First report demonstrating the safety and immunogenicity of the SARS-COV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, observer-blind Phase I study

Fengcai Zhu (jszfc@vip.sina.com)
NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention; Center for Global Health, Nanjing Medical University

Jingxin Li
Jiangsu Provincial Center for Disease Control and Prevention

Aimin Hui
Fosun Pharma

Xiang Zhang
Taizhou City Center for Disease Control and Prevention

Yumei Yang
Fosun Pharma

Rong Tang
Jiangsu Provincial Center for Disease Control and Prevention

Huayue Ye
Taizhou Vaccine Clinical Research Center; Department of Pharmacy, Army Medical University

Ruiru Ji
Fosun Pharma

Mei Lin
Taizhou people's Hospital

Zhongkui Zhu
Taizhou City Center for Disease Control and Prevention

Özlem Türeci
BioNTech SE

Siyue Jia
NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention

Hongxing Pan

NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention

Fuzhong Peng
Taizhou Vaccine Clinical Research Center; Department of Pharmacy, Army Medical University

Zhilong Ma
Taizhou City Center for Disease Control and Prevention

Zhenggang Wu
Taizhou people's Hospital

Yunfeng Shi
NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Contr

Martin Bexon
Bexon Clinical Consulting LLC

Ugur Sahin
Biontech

Li Zhu
Taizhou people's Hospital

Article

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Abstract

An effective vaccine is needed to end the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. Data from the U.S. NCT04368728 and German EudraCT 2020-001038-36 vaccine trials was recently reported, showing the safety, tolerability, and antibody response of the BNT162b1 vaccine candidate. BNT162b1 encodes the SARS-CoV-2 spike glycoprotein receptor-binding domain and is one of several RNA-based SARS-CoV-2 vaccine candidates under study. Here, we report preliminary results from a Phase I trial testing BNT162b1 in 144 healthy Chinese participants. The safety profile was broadly comparable to that seen in the American and German trials, with fever the only Grade 3 adverse event reported. Prime-boost vaccination with 10 μg or 30 μg BNT162b1 induced robust antibody responses in both younger (18 to 55 years of age) and older (65 to 85) Chinese adults, and interferon-γ T-cell responses to RBD antigen challenge were significantly higher in participants receiving BNT162b1 than those in placebo groups. The 30 μg dose induced increased reactogenicity as well as a more favorable vaccine-elicited virus-neutralizing response than the 10 μg dose in both younger and older Chinese adults. In conclusion, this first report of an mRNA vaccine in an Asian population showed similar results to BNT162b1 trials. This trial was funded by Fosun and BioNTech and registered under ChiCTR2000034825 and NCT04523571.

Introduction

Since the first cases of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection were identified in December 2019, the resulting pandemic has led to over 75 million confirmed COVID-19 cases, and over 1.6 million deaths worldwide as of the 16th December 2020[1,2]. The development of an efficacious COVID-19 vaccine is currently the world's leading research priority[3]. According to a survey conducted by the World Health Organization in November 2020, there were 47 vaccine candidates in clinical trials, of which ten were ongoing Phase III trials. A further 155 vaccine candidates were in preclinical trials[4].

Compared with other traditional approaches like inactivated or live virus vaccines or recombinant proteins, the RNA-based prophylactic vaccine platform is a novel, recently developed vaccine technology[5]. The RNA-based platform has enabled rapid vaccine development in response to the COVID-19 pandemic and provided flexibility in antigen design[6,7] and has provided the first COVID19 vaccine to be approved or authorized. At the time of writing, the mRNA vaccine BNT162b2, has been authorized for use in Europe from the EMA and Switzerland from Swissmedic, and has emergency use authorization in UK, the U.S. and other countries as of December 2020[8,9].

BNT162b2 is one of several lipid nanoparticle-formulated, nucleoside-modified messenger RNA vaccines against SARS-CoV-2 developed within "Project Lightspeed" launched by BioNTech, in collaboration with Pfizer and Fosun Pharma. The program involves a series of clinical trials that are currently being conducted in Germany, the United States, and China[10,11], among other countries.

BNT162b2 that encodes an optimized, full-length SARS-CoV-2 spike glycoprotein has been selected based on thorough comparison with BNT162b1 that encodes the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) cloned into the same vector backbone.

Data showing the safety, tolerability and significant neutralizing titers elicited by the BNT162b1 vaccine were recently reported from the ongoing U.S.-based Phase I/II/III NCT04368728[10,11] and Germany-based Phase I/II NCT04380701/EudraCT 2020-001038-36 vaccine trials[12]. In aggregate, interim data showed that local and systemic reactions were dose-dependent, transient, and generally mild to moderate. Prime-boost dosing with 10 μg and 30 μg dose levels elicited significant neutralizing titers in participants aged 18 to 55 and 65 to 85 beyond that seen in a panel of COVID-19 human convalescent sera (HCS), while the planned boost dosing with a 100 μg dose was not performed due to increased reactogenicity and a lack of meaningfully increased immunogenicity after the single priming dose in the younger age group, compared with the 30-μg dose in the U.S. NCT04368728 trial[11]. Similar findings for dose-dependency of RBD-binding IgG and neutralization responses were reported from the German EudraCT 2020-001038-36 trial for the 10 and 30 μg dose levels of BNT162b1 investigated in participants 18 to 55 years of age.

The preliminary safety and immunogenicity data for the vaccine candidate that we present here from the China-based ChiCTR2000034825/NCT04523571 study, investigating BNT162b1 in healthy, young and elderly Chinese participants, suggests that prime-boost vaccination with 10 μg and 30 μg dose levels of the BNT162b1 vaccine induces a strong humoral and cellular immune response in both younger adults of 18 to 55 years of age and older adults of 65 to 85 years of age, with robust RBD-specific antibody and T-cell responses seen in both younger and older participants, 7 days following the second BNT162b1 dose. The vaccine displayed a similar tolerability profile in this population to that seen in the American and German populations previously tested.

In conclusion, we provide the first clinical report on a mRNA-based vaccine in the Chinese population indicating that this vaccine technology performs comparably across ethnicities.

Results

Study design and analysis set

Between July 18, 2020, and August 14, 2020, a total of 296 adults aged between 18-55 years or 65-85 years were screened at Taizhou vaccine clinical research center in Jiangsu Province, in China. 144 eligible participants consented to participate in the trial and were randomized 1:1:1 to receive prime and boost doses of BNT162b1 at 10 μg or 30 μg, or two placebo doses 21 days apart (Figure 1), with an equal allocation for each age group. Following priming doses, two participants (one at 10 μg, one at 30 μg) between the ages of 65 and 85 years had withdrawn from boost dose administration (Extended Data Table 1). The demographic characteristics of the participants are shown in Table 1. The mean age among the younger participants ranged from 37.9 to 42.0 years, and the mean age among the older participants ranged from 68.5 to 70.7 years in the treatment groups, with equal gender distribution across

treatment groups. The medical history or existing underlying disorders of the participants were similar across treatment groups, except for hypertension, which was noted in a higher frequency in the BNT162b1 older participants groups at baseline.

