of the second dose. The trial cannot provide information on persistence of protection after a single dose, because 99% of the participants received the second dose as scheduled during the blinded trial period. A recent trial showed that although nonneutralizing viral antigen–binding antibody levels rise between the first and second BNT162b2 dose, serum neutralizing titers are low or undetectable during this interval.[20] Early protection against Covid-19 without strong serum neutral-



Efficacy End Point	BNT162b2 (N=23,040)			Placebo (N=23,037)			Vaccine Efficacy
	No. of cases	Surveillance time	No. at risk	No. of cases	Surveillance time	No. at risk	
		1000 person-yr			*1000 person-yr*		*% (95% CI)*
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (85.3 to 89.9)
After receipt of first dose up to receipt of second dose	46	1.339	22,505	110	1.331	22,434	58.4 (40.8 to 71.2)
<11 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (–26.1 to 47.3)
≥11 Days after receipt of first dose up to receipt of second dose	5	0.662	22,399	60	0.656	22,369	91.7 (79.6 to 97.4)
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.2 (88.9 to 93.0)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

Figure 2. Efficacy of BNT162b2 against Covid-19 after Receipt of the First Dose (Blinded Follow-up Period).

The top of the figure shows the cumulative incidence curves for the first occurrence of coronavirus disease 2019 (Covid-19) after receipt of the first dose (efficacy analysis population of participants ≥12 years of age who could be evaluated). Each symbol represents Covid-19 cases starting on a given day, and filled symbols represent severe Covid-19 cases. Because of overlapping dates, some symbols represent more than one case. The inset shows the same data on an enlarged y axis through 21 days. The bottom of the figure shows the time intervals for the first occurrence of Covid-19 in the efficacy analysis population, as well as the surveillance time, which is given as the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from after receipt of the first dose to the end of the surveillance period for the overall row and from the start to the end of the range stated for each time interval. Vaccine efficacy was calculated as 100×(1−IRR), where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

ization indicates that neutralizing titers alone do not appear to explain early BNT162b2-mediated protection from Covid-19. Other immune mechanisms (e.g., innate immune responses, CD4+ or CD8+ T-cell responses, B-cell memory responses, and antibody-dependent cytotoxicity) may contribute to protection.[21-26]

Efficacy peaked at 96.2% during the interval from 7 days to less than 2 months after the second dose and declined gradually to 83.7% from

Table 3. Vaccine Efficacy against Covid-19 up to 7 Days after Receipt of the Second Dose among Participants without Evidence of Infection.*

First Occurrence of Covid-19 after Receipt of the First Dose	BNT162b2 (N=20,998)			Placebo (N=21,096)			Vaccine Efficacy (95% CI)‡
	No. of Cases	Surveillance Time†	No. at Risk	No. of Cases	Surveillance Time†	No. at Risk	
		1000 person-yr			*1000 person-yr*		*percent*
Overall population	77	6.247	20,712	850	6.003	20,713	91.3 (89.0 to 93.2)
Age group — yr							
16 or 17	0	0.061	342	10	0.057	331	100 (58.2 to 100)
16 to 55	52	3.593	11,517	568	3.439	11,533	91.2 (88.3 to 93.5)
≥55	25	2.499	8,194	266	2.417	8,208	90.9 (86.3 to 94.2)
≥65	7	1.233	4,192	124	1.202	4,226	94.5 (88.3 to 97.8)
≥75	1	0.239	842	26	0.237	847	96.2 (76.9 to 99.9)
Sex							
Male	42	3.246	10,637	399	3.047	10,433	90.1 (86.4 to 93.0)
Female	35	3.001	10,075	451	2.956	10,280	92.4 (89.2 to 94.7)
Race or ethnic group§							
White	67	5.208	17,186	747	5.026	17,256	91.3 (88.9 to 93.4)
Black or African American	4	0.545	1,737	48	0.527	1,737	91.9 (78.0 to 97.9)
Asian	3	0.260	946	23	0.248	934	87.6 (58.9 to 97.6)
American Indian or Alaska Native	0	0.041	186	3	0.037	176	100 (–119.0 to 100)
Native Hawaiian or other Pacific Islander	0	0.015	54	1	0.008	30	100 (–1961.2 to 100)
Multiracial	3	0.151	518	22	0.128	476	88.5 (61.6 to 97.8)
Not reported	0	0.026	85	6	0.030	104	100 (2.8 to 100)
Ethnicity§							
Hispanic or Latinx	29	1.786	5,161	241	1.711	5,120	88.5 (83.0 to 92.4)
Non-Hispanic and non-Latinx	47	4.429	15,449	609	4.259	15,484	92.6 (90.0 to 94.6)
Not reported	1	0.032	102	0	0.033	109	NA
Country							
Argentina	15	1.012	2,600	108	0.986	2,586	86.5 (76.7 to 92.7)
Brazil	12	0.406	1,311	80	0.374	1,293	86.2 (74.5 to 93.1)
Germany	0	0.047	236	1	0.048	242	100 (–3874.2 to 100)
South Africa	0	0.080	291	9	0.074	276	100 (53.5 to 100)
Turkey	0	0.027	228	5	0.025	222	100 (–0.1 to 100)
United States	50	4.674	16,046	647	4.497	16,046	92.6 (90.1 to 94.5)

