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Article

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

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. By January 2020, a novel coronavirus was identified as the etiologic agent. Within a month, the genetic sequence of the virus became available (MN908947.3). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and the resulting disease, coronavirus disease 2019 (COVID-19), have spread globally. On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic[1]. To date, the United States has reported the most cases globally[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 antigen structure and expression during natural infection. RNA is required for protein synthesis, does not integrate into the genome, is transiently expressed, and is metabolized and eliminated by the body's natural mechanisms and, therefore, is considered safe[4–7]. RNA-based prophylactic infectious disease vaccines and RNA therapeutics 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 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 now being studied clinically incorporates such nucleoside-modified messenger RNA (modRNA) and encodes the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, 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 (U.S., manuscript in preparation)[17]. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection[18]. BNT162b1 is one of several RNA-based SARS-CoV-2 vaccine candidates being studied in parallel

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for selection to advance to a safety and efficacy trial. Here, we present available data, through 14 days after a second dose in adults 18 to 55 years of age, from an ongoing Phase 1/2 vaccine study with BNT162b1, which is also enrolling adults 65 to 85 years of age (ClinicalTrials.gov identifier: NCT04368728).

Study Design and Demographics

Between 04 May 2020 and 19 June 2020, 76 participants were screened, and 45 participants were randomized and vaccinated. Twelve participants per dose level (10 μg and 30 μg) were vaccinated with BNT162b1 on Days 1 and 21, and 12 participants received a 100-μg dose on Day 1. Nine participants received placebo (Figure 1). The study population consisted of healthy male and nonpregnant female participants with a mean age of 35.4 years (range: 19 to 54 years); 51.1% were male and 48.9% were female. Most participants were white (82.2%) and non-Hispanic/non-Latinx (93.3%) (Extended Data Table 1).

Safety and Tolerability

In the 7 days following either Dose 1 or 2, pain at the injection site was the most frequent solicited local reaction, reported after Dose 1 by 58.3% (7/12) in the 10-μg, 100.0% (12/12 each) in the 30-μg and 100-μg BNT162b1 groups, and 22.2% (2/9) in the placebo group. After Dose 2, pain was reported by 83.3% (10/12) and 100.0% of BNT162b1 recipients at the 10-μg and 30-μg dose levels, respectively, and by 16.7% of placebo recipients. All local reactions were mild or moderate in severity except for one report of severe pain following Dose 1 of 100 μg BNT162b1 (Figure 2; Extended Data Table 2).

The most common systemic events reported in the 7 days after each vaccination in both BNT162b1 and placebo recipients were mild to moderate fatigue and headache. Reports of fatigue and headache were more common in the BNT162b1 groups compared to the placebo group. Additionally, chills, muscle pain, and joint pain were reported among BNT162b1 recipients and not in placebo recipients. 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). Following Dose 1, fever (defined as ≥38.0 °C) was reported by 8.3% (1/12) of participants in both the 10-μg and 30-μg groups and by 50.0% (6/12) of BNT162b1 recipients in the 100-μg group. Following Dose 2, 8.3% (1/12) of participants in the 10-μg group and 75.0% (9/12) of participants in the 30-μg group reported fever ≥38.0 °C. Based on 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. (Figure 3a, b, Extended Data Table 3). Most local reactions and systemic events peaked by Day 2 after vaccination and resolved by Day 7.

Adverse events (AEs) (Extended Data Table 4) were reported by 50.0% (6/12) of participants who received either 10 μg or 30 μg of BNT162b1, 58.3% (7/12) of those who received 100 μg of BNT162b1, and 11.1% (1/9) of placebo recipients. Two participants reported a severe AE: 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 AEs were reported by 25% (3/12 in the 10-μg groups) to 50% (6/12 each in 30-μg and 100-μg groups) of BNT162b1 recipients and by 11.1% (1/9) of placebo recipients. No serious adverse events (SAEs) 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 lymphocyte count after Dose 1 in 8.3% (1/12), 45.5% (5/11), and 50.0% (6/12) of 10 μg, 30 μg, and 100 μg BNT162b1 recipients, respectively. One participant each in the 10-μg group (8.3% [1/12]) and 30-μg group (9.1% [1/11]) dose levels and 4 participants in the 100-μg group (33.3% [4/12]) had Grade 3 decreases in lymphocytes. These post-Dose 1 decreases in lymphocyte count, were transient and returned to normal 6 to 8 days after vaccination (Extended Data Figure 1). In addition, Grade 2 neutropenia was noted 6 to 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 AEs or clinical manifestations of neutropenia have been reported to date. None of the postvaccination abnormalities observed were associated with clinical findings.