Preliminary safety and tolerability data

No pre-specified trial-halting rules were met during the study. Only one serious adverse event was reported by a participant of 67 years of age (a humerus fracture caused by a car accident, preventing the participant from receiving the boost dose) which was considered as not related to the vaccine or study procedure. The overall frequencies of injection site adverse reactions post-vaccination were comparable after the BNT162b1 prime and boost doses. Some systematic adverse reactions such as fever (oral temperature ≥38ºC), headache, fatigue, and malaise occurred more commonly after the BNT162b1 boost dose than after the prime dose in younger adults (Extended Data Figure 1). Fevers generally resolved within 48 hours of onset. In contrast to the younger participants, elderly participants did not present increased reactogenicity after the BNT162b1 boost dose (Extended Data Figure 2).

There were no changes reported in blood pressure and respiratory rates among the participants across different treatment groups before and after BNT162b1 administration. Transient increases of temperature and pulse rate 24 hours post-vaccination were noted in both younger and older participants, especially in the 30 μg dose group (Extended Data Figure 3). The most common abnormalities in laboratory values from baseline were transient decreases in lymphocyte and platelet counts and increases in C-reaction protein (CRP). All laboratory abnormalities were self-limited and resolved in a short period of time without clinical manifestations (Extended Data Figure 4). These data are in line with the results seen in EudraCT 2020-001038-36 study, and other RNA vaccine trials that have found CRP levels[15,16] and lymphocyte counts[17] to act as pharmacodynamic markers for the mode-of-action of these vaccines.

Vaccine-induced antibody responses

SARS-CoV-2 neutralization titers as well as RBD-binding and S1-binding antibody titers were assessed at baseline (Day 1, pre-vaccination), 7 and 21 days after the priming dose (Days 8 and 22), and 7 and 21 days after the boost dose (Days 29 and 43). The BNT162b1 induced antibody responses in vaccinated participants were compared with a panel of human COVID-19 convalescent serum obtained at least 14 days after PCR-confirmed diagnosis from 24 Asian COVID-19 hospitalized patients, 21 of whom had symptomatic disease. All participants were seronegative at baseline (Day 1, pre-vaccination) and showed a modest vaccine-induced antibody response 21 days after the priming dose (Day 22) which further increased on Day 29 (Figure 2 and Extended Data Table 3). The highest neutralization titers were observed on Day 43 (i.e., 21 days after the BNT162b1 boost dose) for both younger and older adults, indicating a continuous uptrend in this group of Asian participants after day 29. This is different from previous BNT162b1 reports showing peak titers occurring earlier and subsequently subsiding in the elderly population[16]. The SARS-CoV-2 neutralizing titer is defined as the reciprocal of the highest sample

dilution that protects at least 50% cells from cytopathic effects. The 50% neutralizing geometric mean titers (GMTs) in the 10 μg and 30 μg dose groups were 232.9 (95% CI 151.3 to 358.5) and 254.0 (184.6 to 349.4) in the younger participants, and 80.0 (49.2 to 130.2) and 160.0 (96.7 to 264.6) in the older participants, respectively. The virus-neutralizing responses of younger participants in the 10 μg and 30 μg dose groups were 1.9 and 2.1 times the GMT of the convalescent sera panel (GMT, 119.9; 95% CI, 70.4 to 203.9). In the older participants, the corresponding ratios were 0.7 and 1.3 times in the 10 μg and 30 μg dose groups, respectively (Extended Data Table 4). All the younger recipients seroconverted by Day 43, and the seroconversion rate was 91% at the 10 μg dose and 96% at the 30 μg dose in the older recipients on Day 43, respectively (Extended Data Figure 5). Participants who received the 30 μg dose appeared to have somewhat higher virus-neutralizing antibody responses than those received the 10 μg dose. However, the older participants between the ages of 65 and 85 generally showed a slower virus-neutralizing response and lower peak response than the younger participants between the ages 18 and 55.

Similarly, both doses of BNT162b1 induced high levels of S1-binding and RBD-binding IgG after the prime-boost regimen. The S1-binding and RBD-binding IgG levels after vaccination across all timepoints evaluated in the vaccine recipients were highly correlated with the neutralizing titers regardless of the age and dose groups, with a correlation coefficient of 0.85, and 0.79 ($p<0{\cdot}0001$), respectively (Extended Data Figure 6).

Vaccine-induced T-cell responses

Vaccine-induced T-cell responses were characterized at baseline (pre-prime, Day 1), on Day 29 (7 days after the boost vaccination) and on Day 43 (21 days after the boost vaccination), using a direct ex vivo IFNγ enzyme-linked immunosorbent spot (ELISpot) assay with peripheral blood mononuclear cells (PBMCs). At Day 29, spot-forming units after stimulation with Sp1 peptide pool (which includes the RBD sequence) were significantly higher in participants receiving 10 μg or 30 μg of BNT162b1 groups than those in placebo group in both age groups (Figure 3). Younger participants aged 18 to 55 years had average spot-forming units of 227.5 (95% CI, 146.5 to 308.5) in those who had received 10 μg vaccinations, and 223.5 (181.2 to 265.9) in those who had received the 30 μg vaccinations per 10^5 PBMCs. In older participants aged 65 to 85 years, a slightly lower spot-forming units with averages of 156.5 (84.1 to 229.0) and 171.9 (113.4 to 230.3) were noted post-vaccination across the two dose groups. At Day 43, younger participants receiving the prime-boost BNT162b1 regimen tended to show a mild decrease in their S1-specific IFN-γ ELISpot response compared to that seen on Day 29; no blood samples were collected at this time point from the older participants, this data is accordingly not available. No differences between the BNT162b1 and the placebo groups were observed for IFN-γ ELISpot responses to the Sp2 peptide pool (which does not include peptides of the RBD encoded by BNT162b1) and minor non-specific responses to CD8+ T cells were observed in both dose groups.

Discussion

Both BNT162b1 and BNT162b2 were granted Fast-Track designation by the U.S. FDA in July 2020. This trial was conducted in China in parallel with other BNT162 vaccine candidates in multiple regions[10,12–14]. BNT162b2 was selected as the global lead candidate in late July 2020[20], and was approved in December for use in Europe from the EMA and Switzerland from Swissmedic, and for Emergency Authorization Use in the U.S. by the FDA, and in the UK by The Medicines and Healthcare products Regulatory Agency (MHRA). However, there is little data available for the safety and immunogenicity of mRNA vaccines in Asian populations. This report provides the first evaluation of both the safety and immunogenicity profiles of such an mRNA vaccine in a Chinese population. Obtaining a first understanding of the profile of mRNA vaccines in Chinese populations is important to inform ongoing development of similar products to treat the pandemic.

This is a preliminary report of the clinical trial of the modified-RNA-based SARS-CoV-2 vaccine candidate BNT162b1, which encodes the SARS-CoV-2 RBD, administered to a healthy adult Chinese population. BNT162b1 has been shown to exhibit a broadly similar immunogenicity profile as BNT162b2 (modRNA encoding the full-length SARS-CoV-2 spike glycoprotein, derived from the same nucleoside-modified platform), inducing strong vaccine-induced antibody responses and strong T-cell responses[20]. The clinical safety and immunogenicity of the BNT162b1 vaccine candidate were evaluated within the Phase 1 portions of the German NCT04380701/EudraCT 2020-001038-36 study in younger (18 to 55 years of age) and older healthy adults (56 to 85 years of age), and the United States-based NCT04368728/C4591001 study in younger (18 to 55 years of age) and elderly healthy adults (65 to 85 years of age). Our data show that BNT162b1 exhibited a tolerability, safety and immunogenicity profile consistent with those prior reports at doses of 10 μg and 30 μg in younger and elderly healthy Asian adults (18–55 years and 65–85 years of age).