* This analysis of vaccine efficacy during the blinded, placebo-controlled follow-up period included all participants who had undergone randomization and were 12 years of age or older without baseline evidence of previous infection who had undergone randomization. NA denotes not applicable.

† Surveillance time is the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from 7 days after the second dose to the end of the surveillance period.

‡ Vaccine efficacy was calculated as 100×(1−IRR). The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

§ Race and ethnicity were reported by the participants. The categories shown are those that were used to collect the data.

4 months after the second dose to the data cutoff date — an average decline of approximately 6% every 2 months. Ongoing follow-up is needed to understand persistence of the vaccine effect over time, the need for booster dosing, and timing of such a dose. Most participants who initially received placebo have now been immunized with BNT162b2, ending the placebo-controlled period of the trial. Nevertheless, ongoing observation of participants through 2 years in this trial, together with real-world effectiveness data,[15-18] will determine whether a booster is likely to be beneficial after a longer interval. Booster trials to evaluate safety and immunogenicity of BNT162b2 are under way to prepare for this possibility.

From 7 days after the second dose, 86 to 100% efficacy was observed across diverse demographic profiles, including age, sex, race or ethnic group, and factors that increase the risk of Covid-19, such as high body-mass index and other coexisting medical conditions. BNT162b2 was also highly efficacious in various geographic regions including North America, Europe, South Africa, and Latin America. Although vaccine efficacy was slightly lower in Latin American countries, BNT162b2 had a high efficacy of approximately 86% in Argentina and Brazil. Circulation of SARS-CoV-2 variants — some of which are associated with more rapid transmission and potentially greater pathogenicity[27] — has raised concerns that such variants could evade vaccine-mediated protection. Our studies of in vitro neutralization of a variety of SARS-CoV-2 variants have, to date, showed that all tested BNT162b2-immune sera neutralize all tested variants.[14,28-32] The beta variant, which has shown the greatest reduction in neutralization and was the dominant strain in South Africa during the reported observation period, is still neutralized at serum titers higher than those observed at the onset of protection against Covid-19 after the first vaccine dose.[9,14,20] We found that BNT162b2 had an observed efficacy of 100% (95% CI, 53.5 to 100) against Covid-19 in South Africa (9 cases occurred in the placebo recipients and 0 cases in the BNT162b2 recipients), and 8 of 9 cases for which sequence information could be obtained involved the beta variant of SARS-CoV-2.

Safety data are now available for approximately 44,000 participants 16 years of age or older; 12,006 participants have at least 6 months of safety follow-up data after a second BNT162b2 dose. The safety profile observed at a median of 2 months after immunization was confirmed through 6 months after immunization in the current analysis. No cases of myocarditis were noted.

Before immunization, 3% of the participants 16 years of age or older had evidence of SARS-CoV-2 infection. Although this group had a slightly higher incidence of systemic reactogenicity events after receipt of the first dose than those without evidence of previous infection, the group had a slightly lower incidence of reactogenicity events after the second dose than those without previous infection. Thus, there was minimal observed difference in the overall reactogenicity profile on the basis of infection status at baseline. Nine cases of Covid-19 were observed among participants with previous serologically defined natural infection: two cases were observed among the vaccine recipients and seven among the placebo recipients. These data support the current practice of immunizing without screening for evidence of previous infection.

This report has several limitations. Duration of protection and safety data that could be collected in a blinded, placebo-controlled manner were limited by the ethical and practical need to immunize eligible initial placebo recipients under emergency use authorization and according to the recommendations of public health authorities. The data presented here do not address whether vaccination prevents asymptomatic infection; however, evaluation of that question is ongoing in this trial, and real-world data suggest that BNT162b2 prevents asymptomatic infection.[33,34] Preliminary analyses of breakthrough cases have not yet identified a correlate of protection, since vaccine protection rates remain high. This report does not address vaccine efficacy and safety in pregnant women and in children younger than 12 years of age. Studies evaluating BNT162b2 in these populations are ongoing.