Immunogenicity

RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers were assessed at baseline, and at 7 and 21 days after the first dose, and at 7 (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 (Figure 4a). In comparison, a panel of 38 SARS-CoV-2 infection/COVID-19 convalescent sera drawn at least 14 days after a polymerase chain reaction (PCR)-confirmed diagnosis from patients 18 to 83 years of age had an RBD-binding IgG GMC of 602 U/mL. (Additional information on the convalescent serum panel is presented in 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 to 27,872 U/mL. RBD-binding antibody concentrations among participants who received one dose of 100 μg BNT162b1 did not increase beyond 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 to 16,166 U/mL compared to 602 U/mL in the human convalescent serum panel.

For all doses, small increases in SARS-CoV-2 neutralizing geometric mean titers (GMTs) were observed 21 days after Dose 1 (Figure 4b). Substantially greater serum neutralizing GMTs were achieved 7 days after the second 10 μg and 30 μg dose, reaching 168 to 267. Neutralizing GMTs further increased by 14 days after the second dose to 180 at the 10 μg dose level and 437 at the 30 μg dose level, compared to 94 for the convalescent serum panel. The kinetics and durability of neutralizing titers are being monitored.

Discussion

The RNA-based SARS-CoV-2 vaccine candidate BNT162b1 administered at 10 μg, 30 μg, and 100 μg to healthy adults 18 to 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 titers was observed after Doses 1 and 2 in adults 18 to 55 years of age with a particularly steep dose response between the 10 μg and 30 μg dose levels.

Based on 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 lymphocytes (Grades 1-3) were observed within a few days after vaccination, with lymphocyte counts returning to baseline within 6 to 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 substantially increased 7 days after the second dose given at Day 21. After the first dose, the RBD-binding IgG GMCs (10 μg dose recipients) 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/COVID-19. Post-Dose 1 GMCs were similar in the 30 µg and 100 µg groups and higher than those in the convalescent serum panel. After Dose 2 with 10 µg or 30 µg BNT162b1, the RBD-binding IgG GMCs were ~8.0-fold to ~50-fold that of the convalescent serum panel GMC.

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 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 antibody on the RBDs that are incorporated into the spikes of SARS-CoV-2 virions. Therefore, neutralization provides a measure of vaccine-elicited antibody response that is more relevant to potential protection. Neutralization titers were measurable after a single vaccination at Day 21 for all dose levels. At Day 28 (7 days after Dose 2), substantial SARS-CoV-2 neutralization titers were observed. The virus-neutralizing GMTs after the 10 µg and 30 µg Dose 2 were, respectively, 1.8-fold and 2.8-fold the GMT of the convalescent serum panel. By Day 35 (14 days after Dose 2), despite the decrease in RBD-binding IgG titers since Day 28, neutralizing GMTs continued to rise, to 1.9-fold and 4.6-fold the GMT of the convalescent panel for the 10 µg and 30 µg doses, respectively, consistent with affinity maturation.