In agreement with the previous reports, pain at the injection site was the most common solicited adverse reactions reported in Chinese participants. No injection site reactions were graded as severe (Grade 3). In line with prior reports, fever, headache, fatigue, malaise, joint pain, muscle pain and chills were confirmed in this study as most common systemic solicited adverse reactions. As previously reported, these adverse events were transient and either managed with simple standard of care management, or resolved spontaneously. The observed reactogenicity to BNT162b1 was dose-dependent and a higher frequency of adverse events was generally observed after the second dose. Mild or moderate headache was higher in the younger Chinese participants (79%, 19 out of 24 participants) vs 13% (3 out of 24 participants) in the younger placebo group and 8% (2 out of 24 participants) in the elderly Chinese group. This difference might be attributed to the relatively small sample sizes evaluated in this Phase 1 study. A mild safety profile was observed in elderly Chinese subjects vaccinated with BNT162b1, with fever being the only severe adverse reaction observed in 2 out of 24 participants (8%). In summary, comparative analyses of the BNT162b1 safety profile with prior reports at 30 μg showed a comparable, and in the systemic reactogenicity profile in the older population even a better safety profile in the Asian population vs non-Asian. Furthermore, laboratory investigations showed transient decreases in lymphocyte counts predominantly in the younger recipients at the BNT162b1 30 μg dose level, in line with the reported mode-

of-action of the vaccine, causing the redistribution of lymphocytes into lymphoid tissues by innate immune stimulation[13]. In summary, the preliminary data of our study further complements and expands reporting of BNT162b1 and other RNA-based vaccine candidates from clinical trials conducted in Germany and the United States to an Asian population[10,11,13].

Both doses of the vaccine candidate BNT162b1 were effective at eliciting specific humoral and cellular immune responses, with a clear boost effect of the second vaccination on antibody titers observed in both younger and older adults. BNT162b1 administered at a 30 μg dose as two doses 21 days apart induced a strong immune response in terms of virus-neutralizing antibody to SARS-CoV-2, which was higher than that observed in a panel of convalescent serum samples from Asian subjects with COVID 19, regardless of age. The humoral response in the Chinese participants showed a unique temporal pattern and peaked at Day 43 in both age groups. However, given the small number of participants and methodological differences in the assays used among this and the prior BNT162b1 studies, it is premature to conclude that there is a population-based difference in the humoral immune response to the BNT162b1 modified-RNA-based SARS-CoV-2 vaccine candidate.

Since the vaccine candidate BNT162b1 is a modified RNA vaccine encoding a trimeric version of the RBD, the vaccine recipients in our study demonstrated significant T-cell responses specific to the S1 peptide pool, which is a SARS-CoV-2 S1 peptide pool containing 166 15-mer peptides from the human SARS-CoV-2 virus including the RBD region, but not to the S2 peptide pool which does not cover the RBD. These results indicate that the cellular responses elicited by BNT162b1 are antigen specific. In contrast, the vaccine candidate BNT162b2 encoding an optimized mutant S1 protein showed a different immune response spectrum, inducing strong T-cell responses against both the S1 and S2 peptide pools[13]. Nonetheless, our data show that the BNT162b1 vaccine candidate at the 30 μg dose is highly immunogenic and capable of eliciting strong humoral and cell-mediated responses in healthy Chinese younger and elderly adults.

Our study has several limitations, such as data interpretation based on a limited, small sample size. Further, only adult Chinese participants were included, 18 years of age and older. Evaluating the tolerability, safety and immunogenicity of SARS-COV-2 prophylactic RNA vaccines in Asian children and adolescent populations is further warranted. Secondly, although the serum-neutralizing responses elicited by the BNT162b1 vaccine candidate were compared with that in human convalescent serum panels, the level of serological immunity needed to protect against COVID-19 has not yet been determined[15]. In addition, the human convalescent serum panels that have been used in different trials are not standardized among laboratories, and each have a different distribution of patient characteristics and timepoints of collection, which imposes challenging in immunogenicity comparisons across studies and different vaccines. Further, the persistence of BNT162b1 elicited immune responses are not yet known. However, assessing the vaccine-induced immune persistence is planned in the study protocol and these data will be collected and reported later.

In summary, our study confirms the tolerability and favorable immunogenicity profile of the RNA-based SARS-CoV-2 vaccine candidate BNT162b1, and expands reporting of BNT162b1 and other RNA-based vaccine candidates from clinical trials conducted in Germany and the United States to an Asian population[10,11,13]. BNT162b1 encodes a relatively smaller RBD immunogen, which might induce a narrower spectrum of neutralizing antibodies that are less robust to potential antigenic drift of SARS-CoV-2, compared with BNT162b2, which encodes a full-length spike immunogen[16]. Pfizer and BioNTech have recently announced that the vaccine candidate BNT162b2 was found to be more than 95% effective in preventing COVID-19 in a Phase 3 pivotal study, with strong efficacy equally observed in participants over 65 years of age (NCT04368728)[17]. Currently, we are starting a Phase II clinical trial with the vaccine candidate BNT162b2 in 960 Chinese adults between 18 and 85 years of age in China, consistent with BioNTech's global partnering strategy for the development of the SARS-CoV-2 vaccine (ChiCTR2000040044 and NCT04523571).

Methods

Study design and participants

We performed this randomized, placebo-controlled, observer-blind Phase I trial in healthy young adults between 18 and 59 years old, and older adults between 65 and 85 years of age, in Taizhou, Jiangsu Province, China. Participants were in overall good health established by medical history, physical examination, and laboratory tests at the screening visit. Both males and females were included and agreed to use contraception during the trial. We excluded participants that were pregnant or breast-feeding. Participants that tested positive for SARS-CoV-2 via a commercial rapid diagnostic kit for IgM/IgG antibody to SARS-CoV-2 (manufactured by Livzon diagnostics inc., Zhuhai, China), or via testing with a pharyngeal swab nucleic acid diagnostic test (manufactured by Fosun pharma, Shanghai, China) were excluded. Imaging features of COVID-19 present in a chest CT scan was a further exclusion criterion. Participants with serious cardiovascular disease or chronic conditions such as uncontrolled diabetes and hypertension, human immunodeficiency virus, hepatitis B and hepatitis C were excluded. A complete list of the inclusion and exclusion criteria is provided in the Extended Data Set. Written informed consent was obtained from each participant before the start of the study.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial protocol was reviewed and approved by the Chinese NMPA, and the institutional review board of the Jiangsu Provincial Center of Disease Control and Prevention.

This trial was registered with the Chinese Clinical Trial Registry (ChiCTR2000034825) and with clinicaltrials.gov (NCT04523571).

Randomization and blinding

Eligible participants between 18 and 55 years of age were enrolled in the younger age group, and older participants aged greater than or equal to 65 years and less than or equal to 85 years were enrolled in the older age group. Participants were randomized in a ratio of 1:1:1 to receive the low-dose BNT126b1 or high-dose BNT126b1 or placebo. Participants were stratified by gender, using a Web-based interactive response technology (IRT) system. The blocked randomization list was generated by an independent statistician using SAS software (version 9.4).

