Immunogenicity and safety of BNT162b2 mRNA vaccine in Chinese adults: A phase 2 randomised clinical trial

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Summary

Background BNT162b2, an mRNA vaccine against COVID-19, is being utilised worldwide, but immunogenicity and safety data in Chinese individuals are limited.

Methods This phase 2, randomised, double-blind, placebo-controlled trial included healthy or medically stable individuals aged 18−85 years enrolled at two clinical sites in China. Participants were stratified by age (≤55 or >55 years) and randomly assigned (3:1) by an independent randomisation professional to receive two doses of intramuscular BNT162b2 30 μg or placebo, administered 21 days apart. Study participants, study personnel, investigators, statisticians, and the sponsor's study management team were blinded to treatment assignment. Primary immunogenicity endpoints were the geometric mean titers (GMTs) of neutralising antibodies to live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and seroconversion rates (SCR) 1 month after the second dose. Safety assessments included reactogenicity within 14 days of vaccination, adverse events (AEs), and clinical laboratory parameters. Randomised participants who received at least one dose were included in the efficacy and safety analyses on a complete case basis (incomplete/missing data not imputed). Results up to 6 months after the second dose are reported.

Findings Overall, 959 participants (all of Han ethnicity) who were recruited between December 5th, 2020 and January 9th, 2021 received at least one injection (BNT162b2, n=720; placebo, n=239). At 1 month after the second dose, the 50% neutralising antibody GMT was 294.4 (95% CI; 281.1−308.4) in the BNT162b2 group and 5.0 (95% CI; 5.0 −5.0) in the placebo group. SCRs were 99.7% (95% CI; 99.0%−100.0%) and 0% (95% CI; 0.0%−1.5%), respectively ($p<0.0001$ vs placebo). Although the GMT of neutralising antibodies in the BNT162b2 group was greatly reduced at 6 months after the second dose, the SCR still remained at 58.8%. BNT162b2-elicited sera neutralised SARS-CoV-2 variants of concern. T-cell responses were detected in 58/73 (79.5%) BNT162b2 recipients. Reactogenicity was mild or moderate in severity and resolved within a few days after onset. Unsolicited AEs were uncommon at 1 month following vaccine administration, and there were no vaccine-related serious AEs at 1 month or 6 months after the second dose.

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Interpretation BNT162b2 vaccination induced a robust immune response with acceptable tolerability in Han Chinese adults. However, follow-up duration was relatively short and COVID-19 rates were not assessed. Safety data collection is continuing until 12 months after the second dose.

Research in context

Evidence before this study

We searched PubMed for research articles published up to 21 June 2021 using the search terms "SARS-CoV-2", "COVID-19", "mRNA", "vaccine" and "trial or study"; an update search was run on 8 March 2022. Phase 1/2 trials of BNT162b2 in the US and Germany provided evidence of its immunogenicity and safety at a 30 μg dose in healthy individuals. In a multinational placebo-controlled phase 2/3 trial in 43,448 individuals aged 16 years or older who had no evidence of prior or current SARS-CoV-2 infection, BNT162b2 demonstrated 95% vaccine efficacy against symptomatic laboratory-confirmed SARS-CoV-2 infection. It was generally well tolerated, with a low incidence of serious adverse events (0.6% in the vaccine group and 0.5% in the placebo group), and local and systemic reactogenicity was generally mild or moderate in severity.

Previous studies have reported varying levels of cross reactivity against three early variants of concern (B.1.1.7, B.1.351, B.1.617.2), and that a third dose of BNT162b2 is required to achieve neutralising antibody levels against the Omicron variant (B.1.1.529; the Pango Network split the initially designated B.1.1.529 lineage into sublineages. The original lineage is now designated BA.1) that are broadly similar to but not as high as those achieved with the two-dose regimen against the wild-type and early variants.

Added value of this study

Our ongoing placebo-controlled phase 2 trial is the first providing evidence of the efficacy and safety of BNT162b2 in a Han Chinese population of healthy people or with stable chronic disease. Two 30 μg doses given 21 days apart elicited a robust immune response. Although neutralising antibody titers were higher in individuals aged 18−55 years than in older individuals aged 56−85 years at 1 month after dose two, the seroconversion rate (SCR) was at least 99% in both age groups, consistent with prior findings that the vaccine is

effective in older adults. As expected, geometric mean titers (GMT) of neutralising antibodies and SCR had fallen at 6 months after the second dose, but the latter still remained at 58.8%. BNT162b2-elicited sera at 1 month after the second dose also neutralised three SARS-CoV-2 variants of concern, Alpha, Beta, and Delta, although titer reductions were observed versus wild-type, especially for the Beta and Delta variants. BNT162b2 was generally well tolerated during follow up, 6 months after the second dose, in Han Chinese individuals who were healthy or had stable pre-existing disease.

Implications of all the available evidence

International evidence shows that nationwide vaccination programs with BNT162b2 reduce the risk of severe COVID-19 outcomes. This study confirms that BNT162b2 is effective and has acceptable tolerability in adult individuals of Han ethnicity, and when results of its longer-term safety in this population become available, it may be considered for inclusion in vaccination programs in China. To this end, real-world investigations into its effectiveness in reducing severe COVID-19 outcomes, including hospitalisation and death, in a Chinese population will be important, as will more data of its efficacy against Omicron and its subvariants in Chinese individuals.

Introduction

The ongoing coronavirus disease of 2019 (COVID-19) global pandemic has infected 533,816,957 people and caused 6,309,633 confirmed deaths (as of 15 June 2022).[1]

BNT162b2 (tozinameran) is a lipid nanoparticle −formulated,[2] nucleoside-modified RNA vaccine[3] that encodes the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) protein.[4] In the global pivotal trial, BNT162b2 demonstrated 95% vaccine efficacy (VE) in individuals aged 16 years or older.[5]

It was generally well tolerated, with a low incidence of serious adverse events (AEs; 0.6% vs 0.5% with placebo), and local and systemic reactogenicity was generally mild or moderate in severity and transient.