Assuming that neutralization titers induced by natural infection provide protection from COVID-19 disease, comparing vaccine-induced SARS-CoV-2 neutralization titers to those from sera of convalescent humans provides a benchmark for the magnitude of the vaccine-elicited response and the vaccine's potential to provide protection. Because a protective human neutralizing titer is unknown, these findings are not proof of vaccine efficacy. Efficacy will be determined in a pivotal Phase 3 trial. Because the 100 µg dose level cohort was not boosted, 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 Dose 1. 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. While 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. Further, 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 SAEs for 6 months and COVID-19 infection and multiple additional immunogenicity measurements through up to two years. While our population of healthy adults 55 years of age and younger is appropriate for a Phase 1/2 study, it does not accurately reflect the population at highest risk for COVID-19. Adults 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 enrollment of more diverse populations, including those with chronic underlying health conditions and from racial/ethnic groups 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 encoding the full-length spike, and a parallel trial in Germany, in which additional immune responses, including neutralizing responses against variant strains and cell-mediated responses, are being assessed (U.S. manuscript in preparation)[24]. The resulting comparative data will allow us to address whether a full-length spike immunogen, which presents additional epitopes, is better able than the relatively small RBD immunogen encoded by BNT162b1 to elicit high virus neutralizing titers that are robust to potential antigenic drift of SARS-CoV-2. 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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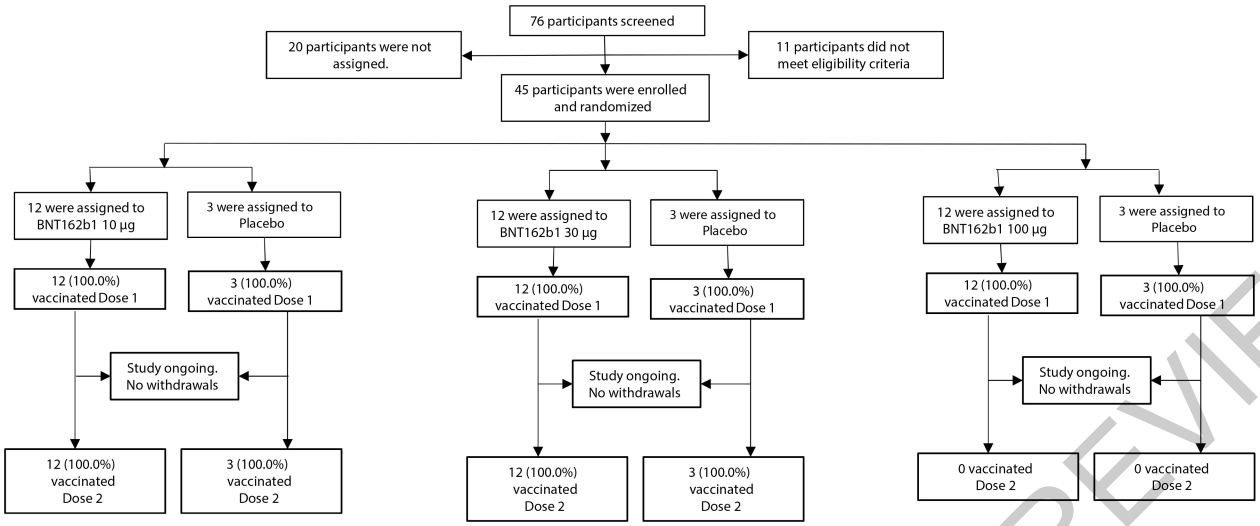


Figure 1 | Disposition of participants. Participants not assigned (n=20) were screened but not randomized because enrollment had closed.