Authorized unblinded pharmacists prepared the vaccines or placebo according to the allocation of participants through the IRT system, and nurses administrated the investigational products to participants. The unblinded staff had no further involvement in the trial, and were forbidden to disclosure allocation information to others. All other investigators, participants, laboratory staff and the sponsor remained blinded throughout the trial.

Vaccine and vaccination

BNT162b1 consists of a Good Manufacturing Practice (GMP)-grade mRNA drug substance encoding the trimerized SARS-CoV-2 spike glycoprotein RBD antigen, formulated with lipids to obtain the RNA–LNP drug product. Vaccine was transported and supplied as a buffered-liquid solution for intramuscular injection, and stored at −80 °C. For details refer to (Sahin et al)[13].

The low-dose and high-dose BNT126b1 contained 10 μg and 30 μg active ingredient, respectively, and the placebo was a commercial saline solution. Each participant received a prime-boost dosing regimen of vaccine candidate BNT162b1 at either 10 μg/0.5 ml or at 30 μg/0.5 ml or placebo of 0.5 ml administered into the deltoid, 21 days apart.

Monitoring of safety and immunogenicity

Each participant was asked to remain at the study site for at least six hours post vaccine administration for safety observation. Vital signs including temperature, blood pressure, pulse, and respiratory rate were measured at baseline, one hour, three hours and six hours post-vaccination. Any adverse events following the vaccination were documented by participants using diaries until Day 28 post-administration of the boost dose. Younger group participants were enrolled and received the vaccination first. Enrollment of the older age group was launched following evaluation of the preliminary safety data of the younger age group for the first 14 days post-prime vaccination. Severity of adverse events and laboratory abnormal changes are graded with both the scale issued by the China State Food and Drug Administration[18] and the U.S. Food and Drug Administration (FDA)[19]. Blood samples for safety laboratory testing were taken at baseline, 24 hours, days 8 after the prime dose, days 8 after the boost dose and months 6 (thyroid function only).

Immunogenicity assessment was twofold. Serum were collected at baseline, days 8 and 22 after each dose, to facilitate measurement of specific IgG antibody responses to RBD-binding and spike glycoprotein S1-binding, and neutralizing antibody to SARS-CoV-2. To assess T-cell response, PBMC samples were collected at baseline, days 8 or 22 (young adult only).

All reported adverse events were reviewed by investigators. Adverse events were categorized as either possibly, probably, or definitely related to the vaccine candidate.

Human convalescent sera

A panel of 24 convalescent human serum samples were obtained from donors 18 to 70 years of age (mean age, 45.8 years) who had recovered from SARS-CoV-2 infection; samples were obtained at least 14 days after a polymerase chain reaction-confirmed diagnosis and after symptom resolution. The disease severities of these patients varied from non-symptomatic (n=3, 13%), mild (n=8, 33%), moderate (n=10, 42%), or severe (n=3, 13%).

Neutralizing GMTs in subgroups of the donors were as follows: 40.0 for the three donors with non-symptomatic infections; 226.3 for the eight donors with mild infection; 91.9 for the ten donors with moderate infection; and 160.0 in the three donors with severe infection. 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. The convalescent serum samples were tested side by side as comparators with the serum samples obtained from participants in this trial.

Enzyme-linked immunosorbent assay (ELISA)

Total anti-SARS-CoV-2 antibodies were determined using an indirect ELISA assay. Briefly, serum samples were diluted in a two-fold series (1:100 to 1:51200) with sample diluent (TBS buffer with 3% BSA and 0.05% Tween-20) and tested in 96 well plates coated with recombinant RBD or S1 (100 ng/100 µL, Sino Biological, China) in sodium carbonate buffer. Bound IgG was detected using an HRP-conjugated secondary antibody (Southern Biotech, USA) and TMB substrate (Surmodics, USA). Data collection was performed using a SpectraMax M5 reader (Molecular Device, USA) at OD 450 nm. To obtain sample titre, the two points adjacent to the assay cut-off value were taken for linear fitting, the sample dilution corresponding to the cut-off value was the titer value. Sample titre was set to 51200 if its OD was greater than the cutoff value at 1:51200 dilution; if sample OD was less than the cutoff at initial dilution 1:100, the sample titre was set at 50.

Microneutralization assay

SARS-CoV-2 specific neutralizing antibody titre in serum was determined by a cytopathy based microneutralization assay using SARS-CoV-2 virus strain BetaCoV/JS02/human/2020 (EPI_ISL_411952)

and Vero-E6 cells (National Collection of Authenticated Cell Cultures, National Academy of Science, China). Briefly, serum samples were heat-inactivated for 30 min at 56℃ and serially diluted in a two-fold series from 1:10 to 1:5120 using Dulbecco's Modified Eagle's Medium (Thermo Fisher Scientific, USA). Serum dilutions were then mixed with the same volume of virus solution to achieve 200 $TCID_{50}$ in each well. The serum-virus mixture was incubated at 37℃ for 1 hour, then added to 96 well plates containing a monolayer of Vero-E6 cells (>80% density). After culturing at 37℃ for 3 days, cytopathic effects (CPE) on VeroE6 were observed under an inverted microscope. The neutralizing titer is the reciprocal of the highest sample dilution that protects at least 50% of cells from CPE. If no neutralization reaction was observed at the initial serum dilution (1:10), and the titre would be reported as 5.

Interferon-γ enzyme-linked immunospot (IFNγ ELISpot)

SAR-CoV-2 viral antigen specific T-cell responses were assessed by an *ex vivo* interferon-γ (INF-γ) enzyme-linked immunospot (ELISpot) assay (ELISpotPro Kit, Mabtech AB, Sweden)[20]. Tests were performed in triplicates with a positive control (anti-CD3 monoclonal antibody). Per well, 1 x 10^5 cryopreserved (baseline samples) or freshly isolated peripheral blood mononuclear cells (PBMCs) were stimulated 21 ± 0.5 hours with different peptide pools: Sp1 overlapping peptide pool, covering the N-terminal half of spike protein, including the RBD; Sp2 overlapping peptide pool, covering the C-terminal half of spike protein (JPT Peptide Technologies, Germany)[21]. CEF peptide pool[22] consisting of 32 MHC class I restricted viral peptides from human cytomegalovirus, epstein-barr virus and influenza virus (Mabtech AB, Sweden). Bound IFNγ was visualized using a secondary antibody directly conjugated with alkaline phosphatase followed by incubation with BCIP/NBT substrate. Plates were scanned using an AID ELISPOT Reader (AID Autoimmun Diagnostika, Germany). Spot counts were displayed as mean values of each triplicate, calculated by subtracting the mean negative control response from the mean of each peptide pool response.

Outcomes

The primary and secondary objectives of this trial were to evaluate safety and immunogenicity of the candidate vaccine BNT162b1 in healthy Chinese adults. The primary endpoints for safety evaluation were the incidence of solicited local reactions at the injection site or systemic adverse reactions within 14 days post-vaccination, and adverse events following the full immunization until 28 days after receiving the boost dose. Any clinical laboratory abnormalities from baseline to 24 hours or 7 days after vaccination, and any serious adverse event (SAE) that occurred were also recorded.