Data for BNT162b2 in Chinese populations are currently limited: in the global pivotal clinical trial there were no study sites in China, and only 4.3% of participants were Asian.[5] We conducted a phase 2 trial of BNT162b2 in Chinese individuals, and report here the immunogenicity, safety and tolerability results up to 6 months after the second dose.

Methods

Study design and participants
This phase 2, randomised, double-blind, placebo-controlled trial was conducted at two clinical sites, one in Lianshui County and one in Taizhou City, in Jiangsu Province, China (ClinicalTrials.gov number NCT04649021). Its design and conduct were based broadly on the global pivotal trial (NCT04368728).[5] However, key methodological differences in the present trial were: early safety monitoring in about 150 participants, solicited reactogenicity assessed for an additional seven days (total 14 days) post-vaccination, and AEs graded using the United States Food and Drug Administration (FDA) grading criteria[6] and the National Medical Products Administration (NMPA) of China criteria.[7]

Eligible participants were recruited from the community and were healthy Chinese adults aged 18−85 years with a negative SARS-CoV-2 antibody test at screening. Individuals with a pre-existing stable condition could be included. Stability was defined as disease not requiring a significant change in therapy or hospitalisation for worsening disease in the 6 weeks before study enrolment, as determined by study investigators from consultation with participants. For the early safety monitoring group, a normal chest computed tomography scan and negative SARS-CoV-2 polymerase chain reaction test were required. Key exclusion criteria included symptoms of COVID-19, known infection with human immunodeficiency virus, hepatitis B or C virus (according to medical history), known or suspected immunodeficiency or treatment with immunosuppressive therapy, and treatment with medications intended to prevent COVID-19 (Supplementary Methods lists all criteria).

The trial protocol was approved by the Institutional Review Board of the Jiangsu Provincial Center for Disease Control and Prevention (Jiangsu, China). The trial was conducted in compliance with the ethical requirements in the Declaration of Helsinki,[8] the Good Clinical Practice guidelines from the International Council for Harmonization, and Chinese laws and regulations related to clinical studies. All participants provided written informed consent.

Randomisation and masking
Participants were stratified into two age groups (18−55 or 56−85 years), with age categories based on recommendations from the NMPA, and randomised 3:1 to receive two doses of BNT162b2 (COMIRNATY®, Pfizer-BioNTech[9]) 30 μg or saline placebo by intramuscular injection, 21 days apart (Supplementary Figure S1). An independent randomisation professional generated a participant randomisation table and performed a block randomisation, assigning participants using an interactive response technology system. Study participants, study personnel at each clinical site, investigators, trial statisticians and the sponsor's management team were blinded to treatment assignment. Randomisation procedures are described in further detail in Supplementary Methods.

Trial procedures
Recruitment began with both age groups. Enrolment of participants aged 56−85 years continued only after a safety review by the safety review committee (SRC) of the first 40 participants enrolled in this age group, who were closely monitored during the 48 hours after the first injection. SRC approval of continued enrolment of participants aged 18−55 years was required after a safety data review of the first 110 participants in this age group who completed one-day observation after their first injection.

Antipyretics and analgesics were allowed to treat symptoms related to the vaccination.

All participants were monitored for at least 30 min after each intramuscular injection (6 h for the first 150 participants). Blood samples were collected from all participants for measurement of humoral immune responses, from the first 98 participants for detecting T-cell responses, and from another 59 randomly selected from the BNT162b2 group for cross-neutralisation assays. Blood and urine samples were collected from the first 150 participants for laboratory safety testing.

Immunogenicity outcomes
Microneutralisation assay using live SARS-CoV-2 (BetaCoV/Jiangsu/JS02/2020), and S1-binding immunoglobulin G (IgG) indirect enzyme-linked immunosorbent assay (ELISA), were conducted using serum samples collected prior to the first dose and at 1 week, 1 month and 6 months after the second dose (described in detail in Supplementary Methods). The microneutralisation assay measured the protection of Vero-E6 cells from SARS-CoV-2-induced cytopathic effects at predetermined serum dilutions, as described in the BNT162b1 phase 1 trial in China;[10] additionally, the current trial used the WHO international standard (NIBSC code 20/136) as the assay reference.[11] Cross-neutralisation analysis of SARS-CoV-2 variants of concern (VOC)

compared with the wild-type strain SARS-CoV-2/INMI1-Isolate/2020/Italy was conducted using Alpha-, Beta- and Delta-specific microneutralisation assays (described in detail in Supplementary Methods).

Ex vivo interferon-γ (IFNγ) enzyme-linked immune absorbent spot (ELISpot) assays were conducted using peripheral blood mononuclear cells (PBMCs) (Supplementary Methods) collected prior to the first dose and 1 week after the second dose.

The primary immunogenicity endpoints were the geometric mean titers (GMTs) against live SARS-CoV-2 and the seroconversion rate (SCR), measured 1 month after the second dose compared with baseline. Secondary immunogenicity endpoints included the GMT and SCR of neutralising antibodies at 1 week and 6 months after the second dose; the geometric mean fold rise (GMFR) in neutralising antibody at 1 week and at 1 month and 6 months after the second dose compared with baseline; and the GMT, SCR, and GMFR versus baseline of S1-binding IgG protein level at 1 week, 1 month and 6 months after the second dose. Cellular immune response (IFNγ ELISpot assay) was an exploratory endpoint.

Safety outcomes

To assess reactogenicity, participants recorded in diary cards any local and systemic solicited events, and antipyretic medication use, in the 14-day period following each injection. Solicited reactions were defined as drug-related solicited events. Treatment-emergent unsolicited AEs were recorded from the time of the first dose up to 1 month after the second dose. AE severity was graded according to the NMPA of China grading standard and/or the US FDA grading criteria (see Supplementary Methods). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Serious AEs (defined as those that resulted in death, were life threatening, required or prolonged inpatient hospitalisation, led to permanent or significant disability/loss of functioning, led to congenital anomaly/birth defects in offspring, or that were considered an important medical event) that occurred up to 6 months after the second dose were also collected by investigators. Anaphylaxis was defined as anaphylactic reaction or shock, and anaphylactoid reaction or shock.