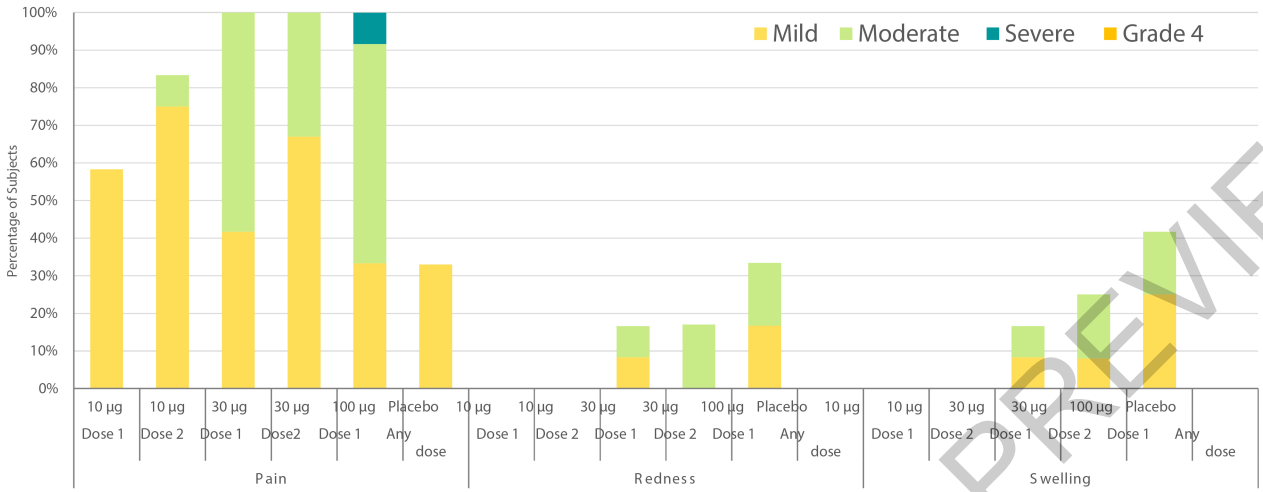
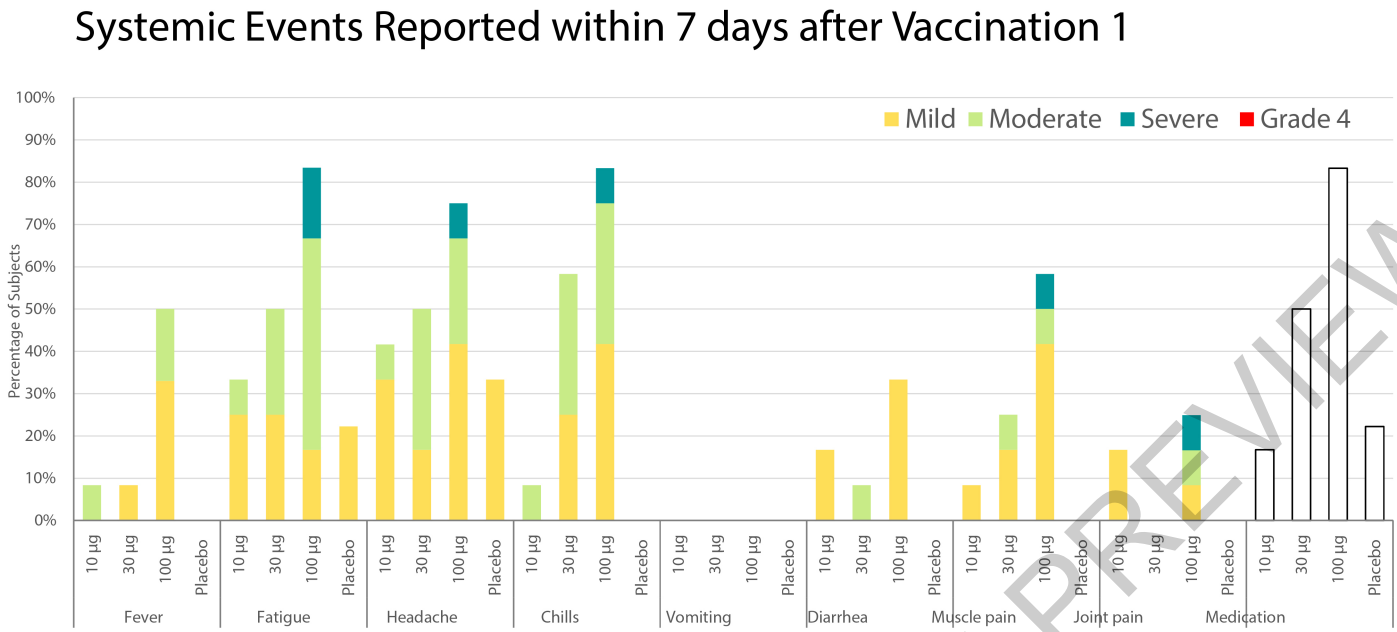


Figure 2 | Local reactions reported within 7 days of vaccination for all dose levels. Solicited injection-site (local) reactions were: pain at injection site (mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization) and redness and swelling (mild: 2.0 to 5.0 cm in diameter; moderate: >5.0 to 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.