The data in this report show that BNT162b2 prevents Covid-19 effectively for up to 6 months after the second dose across diverse populations, despite the emergence of SARS-CoV-2 variants, including the beta variant, and the vaccine continues to show a favorable safety profile.

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CORRESPONDENCE

SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3

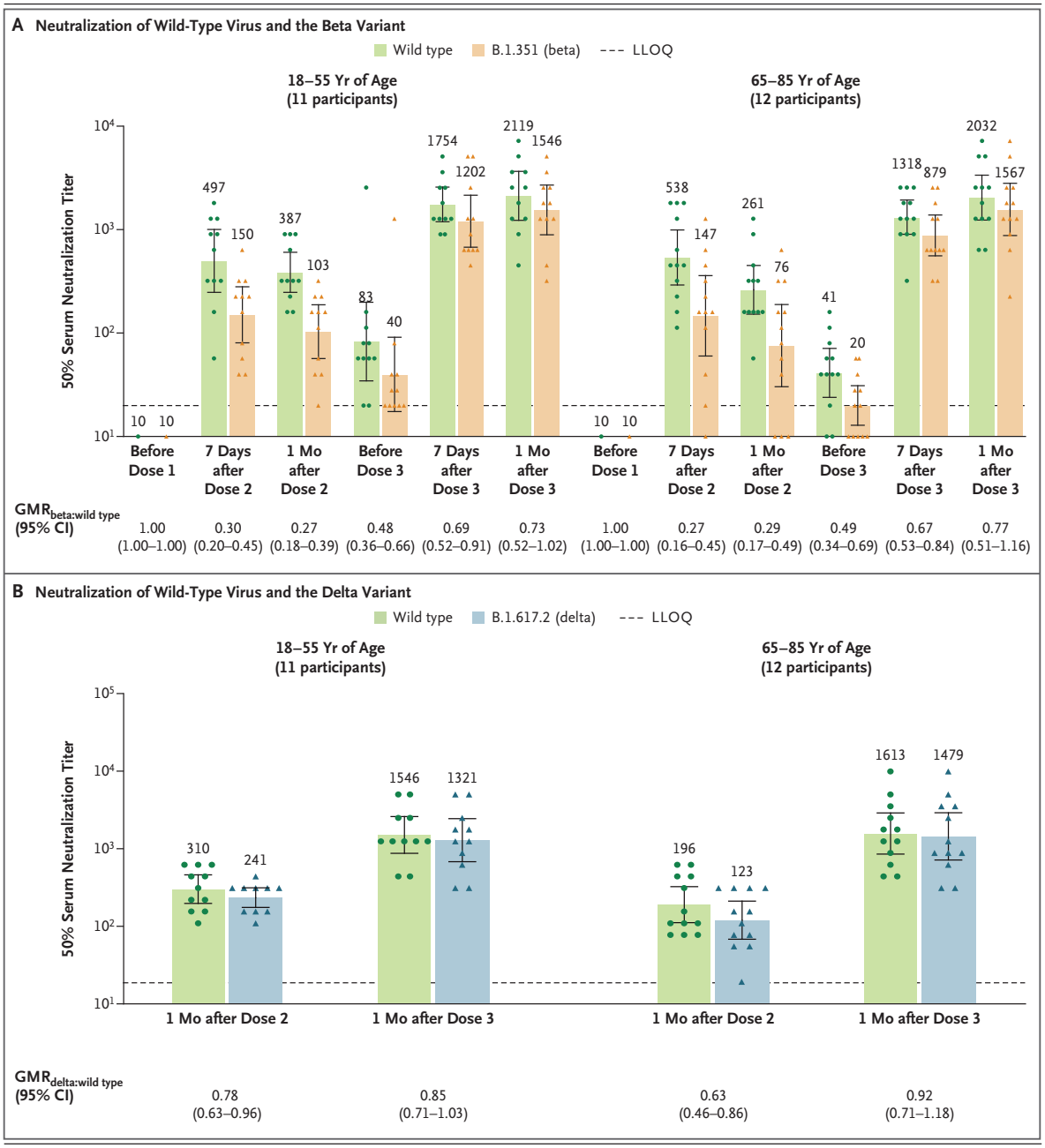
TO THE EDITOR: We conducted a global, randomized, placebo-controlled, phase 1–2–3 pivotal trial in which two 30-μg doses of BNT162b2 (Pfizer–BioNTech) were administered 21 days apart (ClinicalTrials.gov number, NCT04368728). These doses of vaccine had mainly low-grade side effects and provided 95% efficacy against coronavirus disease 2019 (Covid-19) from 7 days to approximately 2 months after dose 2.[1] Efficacy waned to 84% between 4 and approximately 6 months after dose 2.[2] Since vaccine authorization, viral variants have replaced the original strain, with the highly transmissible B.1.617.2 (delta) variant currently dominant.[3] Although the effectiveness of the vaccine against severe disease, hospitalization, and death remains high, waning immunity and viral diversification create a possible need for a third vaccine dose.