Statistical analysis

The intent-to-treat (ITT) and safety populations included all randomised participants who received at least one dose of vaccine. Incomplete/missing data were not imputed; complete case analysis was used. Student's t-test was used to compute *p*-values for comparisons of GMTs, and confidence intervals (CIs) were based on the Wald method. Fisher's exact test was used to derive *p*-values for comparing SCRs and

corresponding CIs were calculated by the Miettinen-Nurminen method.

Post hoc analyses included a Pearson correlation analysis between neutralising antibody and S1-binding IgG titers, and analysis of immunogenicity and safety by comorbidity risk status. 'At risk' was defined as participants with at least one Charlson Comorbidity Index condition[12] and/or who were obese (body mass index $\geq$30 kg/m²).

Statistical analyses were conducted using SAS® version 9·4 or higher (SAS Institute Inc., Cary, NC, USA).

ClinicalTrials.gov registration number: NCT04649021

Results

A total of 960 individuals were randomised between December 5th, 2020 and January 9th, 2021 (Figure 1). The ITT and safety populations included 959 participants who had received $\geq$1 dose of BNT162b2 (*n*=720) or placebo (*n*=239). Almost all participants received both doses of BNT162b2 or placebo (99·3% and 98·8% of participants, respectively) and completed follow-up to 6 months after the second dose (97.6% and 98.3%, respectively). The data cut-off date for this analysis was July 13th, 2021.

Baseline demographic characteristics of participants were similar between the BNT162b2 and placebo groups (Table 1), including in the at-risk and non-risk subgroups (Table S1). Of the 959 individuals who received $\geq$1 dose of BNT162b2 or placebo, 48.8% were female, 11.6% were obese, and 5.1% had at least one Charlson Comorbidity Index condition (Table 1). The median age was 54 years, and 46.0% of participants were aged 56–85 years. All participants were Chinese, of Han ethnicity.

Neutralising antibody titers were undetectable for all participants prior to vaccination. All BNT162b2 recipients had strong neutralising antibody responses (ITT population; Table 2; Table S2), regardless of comorbidity status (Table S3). This response was more pronounced 1 month after the second dose than at 1 week after the second dose, reaching a GMT of 294.44 (equivalent to 1840.25 IU/mL per WHO standard units) versus 196.09 (1225.56 IU/mL) (Figure 2a). At 6 months after the second dose, antibody responses were markedly reduced compared with those observed at 1 month after the second dose (Table 2; Table S2), dropping to 18.90 (118.12 IU/mL). While the neutralising
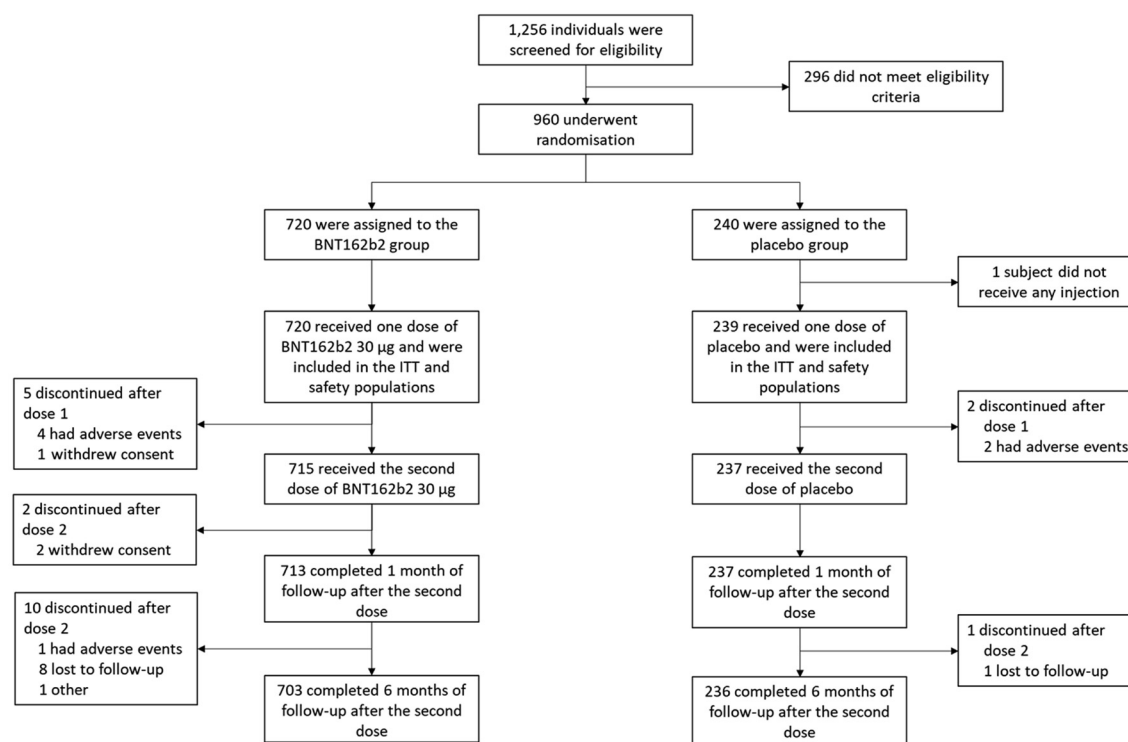
Figure 1. Disposition of subjects in the trial.
The intent-to-treat (ITT) population and safety population included all participants who underwent randomisation and received at least one dose of study drug.