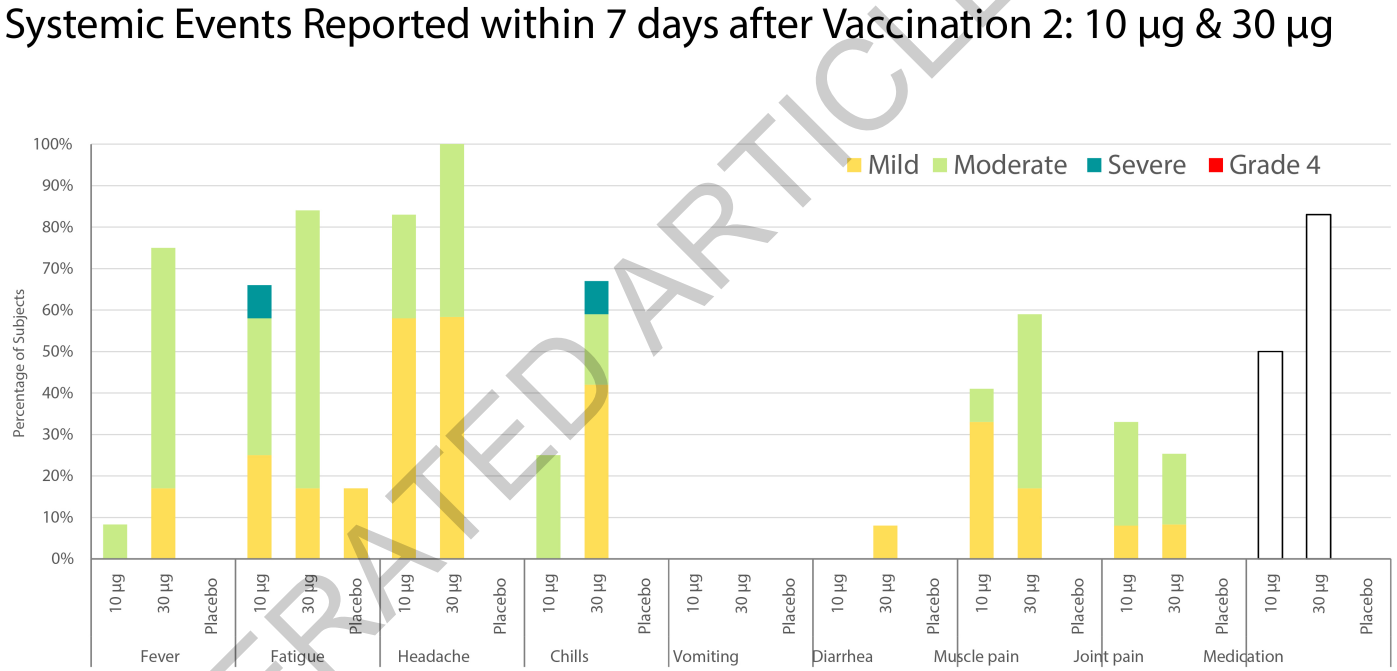


Figure 3 | a. Systemic events and medication use reported within 7 days after Vaccination 1 for all dose levels and b. After Vaccination 2 for the 10-µg and 30-µg dose levels. Solicited systemic events were: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does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