The secondary endpoints for immunogenicity were geometric mean titer (GMT), seroconversion rates and fold increase of virus-neutralizing antibody, or ELISA IgG antibodies binding to S1 or RBD measured at days 8, 22 after each vaccination. Seroconversion is defined as an increase by a factor of four or more in antibody titer over the baseline, or the lower limit value if the baseline titer is below the limit of detection. The serum dilution for ELISA started at 1:100, while that for microneutralization assay started at 1:10.

Cellular immune responses in terms of the number of positive cells with interferon gamma (IFN-γ) secretion among PBMCs at a concentration of 1×10^5/well at Day 8 and 22 after the boost dose were explored as an exploratory endpoint.

Statistical analysis

The total sample size in this study was 144 participants, 24 participants of each age group was included in each treatment group. The probability to observe a particular adverse event with incidence of 8% at least once in 24 participants in each dose group was 86.5%.

All randomized participants who received at least one dose of the investigational vaccine were included in the safety analysis. Safety endpoints were described as frequencies (%) with 95% confidence interval (CI) of the adverse reactions or events during the observation period. We compared the proportions of the participants with adverse reactions or events across the groups using Chi-square or Fisher exact. All participants who received at least one vaccination and had results of serologic measurements baseline or after vaccination were included in the immunogenicity analysis. The immunological endpoints were descriptively summarized at the specified time points, and compared across the groups, using ANOVA for log-transformed antibody titers, or Wilcoxon rank-sum test for non-normal data. The neutralizing antibody responses of the participants in each dose group were compared with those of patients who had PCR-confirmed SARS-CoV-2 infection. Any serologic values below the lower limit of detection were set to half of the value (1:50 for ELISA and 1:5 for microneutralization assay), while the values above the highest dilution titer were assigned values of the highest dilution for calculation. Pearson correlation analysis of the RBD-binding or S1-binding specific ELISA antibody and neutralizing antibody was performed to assess the relationship between responses on different assays.

Declarations

Funding source

BioNTech RNA Pharmaceuticals GmbH, and Shanghai Fosun Pharmaceutical Development, Inc funded this clinical trial. BioNTech was the regulatory sponsor, manufactured the BNT162b1 clinical trial material, advised on the study design, oversaw the trial execution, and contributed to the interpretation of the data and the writing of the manuscript. Shanghai Fosun was the execution organization of the trial. Fosun was responsible for the study design and conduct of the trial, data collection, data analysis, data interpretation and writing of the clinical study report, advised on the manuscript. All the authors had full access to all the data in the trial and had final responsibility for the decision to submit the manuscript for publication.

Data availability

We support data sharing of individual participant data. The individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and extended data) will be shared. The raw data will be available beginning 3 months and ending 1 year after publication. Researchers who provide a scientifically sound proposal will be allowed access to the individual participant data. Proposals should be directed to jszfc@vip.sina.com or aimin.hui@fosunpharma.com. These proposals will be reviewed and approved by the sponsor based on scientific merit.

Code availability

All code used to produce the results will be accessed by sending a scientifically sound proposal to jszfc@vip.sina.com or aimin.hui@fosunpharma.com. The code will be available with the raw data.

Author contributions

Co-first authors: Jingxin Li, Aimin Hui.

Joint-corresponding authors: Aimin Hui, Li Zhu, Fengcai Zhu

Fengcai Zhu is the principal investigator of this trial. Jingxin Li worked as co-principal investigator of this trial. Fengcai Zhu, Aimin Hui, Jingxin Li, Yumei Yang designed the trials and the study protocol. Jingxin Li drafted of the manuscript. Aimin Hui and Li Zhu contributed to critical review and revising of the report. Ugur Sahin, and Özlem Türeci designed and manufactured the vaccine candidate, and provided feedback on the study design. Martin Bexon contributed in revising the manuscript. Xiang Zhang, Rong Tang, Huayue Ye, Ruiru Ji, Mei Lin, Zhongkui Zhu, Siyue Jia, Hongxing Pan, Fuzhong Peng, Zhilong Ma, Zhenggang Wu, Yunfeng Shi led and participated in the site work, including the recruitment, follow-up, and data collection. Ruiru Ji and Li Zhu were responsible for laboratory analyses.

Competing interest

Aimin Hui, Yumei Yang, and Ruiru Ji are employees of Fosun Pharma 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. All other authors declare no competing interests.

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Tables

Table 1. Baseline characteristics of the participants, by age groups.

	Younger participants aged 18-55 years			Older participants aged 65-85 years		
Characteristic	**10 μg**	**30 μg**	**Placebo**	**10 μg**	**30 μg**	**Placebo**
No. of participants	24	24	24	24	24	24
Age, mean (SD), years	37.9 (9.6)	39.7 (9.0)	42.0 (8.7)	70.5 (5.0)	68.5 (3.0)	70.7 (4.4)
Sex (female)	12 (50%)	12 (50%)	12 (50%)	12 (50%)	12 (50%)	12 (50%)
Body-mass index, kg/m²	24.7 (3.2)	23.0 (2.7)	24.3 (3.4)	24.0 (3.0)	24.8 (2.9)	23.5 (2.5)
Medical history or existing disorder						
Cardiac ischemia	2 (8%)	2 (8%)	2 (8%)	0	0	0
Sinus bradycardia	0	2 (8%)	1 (4%)	0	0	0
Hyperuricemia	3 (13%)	1 (4%)	1 (4%)	3 (13%)	2 (8%)	2 (8%)
Nasopharyngitis	2 (8%)	0	0	0	0	0
Blood uric acid increased	2 (8%)	1 (4%)	1 (4%)	0	0	0
Hypertension	3 (13%)	0	1 (4%)	12 (50%)	9 (38%)	7 (29%)
Diabetes	0	0	0	1 (4%)	2 (8%)	1 (4%)
Gastric inflammation	0	0	0	0	0	2 (8%)
Others*	3 (13%)	5(21%)	1 (4%)	3 (13%)	3 (13%)	4 (17%)

Data shown were mean (SD) or n (%). * “Others” included tonsillitis, helicobacter infection, human papilloma virus infection, periodontitis, electrocardiogram high voltage, lymphadenopathy, anemia, hepatic cyst, oropharyngeal discomfort, hyperthyroidism, noninfective gingivitis, hyperlipidaemia, benign prostatic hyperplasia, prostatitis, blindness unilateral, cerebral infarct, limb injury, deformity of spine, calculus urinary and lymphadenopathy.

Table 2 Solicited adverse reactions within 7 days post the prime and boost vaccinations, and unsolicited adverse reactions till day 43, graded by FDA criteria, by age groups.