Characteristic	BNT162b2	Placebo	Total
No. of participants	720	239	959
Sex − no. (%)			
Male	368 (51.1)	123 (51.5)	491 (51.2)
Female	352 (48.9)	116 (48.5)	468 (48.8)
Age group − no. (%)			
18−55 years	389 (54.0)	129 (54.0)	518 (54.0)
56−85 years	331 (46.0)	110 (46.0)	441 (46.0)
Age at vaccination − years			
Mean (standard deviation)	52.9 (11.8)	52.3 (12.2)	52.7 (11.9)
Median (range)	54 (19−84)	53 (18−80)	54 (18−84)
Body mass index − kg/m^2			
Mean (standard deviation)	25.7 (3.3)	25.9 (3.5)	25.8 (3.3)
Median (range)	25.6 (17.9−40.5)	25.7 (19.0−37.2)	25.6 (17.9−40.5)
Body-mass index ≥30.0 kg/m^2 (obese) − no. (%)	83 (11.5)	28 (11.7)	111 (11.6)
Subjects with Charlson comorbidity − no. (%)			
Diabetes	28 (3.9)	9 (3.8)	37 (3.9)
Chronic pulmonary disease	2 (0.3)	0 (0)	2 (0.2)
Cerebrovascular disease	7 (1.0)	3 (1.3)	10 (1.0)
Rheumatic disease	1 (0.1)	1 (0.4)	2 (0.2)
Peptic ulcer disease	1 (0.1)	0 (0)	1 (0.1)
Any Charlson comorbidity	37 (5.1)	12 (5.0)	49 (5.1)

Table 1: **Baseline demographic and clinical characteristics.**

Endpoint	BNT162b2			Placebo	BNT162b2 vs Placebo
	Participants 18−55 Years of Age	Participants 56−85 Years of Age	Total	Total	
No. of participants	389	331	720	239	
Neutralizing antibody geometric mean titer (95% CI)[b,c]					**Geometric mean ratio (95% CI)[d]**
Baseline (pre-dose)	5.00 (5.00 to 5.00)	5.00 (5.00 to 5.00)	5.00 (5.00 to 5.00)	5.00 (5.00 to 5.00)	..
1 week	196.24 (181.80 to 211.84)	195.90 (178.32 to 215.21)	196.09 (184.74 to 208.13)	5.00 (5.00 to 5.00)	39.22[a] (35.36 to 43.49)
1 month	324.35 (305.14 to 344.77)	262.75 (245.24 to 281.50)	294.44 (281.13 to 308.39)	5.00 (5.00 to 5.00)	58.89[a] (54.35 to 63.81)
6 months	20.35 (19.12 to 21.66)	17.33 (16.15 to 18.58)	18.90 (18.04 to 19.81)	5.01 (4.99 to 5.02)	3.78[a] (3.48 to 4.10)
Neutralizing antibody geometric mean fold rise (95% CI)[b]					
1 week	39.25 (36.36 to 42.37)	39.18 (35.66 to 43.04)	39.22 (36.95 to 41.63)	1.00 (1.00 to 1.00)	..
1 month	64.87 (61.03 to 68.95)	52.55 (49.05 to 56.30)	58.89 (56.23 to 61.68)	1.00 (1.00 to 1.00)	..
6 months	4.07 (3.82 to 4.33)	3.47 (3.23 to 3.72)	3.78 (3.61 to 3.96)	1.00 (1.00 to 1.00	..
Neutralizing antibody seroconversion rate, n (%), (95% CI)[b,e]					**Difference in seroconversion rate, % (95% CI)[f]**
1 week	384 (99.2) (97.8 to 99.8)	323 (98.8) (96.9 to 99.7)	707 (99.0) (98.0 to 99.6)	0 (0.0 to 1.5)	99.0[a] (97.4 to 99.5)
1 month	383 (99.5) (98.1 to 99.9)	327 (100.0) (98.9 to 100.0)	710 (99.7) (99.0 to 100.0)	0 (0.0 to 1.5)	99.7[a] (98.1 to 99.9)
6 months	239 (62.9) (57.8 to 67.8)	173 (53·9) (48.3 to 59.4)	412 (58.8) (55.0 to 62.4)	0 (0.0 to 1.6)	58.8[a] (55.1 to 62.4)
Anti-S1 IgG antibody geometric mean titer (95% CI)					**Geometric mean ratio (95% CI)**
Baseline (pre-dose)	75.05 (69.52 to 81.03)	81.37 (73.76 to 89.75)	77.89 (73.27 to 82.80)	74.79 (67.54 to 82.82)	..
1 week	27469.27 (25319.45 to 29801.63)	19874.39 (17922.87 to 22038.41)	23685.15 (22179.88 to 25292.58)	72·.87 (66.18 to 80.23)	325.05[a] (286.39 to 368.93)
1 month	32203.76 (30304.13 to 34222.48)	31235.22 (29307.34 to 33289.93)	31755.27 (30390.78 to 33181.02)	75.26 (68.11 to 83.16)	421.95[a] (383.60 to 464.13)
6 months	2397.11 (2179.38 to 2636.60)	3146.00 (2901.24 to 3411.41)	2714.91 (2546.07 to 2894.93)	121.61 (102.98 to 143.61)	22.33[a] (19.28, 25.85)
Anti-S1 IgG antibody geometric mean fold rise (95% CI)					
1 week	365.23 (327.22 to 407.67)	244.13 (212.05 to 281.05)	303.70 (277.89 to 331.91)	0.97 (0.92 to 1.03)	..
1 month	427.28 (389.24 to 469.03)	383.67 (341.11 to 431.56)	406.67 (377.73 to 437.82)	1.00 (0.94 to 1.07)	..
6 months	31.99 (28.51 to 35.88)	38.29 (33.88 to 43.29)	34.73 (31.94 to 37.78)	1.63 (1.39 to 1.91)	..
Anti-S1 IgG antibody seroconversion rate, n (%), 95% CI					**Difference in seroconversion rate, % (95% CI)**
1 week	387 (100.0) (99.1 to 100.0)	325 (99.4) (97.8 to 99.9)	712 (99.7) (99.0 to 100.0)	2 (0.8) (0.1 to 3.0)	98.9[a] (96.7 to 99.6)
1 month	385 (100.0) (99.1 to 100.0)	326 (99.7) (98.3 to 100.0)	711 (99.9) (99.2 to 100.0)	3 (1.3) (0.3 to 3.7)	98.6[a] (96.2 to 99.5)
6 months	362 (95.3) (92.6 to 97.2)	310 (96.6) (94.0 to 98.3)	672 (95.9) (94.1 to 97.2)	36 (15.4) (11.0 to 20.7)	80.5[a] (75.1 to 84.8)

Table 2: **Immunogenicity pre-vaccination and at 1 week, 1 month and 6 months after the second vaccine dose.**

CI, confidence interval; IgG, immunoglobulin; S1, spike glycoprotein.