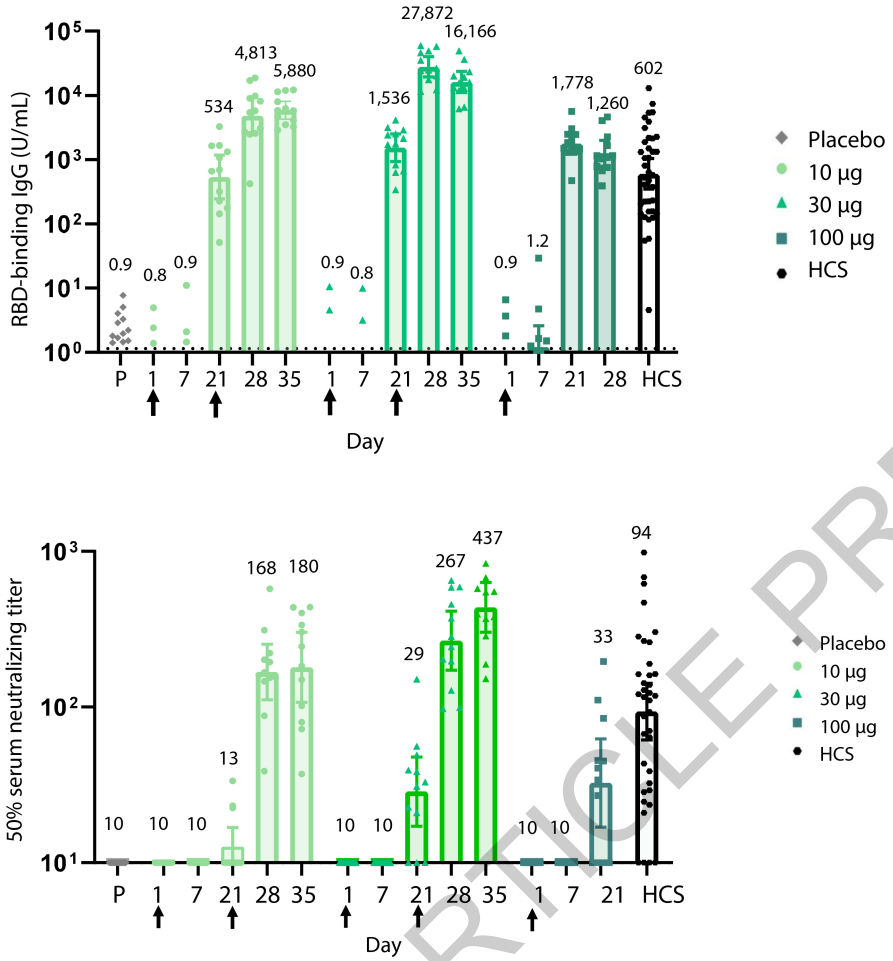


Figure 4 | Immunogenicity of BNT162b1. Participants in groups of 15 were vaccinated with the indicated dose levels of BNT162b1 (n=12) or with placebo (n=3) on Days 1 (all dose levels and placebo) and 21 (10 µg and 30 µg dose levels and placebo). Reponses in placebo recipients for each of the dosing groups are combined. The 28-day bleed is 7 days after the second vaccination. Sera were obtained before vaccination (Day 1) and 7, 21, and 28 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 Luminex assay measured antibody concentrations are in arbitrary units, they cannot be directly translated into concentrations on a molar or mass basis. Lower limit of quantitation is 1.15. **b**. 50% SARS-CoV-2 neutralizing GMTs. Each data point represents a serum sample, and each vertical bar represents a geometric mean with 95% CI. The number above the bars are either the GMC or GMT for the group. Arrows indicate timing of vaccination (blood draws were conducted prior to vaccination on vaccination days).

Methods

Study design

This study was conducted in healthy men and nonpregnant women 18 to 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 United States. This study utilized a sentinel cohort design with progression and dose escalation taking place after review of data from the sentinel cohort at each dose level.

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 (NAAT)-positive nasal swab within 24 hours before study vaccination.

The final protocol and informed consent document were approved by institutional review boards for each of the participating investigational centers. This 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. A signed and dated informed consent form was required before any study-specific activity was performed.

Endpoints

In this report, results from the following study primary endpoints are presented: the proportion of participants reporting solicited local reactions, systemic events, and use of antipyretic and/or pain medication within 7 days after vaccination, AEs and 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 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 were to receive two 0.5-mL doses of either BNT162b1 or placebo, administered by intramuscular injection into the deltoid muscle.

BNT162b1 incorporates a Good Manufacturing Practice (GMP)-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 code MN908947.3. The mRNA is formulated with lipids as the mRNA-LNP 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-hour observation after vaccination (for the first 5 participants vaccinated in each group), or a 30-minute observation (for the remainder of participants) for immediate AEs. 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, diarrhea, 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 AEs and SAEs after vaccination. Hematology and chemistry assessments were conducted at screening, 1 and 7 days after Dose 1, and 7 days after Dose 2.

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 prior to the publication of this report.

Human convalescent serum panel

The 38 human SARS-CoV-2 infection/COVID-19 convalescent sera were drawn from participants 18 to 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 titer for the one hospitalized individual was 618. The sera were obtained from Sanguine Biosciences (Sherman Oaks, CA), the MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY).