Adverse reactions	Younger participants aged 18-55 years				Older participants aged 65-85 years			
	10 μg (n=24)	30 μg (n=24)	Placebo (n=24)	P value	10 μg (n=24)	30 μg (n=24)	Placebo (n=24)	P value
Solicited adverse reactions within 7 days								
Any	21 (88%)	24 (100%)	4 (17%)	<0.0001	20 (83%)	22 (92%)	2 (8%)	<0.0001
Grade 3	1 (4%)	4 (17%)	0	0.0015	0	2 (8%)	0	0.3239
Injection-site adverse reactions								
Any	21 (88%)	24 (100%)	2 (8%)	<0.0001	18 (75%)	21 (88%)	0	<0.0001
Grade 3	0	0	0	-	0	0	0	-
Pain	21 (88%)	23 (96%)	2 (8%)	<0.0001	16 (67%)	21 (88%)	0	<0.0001
Redness	6 (25%)	8 (33%)	0	0.0059	3 (13%)	4 (17%)	0	0.1492
Swelling	5 (21%)	7 (29%)	0	0.0137	0	5 (21%)	0	0.0091
Induration	0	3 (13%)	0	0.1018	0	1 (4%)	0	1.0000
Systemic adverse reactions								
Any	17 (71%)	21 (88%)	3 (13%)	<0.0001	4 (17%)	18 (75%)	2 (8%)	<0.0001
Grade 3	1 (4%)	4(17%)	0	0.0015	0	2 (8%)	0	0.3239
Fever*	9 (38%)	18 (75%)	0	<0.0001	1 (4%)	16 (67%)	0	<0.0001
Grade 3	1 (4%)	4 (17%)	0	0.1185	0	2 (8%)	0	0.3239
Grade 3 by NMPA criteria	3 (13%)	9 (38%)	0	0.0015	0	2 (8%)	0	0.3239
Headache	11 (46%)	19 (79%)	3 (13%)	<0.0001	1 (4%)	2 (8%)	0	0.7682
Fatigue	12 (50%)	16 (67%)	0	<0.0001	3 (13%)	8 (33%)	0	0.0045
Malaise	8 (33%)	9 (38%)	0	0.0013	2 (8%)	4 (17%)	1 (4%)	0.4858
Joint pain	4 (17%)	10 (42%)	1 (4%)	0.0067	0	1 (4%)	0	1.0000
Muscle pain	2 (8%)	10 (42%)	0	<0.0001	0	1 (4%)	0	1.0000
Chills	4 (17%)	7 (29%)	0	0.0118	1 (4%)	4 (17%)	0	0.1185
Nausea	3 (13%)	3 (13%)	0	0.2330	0	0	0	-
Anorexia	1 (4%)	4 (17%)	0	0.1185	0	3 (13%)	1 (4%)	0.3143
Diarrhea	2 (8%)	1 (4%)	1 (4%)	1.0000	0	0	0	-
Vomiting	0	2 (8%)	0	0.3239	0	0	0	-
Unsolicited adverse reactions until 43 days								
Any	9 (38%)	10 (42%)	1 (4%)	0.0046	4(17%)	9 (38%)	2(8%)	0.0590
Fever†	0	0	0	-	0	1 (4%)	0	1.0000
Temperature intolerance	2(8%)	6(25%)	0	0.0230	0	4(17%)	0	0.0310
Injection-site discomfort	3(13%)	4(17%)	0	0.1492	2(8%)	3(13%)	0	0.3580
Injection-site pruritus	2(8%)	3(13%)	0	0.3580	0	1 (4%)	0	1.0000
Pain not at injection-site	1(4%)	1(4%)	0	1.0000	0	0	0	-
Dizziness	3(13%)	1(4%)	0	0.3142	0	3(13%)	0	0.1018
Blood uric acid increased	1(4%)	1(4%)	0	1.0000	2(8%)	1(4%)	2(8%)	1.0000

FDA: US Food and Drug Administration. FDA criteria[13]: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Vol. 2020 (2007), which defines Grade 3 fever* as an oral temperature of 39℃~40℃.

Data were shown as the percent of participants with specific event (%). Grade 3 reactions were regarded as the vaccination-related severe enough to prevent normal activities. SAEs= Serious Adverse Events. A participant was only counted once in the specific reaction category, also with more than one episode of the adverse reaction. Only unsolicited adverse reactions reported by two or more participants were listed. †One participant experienced Grade 3 fever accompanied with pain, itching and pruritus at the injection site after the prime dose, and electively withdrew from the boost vaccination.

Table 3 Solicited adverse reactions within 14 days post the prime and boost vaccinations, and unsolicited adverse reactions until day 43, graded by NMPA criteria, by age groups.

Adverse reactions	Younger participants aged 18-55 years				Older participants aged 65-85 years			
	10 μg (n=24)	30 μg (n=24)	Placebo (n=24)	P value	10 μg (n=24)	30 μg (n=24)	Placebo (n=24)	P value
Solicited adverse reactions within 14 days								
Any	21 (88%)	24 (100%)	4 (17%)	<0.0001	21 (88%)	23 (96%)	2 (8%)	<0.0001
Grade 3	3 (13%)	9 (38%)	0	0.0015	0	2 (8%)	0	0.3239
Injection site adverse reactions								
Any	21 (88%)	24 (100%)	2 (8%)	<0.0001	18 (75%)	21 (88%)	0	<0.0001
Grade 3	0	0	0	-	0	0	0	-
Pain	21 (88%)	23 (96%)	2 (8%)	<0.0001	16 (67%)	21 (88%)	0	<0.0001
Redness	6 (25%)	8 (33%)	0	0.0059	3 (13%)	4 (17%)	0	0.1492
Swelling	5 (21%)	7 (29%)	0	0.0137	0	5 (21%)	0	0.0091
Induration	0	3 (13%)	0	0.1018	0	1 (4%)	0	1.0000
Systemic adverse reactions								
Any	17 (71%)	22 (92%)	3 (13%)	<0.0001	9 (38%)	19 (79%)	2 (8%)	<0.0001
Grade 3	3 (13%)	9 (38%)	0	0.0015	0	2 (8%)	0	0.3239
Fever*	14 (58%)	21 (88%)	1 (4%)	<0.0001	7 (29%)	19 (79%)	1 (4%)	<0.0001
Grade 3	3 (13%)	9 (38%)	0	0.0015	0	2 (8%)	0	0.3239
Headache	11 (46%)	19 (79%)	3 (13%)	<0.0001	1 (4%)	2 (8%)	0	0.7682
Fatigue	12 (50%)	16 (67%)	0	<0.0001	3 (13%)	8 (33%)	0	0.0045
Malaise	8 (33%)	9 (38%)	0	0.0013	2 (8%)	4 (17%)	1 (4%)	0.4858
Joint pain	4 (17%)	10 (42%)	1 (4%)	0.0067	0	1 (4%)	0	1.0000
Muscle pain	2 (8%)	10 (42%)	0	<0.0001	0	1 (4%)	0	1.0000
Chills	4 (17%)	7 (29%)	0	0.0118	1 (4%)	4 (17%)	0	0.1185
Nausea	3 (13%)	3 (13%)	0	0.2330	0	0	0	-
Anorexia	1 (4%)	4 (17%)	0	0.1185	0	3 (13%)	1 (4%)	0.3143
Diarrhea	2 (8%)	0	1 (4%)	0.7682	0	0	0	-
Vomiting	0	2 (8%)	0	0.3239	0	0	0	-
Unsolicited adverse reactions until 43 days								
Any	9 (38%)	10 (42%)	1 (4%)	0.0046	4 (17%)	9 (38%)	2 (8%)	0.0590
Fever†	0	0	0	-	0	1 (4%)	0	1.0000
Temperature intolerance	2 (8%)	6 (25%)	0	0.0230	0	4 (17%)	0	-
Injection-site discomfort	3 (13%)	4 (17%)	0	0.1492	2 (8%)	3 (13%)	0	0.3580
Injection-site pruritus	2 (8%)	3 (13%)	0	0.3580	0	1 (4%)	0	1.0000
Pain not at injection-site	1 (4%)	1 (4%)	0	1.0000	0	0	0	-
Dizziness	3 (13%)	1 (4%)	0	0.3142	0	3 (13%)	0	0.1018
Blood uric acid increased	1 (4%)	1 (4%)	0	1.0000	2 (8%)	1 (4%)	2 (8%)	1.0000

NMPA: China National Medical Products Administration. NMPA criteria[14]: Guidances for grading adverse reactions in clinical trials of preventive vaccines. Vol. 2020 (2008), released by Center for Drug Evaluation, NMPA, which defines Grade 3 fever* as an axillary temperature of 38.5℃~<39.5℃.