[a] $P<0.0001$ vs placebo.

[b] Values missing for 2, 4, 6 and 2 participants at 1 week in the BNT162b2 18−55 years' age group, BNT162b2 56−85 years' age group, overall BNT162b2 group, and placebo group, respectively, as well as for 4, 4, 8 and 2 participants at 1 month and 9, 10, 19 and 6 participants at 6 months, respectively.

[c] Data are functional 50% SARS-CoV-2 neutralizing geometric mean titer (ID_{50} GMT). An arbitrary titer of 5 (half of the limit of detection [LOD]) is given if no neutralization reaction was observed at the initial serum dilution (1:10). The lower limit of quantitation was defined as 20, with titers below this considered as seronegative. Conversion of GMTs to equivalent World Health Organization reference standard units is provided in Supplementary Table S2.

[d] The geometric mean ratio was determined using the Wald method, and the associated P-value with a t-test, both after logarithmic transformation.

[e] Seroconversion was defined as a ≥4-fold rise in antibody titers from before vaccination to 1 month and 6 months after dose 2.

[f] The between-group difference in seroconversion rate was calculated using the Miettinen-Nurminen method, and the associated P-value using Fisher's exact test.

antibody GMTs were generally consistent between age groups at 1 week after the second dose, by 1 month after they were numerically lower in the older than younger age group of BNT162b2 recipients. SCRs with BNT162b2 were at least 99% at 1 week (18−55 years: 99.2%; 56−85 years: 98.8%) and 1 month (18−55 years: 99.5%; 56−85 years: 100%) after the second dose, and had fallen to approximately 50−60% at 6 months after the second dose (18−55 years: 62.9%; 56−85 years: 53.9%) (Table 2).

BNT162b2-elicited sera at 1 month after the second dose also neutralised SARS-CoV-2 VOCs Alpha, Beta, and Delta (Figure 2b, Table S4). Neutralising GMT against the Alpha variant was slightly lower than the wild-type strain (Alpha to Italy-INMI1/2020 GMT ratio [GMR]: 0.81, 95% CI, 0.72−0.93). Reductions in GMTs were even more pronounced for the Beta and Delta variants, with GMRs versus the wild-type strain of 0.17 (95% CI; 0.14−0.20) and 0.38 (95% CI; 0.34−0.43), respectively.

BNT162b2 induced high S1-binding IgG titers after the second dose in both age groups, with an increase in these titers from 1 week to 1 month (Table 2, Figure 2c). Titers had fallen at 6 months after the second dose, but the SCR still remained above 95% (Table 2). Positive correlations were observed between S1-binding IgG and neutralising antibody titers (post hoc analysis, $P \leq 0.0001$; Figure 2d), regardless of age.

At 1 week after the second dose, robust SARS-CoV-2 S-specific T-cell responses were detected in the BNT162b2 recipients (n=74). The geometric mean IFNγ spot counts per 100,000 PBMCs were 73.5 and 73.7 when cells were stimulated with overlapping peptide pools covering the N-terminal 'S pool 1' (amino acids 1−643) and C-terminal 'S pool 2' (amino acids 633−1273) of the spike protein, respectively, higher than the response to the CEF peptide pool positive control, which was 16.9 (Figure 2f). A strong IFNγ response was elicited in both age groups (Figure 2e). The majority (79.5%) of BNT162b2 recipients had a positive T-cell response (Table S5).

Within 7 days after each dose, both local and systemic solicited events occurred more frequently in BNT162b2 recipients (local: 67.4%; systemic: 56.3%) than placebo recipients (local: 5.4%; systemic: 8.8%), and were more common in individuals aged 18−55 years (local: 80.2%; systemic: 66.1%) than in those aged 56−85 years (local: 52.3%; systemic: 44.7%). Non-risk individuals experienced solicited events more frequently than at-risk individuals (local: 68.3% vs. 62.6%; systemic: 57.9% vs. 49.6%) (Table S6).

All solicited local events reported within the 7 days after each dose were considered treatment related and were of mild or moderate severity (per the US FDA grading criteria), transient in nature, and were slightly more frequent after the first than the second dose. Injection site pain was the most frequent of these in the

BNT162b2 recipients (Figure 3a). Figure S2 presents treatment-related solicited local reactions reported in the 14-day period after each vaccination (per the Chinese NMPA grading criteria). Only two local reactions (pain), one in each age group, were reported between 7 and 14 days after a BNT162b2 dose.

Almost all solicited systemic events that occurred within 7 days were of mild or moderate severity (Figure 3b). Solicited systemic events occurred rarely (two for BNT162b2 and three for placebo, respectively) between 7 and 14 days after vaccination (Figure S3). The majority of solicited systemic reactions were transient, resolving within 1 to 3 days and were more likely to occur, or be more severe after the second dose than the first. Treatment-related fever was the most common solicited systemic event (Figure 3b); only 4.0% of BNT162b2 recipients had grade 3 fever per the US FDA grading criteria. One BNT162b2 recipient had a peak temperature of 40 °C, which began approximately 30 minutes after the second dose and resolved without sequelae within 24 h.

Use of analgesic/antipyretic medication was more common after the second (22.4%) than first (2.4%) dose of BNT162b2 and more common after the second dose among individuals aged 18−55 years (29.5%) than 56−85 years (14.0%).

Treatment-emergent unsolicited AEs occurred at a relatively low frequency between the first dose and 1 month after the second dose (BNT162b2: 11.0% vs. placebo: 8.0%) (Tables S7, S8), and were less common in at-risk than non-risk individuals (Table S6). Treatment-related unsolicited AEs were also relatively uncommon during this period (BNT162b2: 8.1%; placebo: 3.8%). No treatment-related unsolicited AEs were reported between 1 month and 6 months after the second dose. No deaths, grade 3 unsolicited AEs or serious AEs related to BNT162b2 or placebo were reported within 6 months after the second dose. Further, no BNT162b2-related cardiac disorders, nor any cases of myocarditis, pericarditis or anaphylaxis (in either vaccine group), were reported.