Immunogenicity assessments

50 mL of blood was collected for immunogenicity assessments before each study vaccination, at 7 and 21 days after Dose 1, and at 7 and 14 days after Dose 2. In the RBD-binding IgG assay, a recombinant SARS-CoV-2 RBD containing a C-terminal Avitag™ (Acro Biosystems Cat# SPD-C82E9) and no foldon domain was bound to streptavidin-coated Luminex® microspheres. Briefly, 1.25×10^7 microspheres/mL were coated with streptavidin by 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC) reaction. Recombinant RBD Avitag was coupled to streptavidin beads by incubating for 90 minutes at room temperature with shaking (35 RPM). Beads were blocked in 1% BSA buffer for 30 minutes at room temperature. Heat-inactivated subject serum was diluted 1:500, 1:5000, and 1:50000 in assay buffer (PBS with 0.5% BSA, 0.05% Tween, and 0.02% sodium azide). Following a 16- to 20-hour 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 minutes 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 post 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 PFU/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]. Briefly, serial dilutions of heat inactivated sera were incubated with the reporter virus to yield approximately a 10% to 30% infection rate of the Vero

monolayer) for 1 hour at 37 °C before inoculating Vero CCL81 cell monolayers (targeted to have 8,000 to 15,000 cells per well) in 96 well plates to allow 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 to 24 hours after inoculation with a Cytation™ 7 Cell Imaging Multi-Mode Reader (BioTek) with Gen5 Image Prime version 3.09. Titers were calculated in GraphPad Prism version 8.4.2 by generating a 4-parameter (4PL) logistical fit of the percent neutralization at each serial serum dilution. The 50% neutralization titer (VNT_{50}) was reported as the interpolated reciprocal of the dilution yielding 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 hematology and chemistry laboratory parameters, AEs, and SAEs 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, with the database 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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26. Muruato, A.E., Fontes-Garfias, C.R., Ren, P. *et al*. A high-throughput neutralizing antibody assay for COVID-19 diagnosis and vaccine evaluation. *bioRxiv*. https://doi.org/10.1101/2020.05.21.109546 (2020).

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Author contributions KUJ, PRD, WCG, NK, SL, AG, RB, and US were involved in the design of the overall study and strategy. KN, MJM, EEW, RF, and ARF provided feedback on the study design. WK, DC, KAS, KRT, CFG and PYS performed the immunological analyses. MJM, KN, EEW, RF, ARF, KEL, and VR collected data as study investigators. PL and KK developed the statistical design and oversaw the data analysis. JA, KUJ, PRD, and WCG drafted the initial version of the manuscript. All authors reviewed and edited the manuscript and approved the final version.

Competing interests NK, JA, AG, SL, RB, KAS, PL, KK, WK, DC, KRT, PRD, WCG, and KUJ are employees of Pfizer and may hold stock options. US and ÖT are stock owners, management board members, and employees at BioNTech SE (Mainz, Germany) and are inventors on patents and patent applications related to RNA technology. MJM, KEL, KN, EEW, ARF, RF, and VR received compensation from Pfizer for their role as study investigators. CFG and PYS received compensation from Pfizer to perform the neutralization assay.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41586-020-2639-4.

Correspondence and requests for materials should be addressed to J.A.