Data were shown as the percent of participants with specific event (%). Grade 3 reactions were regarded as the vaccination-related severe enough to prevent normal activities. SAEs= Serious

Adverse Events. A participant was only counted once in the specific reaction category, also with more than one episode of the adverse reaction. Only unsolicited adverse reactions reported by two or more participants were listed. †One participant experienced Grade 3 fever accompanied with pain, itching and pruritus at the injection site after the prime dose, and electively withdrew from the boost vaccination.

Figures

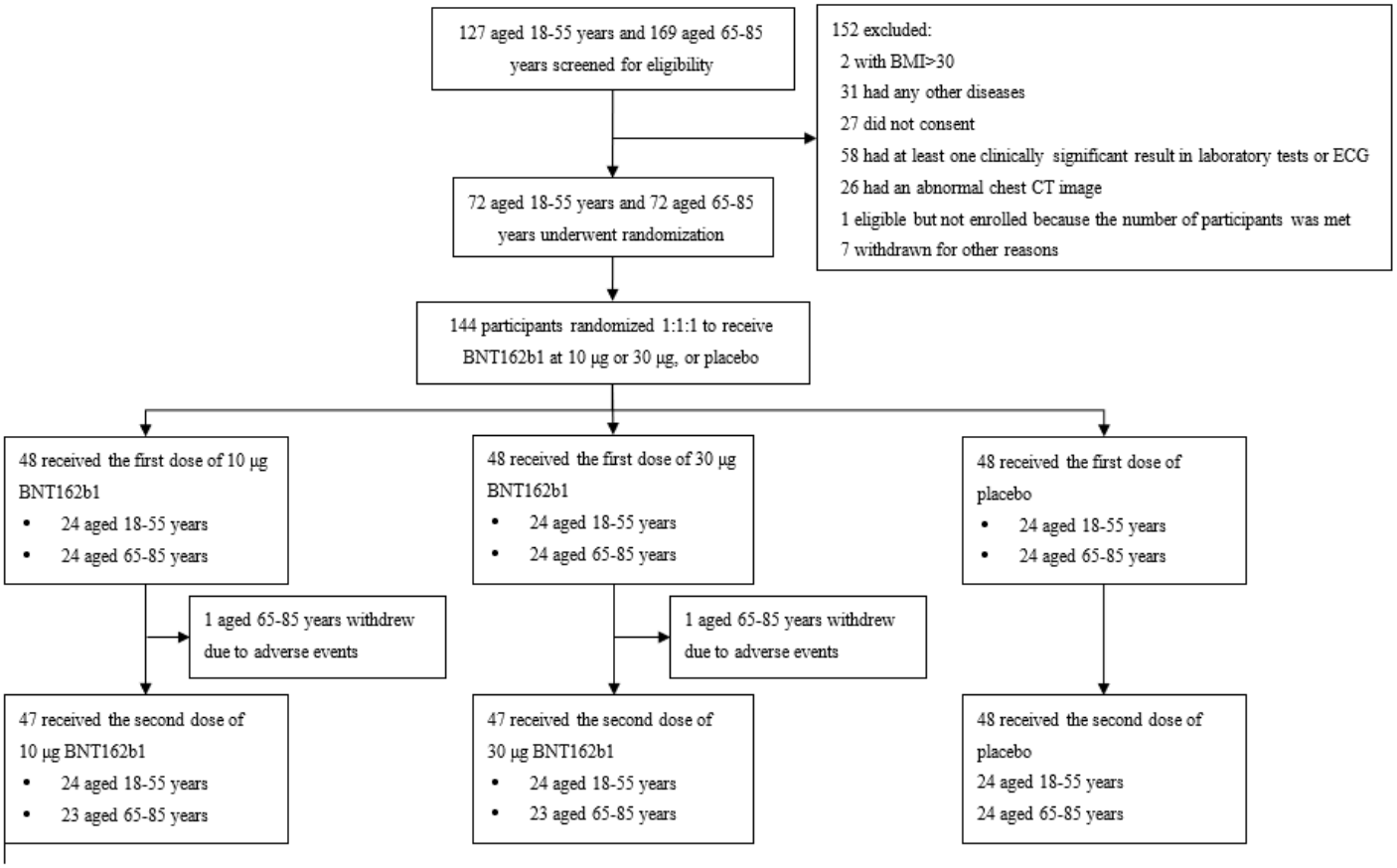

Figure 1

Study flow diagram. BMI=body-mass index. ECG=electrocardiograph. CT=computerized tomography.