Therefore, we administered a third 30-μg BNT162b2 dose 7.9 to 8.8 months after dose 2 to 11 participants 18 to 55 years of age and to 12 participants 65 to 85 years of age from U.S. sites in the phase 1 part of the ongoing pivotal trial (additional details of the trial are provided in Table S1 and text within the Supplementary Appendix, as well as in the trial protocol, both of which are available with the full text of this letter at NEJM.org). Local reactions and systemic events after dose 3 were predominantly mild to moderate and were similar to those after dose 2 (Figs. S1 and S2). No unsolicited adverse events were reported in the month after dose 3.

We determined 50% serum neutralization titers against wild-type (USA-WA1/2020) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and a recombinant beta variant strain (i.e., the beta variant spike gene on wild-type genetic background), as described previously.[4] Serum specimens were obtained before dose 1, at 7 days and 1 month after dose 2, and before and 7 days and 1 month after dose 3 (Fig. 1A). These data supported four key conclusions. First, during the approximately 8 months from 7 days after dose 2 to before dose 3, SARS-CoV-2 neutralization geometric mean titers (GMTs) in this subgroup of participants from phase 1 of the trial declined far more rapidly than vaccine efficacy declined in participants in the phase 2–3 pivotal trial.[2] Second, by 1 month after dose 3, neutralization GMTs against wild-type virus increased to more than 5 times as high (in 18-to-55-year-olds) and to more than 7 times as high (in 65-to-85-year-olds) as the GMTs 1 month after dose 2. Third, neutralization GMTs against the beta variant increased more after dose 3 than

Figure 1 (next page). Neutralizing Responses after Two and Three Doses of BNT162b2.

The 50% neutralization titers against a wild-type target strain (USA-WA1/2020) and against B.1.351 (beta) lineage and B.1.617.2 (delta) lineage target strains are shown for both age groups. Geometric mean titers from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plaque-reduction neutralization testing are shown for serum specimens obtained at the time points shown on the x axes from participants in the dose 3 immunogenicity population (11 participants in the 18-to-55-year age group and 12 participants in the 65-to-85-year age group). I bars indicate 95% confidence intervals. Neutralization titers against wild-type virus were determined twice (once together with titers against each variant), and each titer against wild-type virus is reported separately with the corresponding variant titer. Differences among the determinations of the neutralization titer against wild-type virus represent experimental variation on repeat testing. Values above the error bars are geometric mean titers. Data points shown on the bar graph represent individual 50% neutralization titers. Individual titers for all participants are shown for all time points except for before dose 1, when all values were below the lower limit of quantitation (LLOQ) of 20; results below the LLOQ were set to 0.5 times the LLOQ. Geometric mean ratios (GMRs) of the titers against the variants and wild-type virus are shown below the graph. In Panel A, the geometric mean fold rises (GMFRs) in titers against the wild-type strain from before dose 3 to 1 month after dose 3 were 25.7 (95% confidence interval [CI], 12.4 to 53.3) for younger adults and 49.4 (95% CI, 29.2 to 83.3) for older adults. The corresponding GMFRs against the beta variant were 38.7 (95% CI, 19.8 to 75.5) and 78.3 (95% CI, 40.7 to 150.6), respectively.



did GMTs against wild-type virus, to more than 15 times as high (in younger adults) and more than 20 times as high (in older adults) as those after dose 2, reducing the gap between neutralization of wild-type virus and the beta variant. Fourth, neutralization GMTs decreased from 7 days to 1 month after dose 2 but increased from 7 days to 1 month after dose 3. A similar pattern of broader neutralization (i.e., against variant strains) and higher GMTs after dose 3 was seen in assays of neutralization GMTs against recombinant virus with delta variant spike protein on

a wild-type genetic background: the geometric mean ratio of neutralization GMTs (delta variant to wild type) 1 month after dose 3 was 0.85 in younger adults and 0.92 in older adults (Fig. 1B).

Increases in the magnitude and breadth of neutralization and improvements in the kinetics of the humoral response have also been observed with booster doses of prepandemic influenza vaccine administered after a primary immunization series.[5] The safety and immunogenicity of a booster dose of BNT162b2 administered 7 to 9 months after the primary two-dose series suggest that a third dose could prolong protection and further increase the breadth of protection.

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On request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices for indications that have been approved in the United States or European Union or in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after trial completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, through a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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