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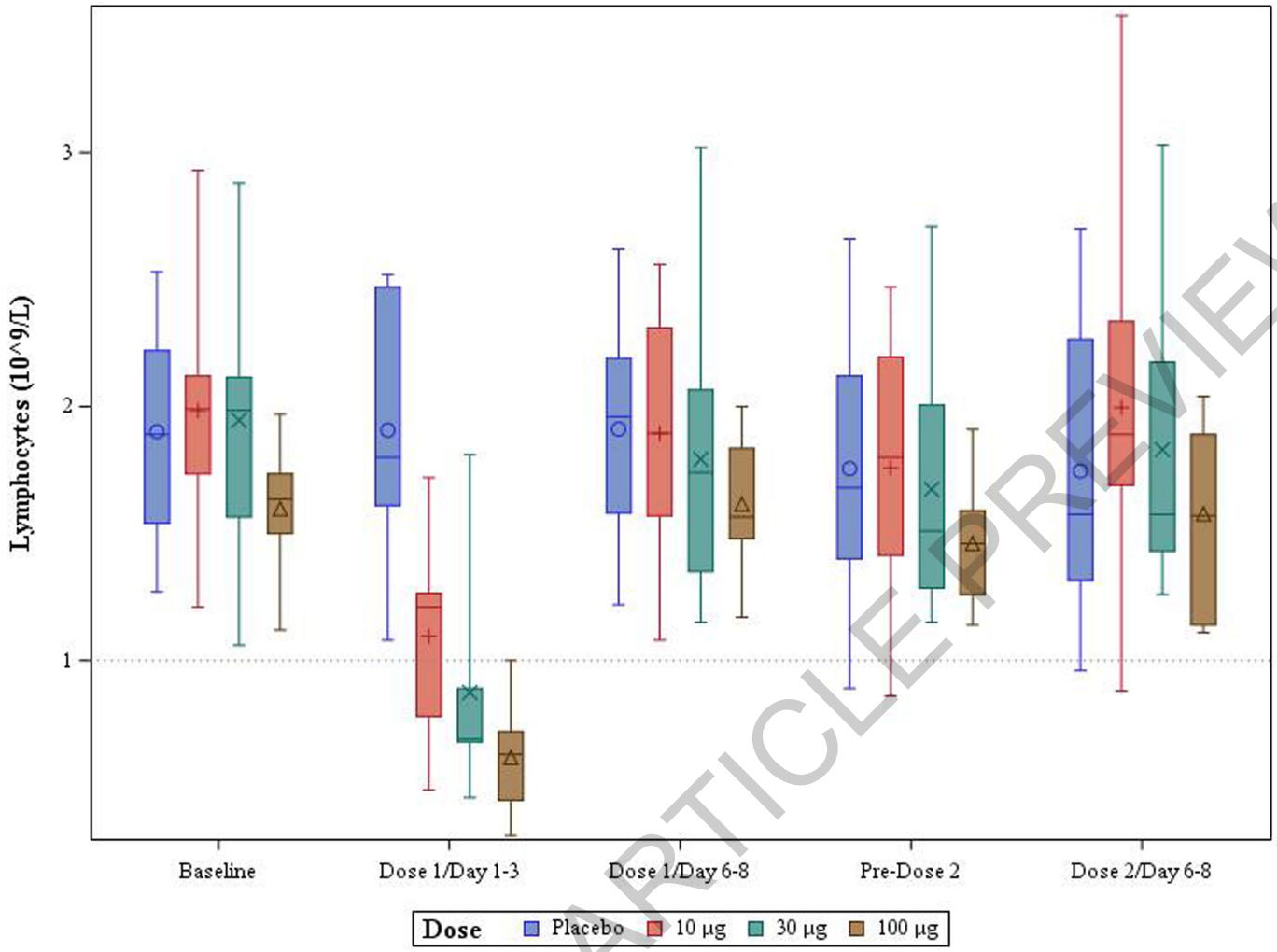

Extended Data Figure 1 | Post Vaccination Changes in Lymphocyte Count Over Time. Figure represents box-and-whisker plots for observed values at the following timepoints: Dose 1/Day 1-3: -1 day after Dose 1; Dose 2/Day 6-8: -7 days after Dose 1; Pre-Dose 2: before Dose 2; Dose 2/Day 6-8: -7 days after Dose 2. Symbols denote group means – O: placebo; +: 10 µg; X: 30 µg; Δ: 100 µg. Center line of box denotes median; lower and upper edges denote first and third quartiles; lower and upper whiskers denote minimum and maximum.

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 = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations. n = Number of subjects 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: number of subjects in the specified group or the total sample. This value is the denominator for the percentage calculations. n: number of subjects reporting at least 1 occurrence of the specified adverse event category. For "any event", n: the number of subjects reporting at least 1 occurrence of any adverse event; Related: Assessed by the investigator as related to 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)
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☒	☐	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

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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 lgG geometric mean concentrations (GMCs) 7 and 21 days after Dose 1 and 7 and 14 days after Dose 2