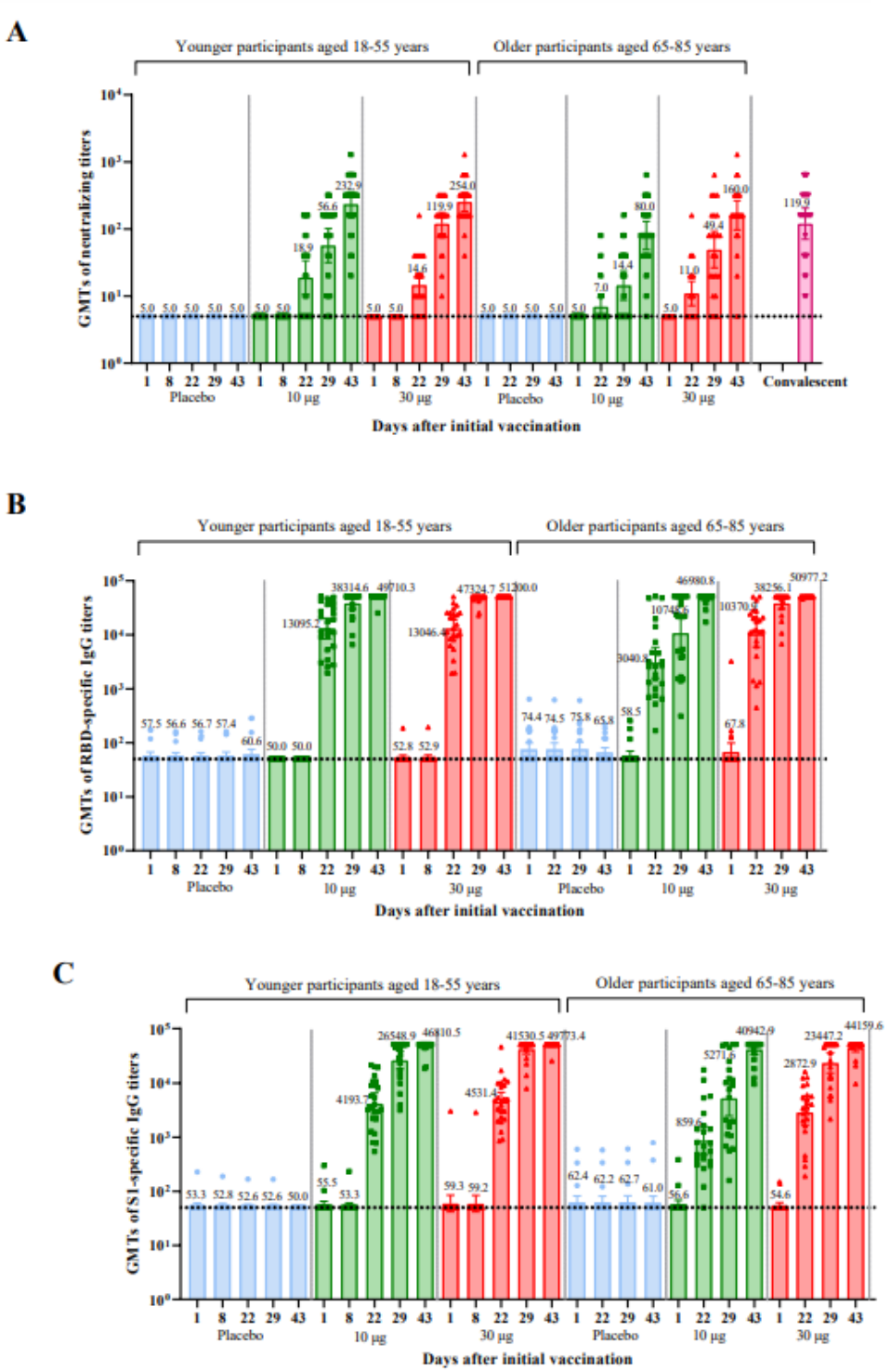

Figure 2

BNT162b1-induced 50% virus-neutralizing antibody concentrations, and specific RBD-binding and S1-binding antibody responses, compared with placebo. RBD=receptor-binding domain. GMT=geometric mean titer. Serum samples were obtained at baseline (pre-prime, day 1) and days 8, 22 (pre-boost), 29, and 43 in the younger adult group, and at baseline (pre-prime, day 1) and days 22 (pre-boost), 29, and 43 in the older adult group. A panel of human COVID-19 convalescent serum (n=24) were obtained at least

14 days after PCR-confirmed diagnosis in COVID-19 patients. A dashed line at the Y axis represents the lower limit of detection. (A) the GMTs of 50% SARS-CoV-2 neutralizing antibodies. (B) the GMTs of RBD-binding antibodies measured by ELISA. (C) the GMTs of S1-binding antibodies. Each point represents a serum sample, and each vertical bar represents a geometric mean with 95% CI.

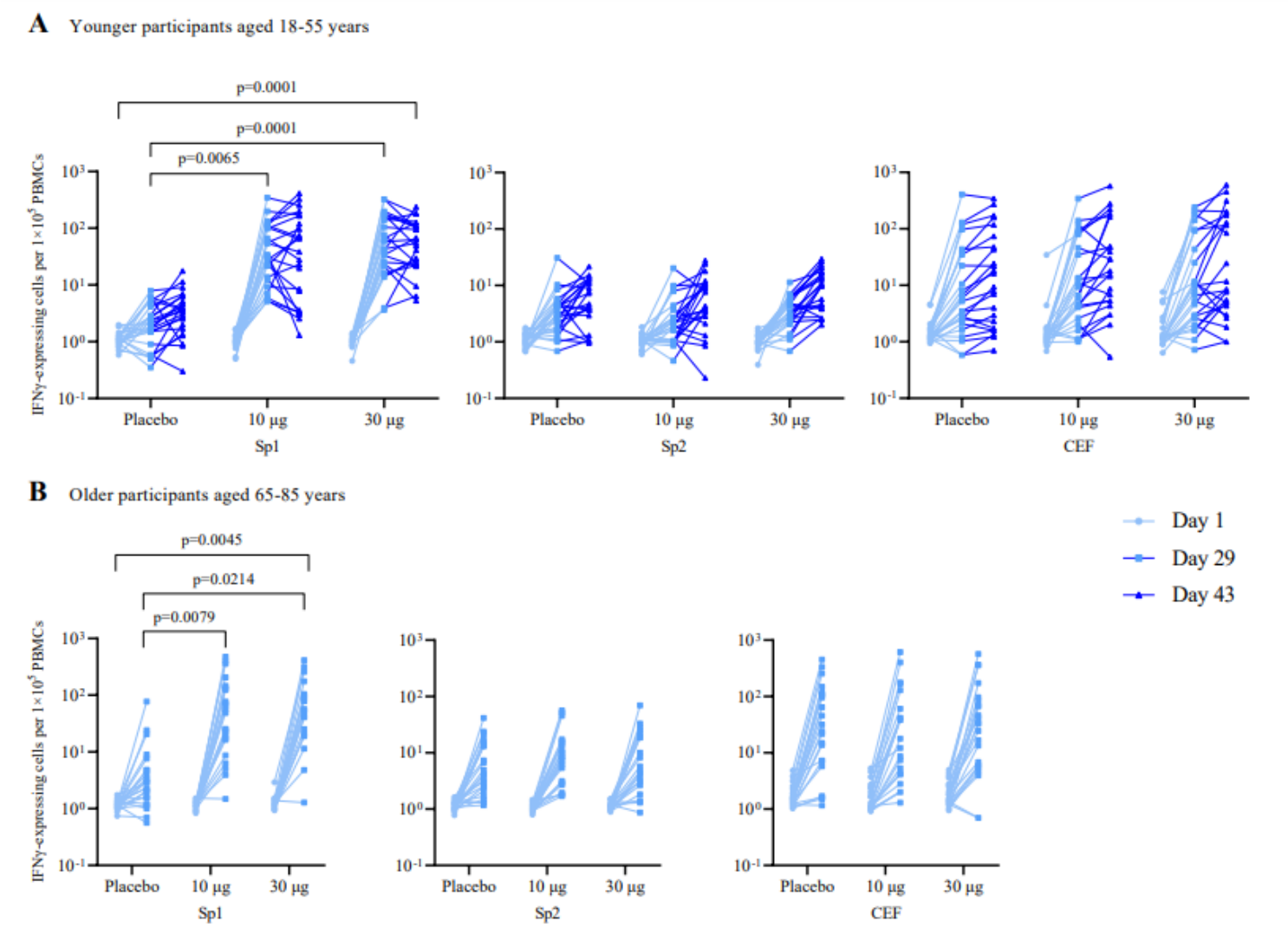

Figure 3

T-cell response in participants before and after vaccination measured by IFN-γ ELISpot. IFN=interferon. PBMC=peripheral blood mononuclear cells. The S1 peptide pool covers the N-terminal half of SARS-CoV-2 spike, including RBD. S2 peptide pool covers the C-terminal of SARS-CoV-2 spike, not including RBD. The CEF peptide pool consists of 32 MHC class I restricted viral peptides from human Cytomegalovirus, Epstein-Barr virus and Influenza virus. Panel A shows the number of specific T cells with secretion of IFN-γ at days 1, 29, and 43 in the younger participants aged 18-55 years. Panel B shows the number of specific T cells with secretion of IFN-γ at days 1 and 29 in the older participants aged 65-85 years. P value was only calculated for T-cell response in participants at day 29 after prime vaccination.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ExtendedData.docx