None of the treatment-emergent serious AEs were considered to be treatment related. Few treatment-emergent serious AEs were reported between the first dose and 6 months after the second dose (Table S9), and the incidence was numerically lower in the BNT162b2 group (2.4%) than the placebo group (3.4%). The most common treatment-emergent serious AEs, by MedDRA System Organ Class, in BNT162b2 recipients were nervous system disorders (5 subjects vs. 3 subjects in the placebo group), injury, poisoning and procedural complications (4 vs. 0), neoplasms benign, malignant and unspecified (including cysts and polyps) [2 vs. 1], and musculoskeletal and connective tissue disorders (2 vs. 0). Treatment-emergent serious AEs were more frequent in individuals aged 56−85 years (3.9%) than in those aged 18−55 years (1.0%).
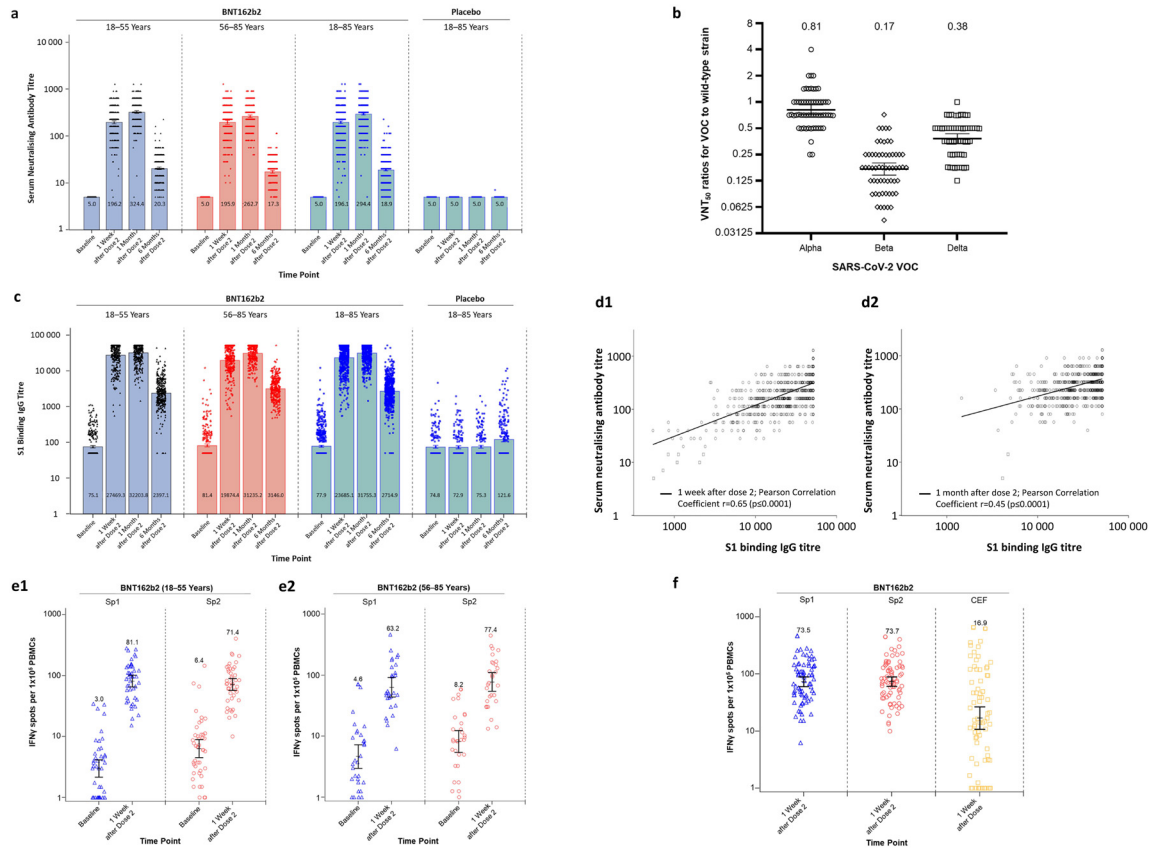
Figure 2. BNT162b2-induced antibody responses and T-cell responses.

Panel **a** shows BNT162b2-induced neutralising antibody responses at various time-points after the second dose compared with baseline; Panel **b** shows the ratios of the 50% virus neutralising titers (VNT_{50}) for the SARS-CoV-2 variants of concern (VOC) Alpha, Beta, and Delta to the wild-type strain VNT_{50}; Panel **c** shows BNT162b2-induced S1-binding immunoglobulin G (IgG) responses at various time-points after the second dose compared with baseline; Panel **d** shows the Pearson correlation between the VNT_{50} values (from Panel **a**) and the spike protein (S1)-binding IgG geometric mean titers (GMTs) (from Panel **c**); and Panels **e1**, e2 and **f** show BNT162b2-induced T-cell responses at various time-points after the second dose compared with baseline. Further detail regarding the time points specified in this figure can be found in Supplementary Figure S1, which presents the vaccination and serum sampling schedule. In Panels **a** and **c**, functional 50% SARS-CoV-2 neutralising antibody GMTs, and IgG GMTs, as well as 95% confidence intervals, were plotted. In Panel **b**, geometric mean ratios (horizontal lines; numbers above data points) were calculated from the individual VNT_{50} ratios of the Alpha, Beta, and Delta SARS-CoV-2 variants to the wild-type strain, confidence intervals are indicated on the graph by errors bars. Sera for these cross-neutralisation analyses were drawn 1 month after the second dose of BNT162b2. The clinical isolate Italy-INMI1/2020 was used as the wild-type virus in this analysis. In Panel **d**, the square data points represent individual values outside the lower limit of quantitation. Calculation of the correlation coefficient (r) excluded any values above or below the limits of quantitation. Results shown in Panels **e1, e2** and **f** are from interferon-γ (IFNγ) enzyme-linked immune absorbent spot (ELISpot) assays conducted on peripheral blood mononuclear cells obtained from participants ($n=74$, 18—85 years) at baseline (pre-vaccination) and 1 week after the second dose, which were stimulated overnight with overlapping S peptide pools (S pool 1 [Sp1] and S pool 2 [Sp2]). Each data point in Panels **e** to **f** represents the mean spot count from quadruple wells for one study participant, after subtraction of the medium-only control. If the spot count was less than one, it was reset to one. Values above each group of data points are the geometric mean spot count of all participants in that group, indicated by a horizontal bar (with error bars indicating the 95% confidence intervals). Panels **e1** and **e2** show S-specific T-cells (Sp1 and Sp2) producing IFNγ as a fraction of peripheral blood mononuclear cells (PBMCs) from baseline, and 1 week after the second dose, by age group. Panel **f** shows T-cell responses to Sp1, Sp2 and to the recall antigen (CEF).

There were no abnormalities in clinical chemistry parameters with clinical manifestation, including thyroid function and coagulation tests in either group (not shown); transient non-clinically significant decreases in lymphocyte and platelet counts were observed in the BNT162b2 group (Table S10).

Discussion

Our trial is the first to show that BNT162b2 administered as a two-dose regimen at 30 μg, 21 days apart, elicited a robust immune response and was generally well tolerated in Chinese adults who were healthy or had stable pre-existing disease.
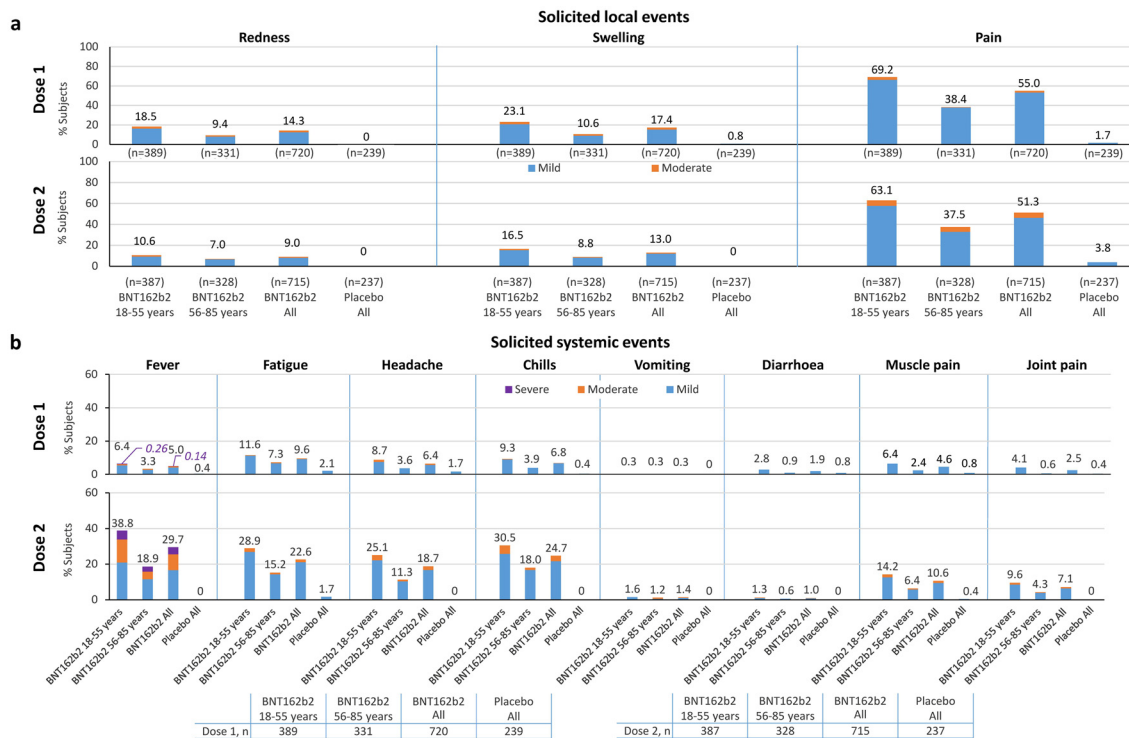
Figure 3. The incidence of solicited local reactions (Panel a) and systemic reactions (Panel b) by maximum severity within 7 days after each dose of BNT162b2 30 μg or placebo.

In both Panels **a** and **b**, the number above each column is the overall incidence (grade 1−3), and data are for subsets of the safety population by doses received: the safety population for dose one included recipients of the first dose (n=959) and for dose two, recipients of both doses (n=952). Grade 1 reactions were labelled mild and grade 2 moderate, and in Panel **b**, grade 3 severe. Grading was per the United States Food and Drug Administration criteria. "Related" means "possibly related", "probably related" or "definitely related" to randomised treatment.

Overall, our trial confirmed the results of prior studies showing that BNT162b2 vaccination induces a high neutralising antibody response against SARS-CoV-2 in adults.[13,14] In the global pivotal trial, antibody response induced by BNT162b2 translated into 95% VE against COVID-19.[5] In our trial, the neutralising antibody GMT in BNT162b2 recipients 1 month after the second vaccination was equivalent to 1840 neutralising antibody units (IU)/mL (95% CI; 1757−1927) using the WHO international standard (NIBSC code 20/136).[11] This is substantially higher than the value of 26 IU/mL required for 80% VE against symptomatic SARS-CoV-2 infection reported by Feng and colleagues when using a pseudovirus in the virus neutralisation test.[15] As expected, the neutralising antibody titers and seroconversion rates had fallen considerably at 6 months after the second dose in the total cohort. These findings support the recommendation of a third dose of BNT162b2 at 4 to 6 months after the primary vaccination series to provide ongoing protection against VOC.[16]

In our trial, Chinese individuals vaccinated with BNT162b2 had antibodies with cross-reactivity against three VOCs (B.1.1.7, B.1.351, B.1.617.2) and, although titer reductions were observed, especially for the Beta and Delta variants, these were broadly in line with previously published cross-neutralisation analyses of BNT162b2 immune sera.[13,17−19]

The Omicron variant (B.1.1.529) has now emerged globally, with five major lineages (BA.1−BA.5) and a further sublineage (BA.2.12.1) identified [preprint].[20,21] While BA.2 is replacing the initial BA.1 lineage worldwide, the newer BA.4/BA.5 lineages show more infectious potential than BA.2; BA.4 and BA.5 have become the dominant lineages in some countries[21−24] and accounted for 21.6% of COVID variants in the United States as of June 2022.[25] These newer lineages exhibit increased immune escape from neutralising antibodies induced by both vaccination and infection [preprint].[21,26] Neutralising antibody titers to BA.4 and BA.5, and to a lesser extent to BA.2.12.1, are lower than to BA.1 and BA.2 [preprint].[21] Three doses of BNT162b2 have been shown to be required to achieve adequate levels of neutralising antibodies to BA.2, although these levels are lower than to wild-type [preprint],[27,28] and there is some evidence that levels are lower than to BA.1 [preprint].[28] Further, breakthrough BA.1 infection in

individuals who have received two or three doses of BNT162b2 appears to augment neutralising antibodies to BA.1 and/or BA.2, but not to BA.4 and BA.5 [preprint].[29,30] Additional studies are required to confirm these initial results suggesting that BNT162b2 has limited efficacy against BA.4 and BA.5.

Cellular immunity is an important aspect of the immune response to SARS-CoV-2 infection; virus-specific T-cell responses are critical in elimination of the virus-infected cells and in optimising the humoral immune response.[31] Furthermore, SARS-CoV-2-specific IFNγ-producing CD8+ T-cells and CD4+ T-cells have been associated with less severe disease.[32] In our trial, BNT162b2 induced a strong SARS-CoV-2-specific T-cell response in the majority (79.5%) of participants at 1 week after the second dose, as shown by cellular immunoassay IFNγ spot counts. These results are in line with those of a previous BNT162b2 study.[13] The only other SARS-CoV-2 mRNA vaccine currently available likewise elicits a Th-1 directed T-cell response.[33,34]

BNT162b2 was well tolerated in Chinese individuals. Reactogenicity events were as anticipated, with the majority being transient in nature. Injection site pain was the most common solicited local event and fever the most common solicited systemic event. The fever incident was higher than in the global study;[14] the reasons for this difference may be the use of different criteria for defining fever in the two trials, and difference in the use of antipyretics (there was a lower usage of antipyretics in the current trial, possibly resulting in a greater likelihood of fever developing). Overall, the reactogenicity profile of BNT162b2 in Chinese participants in this analysis was consistent with that observed in the global pivotal trial.[5] Reactogenicity after each dose of vaccine was generally milder and less frequent in older than younger adults, and was similar between 'at risk' and 'non-risk' participants, although this particular subgroup analysis was post hoc, and should be confirmed in prospective analyses. No treatment-related serious AEs were observed 6 months after the second dose, and no cases of myocarditis, pericarditis or anaphylaxis were reported. The risk of severe cardiac AEs after BNT162b2 vaccination is small but not as substantial as after SARS-CoV-2 infection.[35]

Few studies have compared the effectiveness and tolerability of BNT162b2 with other COVID-19 vaccines, particularly in Chinese individuals. In those that have, a more robust humoral response against SARS-CoV-2 (including the Omicron BA.1 variant) has been observed after three dose of BNT162b2 than after three doses of CoronaVac (an inactivated whole-virus vaccine) in individuals from Hong Kong.[36,37] A dose of BNT162b2 also improved neutralising antibodies levels against Omicron BA.1 in individuals who had previously received two doses of CoronaVac.[37] The effect of BNT162b2 and CoronaVac against the Omicron BA.2 variant has been recently investigated.[38] A more robust response was observed in individuals who received three doses of BNT162b2 or two doses of CoronaVac plus one dose of BNT162b2 than in those who received three doses of CoronaVac. These data suggest that mRNA vaccination, whether three doses of BNT162b2 or a dose of BNT162b2 following two previous doses of an inactivated whole-virus vaccine, provides increased protection against wild-type and variants of SARS-CoV-2. Thus far, no mRNA COVID-19 vaccines are available in mainland China; if approved, BNT162b2 could be used to supplement current vaccination programs in China.

As an interim analysis, our results have some limitations, specifically the absence of data on COVID-19 rates and outcomes. Given the evidence that BNT162b2 vaccination reduces SARS-CoV-2 infection rates, as well as the risk of serious COVID-19—related outcomes such as hospitalisation for COVID-19, severe or critical COVID-19, and COVID-19—related death, similar data will be required to confirm the real-world effectiveness of BNT162b2 vaccination in a Chinese population.[39] Further, our results may not be generalisable to special patient populations in China, such as immunocompromised individuals, adolescents or pregnant women. However, it has been reported that in general, immunocompromised individuals are less likely to develop vaccine antibody responses compared with healthy subjects,[40,41] and may therefore need a different vaccination schedule. Also, a prior study conducted in Hong Kong found that immunogenicity responses of adolescents after two doses of BNT162b2 were non-inferior to adults.[41] Although global studies showed that BNT162b2 vaccination in special patient populations was generally safe and generated protection from COVID-19 infection, more studies are needed to explore their use in special patient populations in China. Our study cohort, while of a reasonable size, does represent a small sample of the Chinese population and, therefore, studies with larger sample sizes and utilising more study sites would be useful to confirm our findings. Further, the sample size may have limited the ability of this study to detect infrequent but severe AEs that might be associated with BNT162b2. To confirm the clinical significance of the immunogenicity reported here, additional studies are required using the same neutralisation assays to compare the immunogenicity of BNT162b2 in Chinese individuals with individuals from the global pivotal trial, since VE in that trial was 95%.[5] Long-term follow-up data are required to better characterise the long-term persistence of immunogenicity, and long-term safety, in a Chinese population. Safety data collection from participants in this trial is therefore continuing until 12 months after the second dose.

Conclusions

Robust SARS-CoV-2 neutralising antibody and strong SARS-CoV-2-specific T-cell responses were detected

after BNT162b2 vaccination in the first phase 2 trial of an mRNA COVID-19 vaccine conducted in a Han Chinese population. BNT162b2 had acceptable tolerability up to 6 months after the second dose, indicating a favourable risk-benefit profile for Chinese adults.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100586.

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