Supplementary Material

Immunogenicity and Safety of BNT162b2 mRNA Vaccine in Chinese Adults: A Randomised Clinical Trial

Table of Contents

Methods

Trial Inclusion and Exclusion Criteria

Inclusion Criteria

Participants were eligible to be included in the trial only if all of the following criteria applied:

Age and Sex

1. Male or female participants between the ages of 18 and 85 years, inclusive, at randomisation.
2. Male participants, and female participants who are not pregnant or breastfeeding and who are of child-bearing potential are to use a medically acceptable method of effective contraception during the entire study period, as described in the detail in the study protocol.

Type of Participant and Disease Characteristics

3. Participants who were willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
4. Healthy participants who were determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.
5. Note: Healthy participants with stable pre-existing disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrollment, could be included.

Informed consent

6. Capable of giving personal signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and this protocol.

SARS-CoV-2 Screening

7. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody test screening was negative.
8. Negative SARS-CoV-2 test in throat swabs by reverse transcriptase-polymerase chain reaction (only for the first approximately 150 subjects).
9. Normal in chest computed tomography scans (no imaging features of COVID-19, only for the first approximately 150 subjects).

Exclusion Criteria

Participants were excluded from the trial if any of the following criteria applied:

Medical conditions

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase risks associated with study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s).
4. Receipt of medications intended to prevent COVID-19.
5. Immunocompromised individuals with known or suspected immunodeficiency, determined by history and/or laboratory/physical examination.
6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

7. Women who were pregnant or breastfeeding.

Prior and Concomitant Treatment

8. Previous vaccination with any coronavirus vaccine.
9. Individuals who were receiving treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids had been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulised, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
10. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study

Prior/contemporaneous clinical study experience

11. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.
12. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Epidemiological history screening

13. Had contact with confirmed COVID-19 patients or persons who tested positive for SARS-CoV-2 within the 30 days prior to the Screening Visit
14. Travelled to or lived in any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit) within the 14 days prior to Screening Visit.
15. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
16. Fever, defined as axillary temperature ≥37.3ºC or oral temperature ≥38.0ºC.
17. History of Severe Acute Respiratory Syndrome (SARS), SARS-CoV-2 or Middle East Respiratory Syndrome (MERS) infection. Suspected SARS patients were screened for SARS antibodies.

Other Exclusions

18. Investigator site staff or Fosun employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Randomisation procedures

An independent randomisation professional generated a participant randomisation table (using SAS version ≥9.4) and imported it into an interactive response technology (IRT) system, which was used to perform the randomisation. Block randomisation was performed. Study participants were stratified by age (18–55 years' old vs >55 years' old). The principal investigator enrolled participants and assigned participants to the trial groups through the IRT system. According to a blinding maintenance plan, only authorised personnel had access to the randomisation list (i.e., had unblinded access to treatment assignments): the IRT vendor, the Independent Data Monitoring Committee, the independent statistician, the unblended data manager, the unblinded pharmacist or nurses who prepared the blinded vaccine for the study vaccine and placebo, and any site personnel for whom this information was important to ensure the safety of the study participant in the case of a life-threatening medical emergency. Study participants, study personnel at each clinical site, investigators, trial statisticians, and the sponsor's study management team were blinded to treatment assignment (see the study protocol for further detail).

Cross-neutralisation analysis of SARS-CoV-2 variants of concern

Cross-neutralisation analysis of SARS-CoV-2 variants of concern was conducted at VisMederi S.r.l., Siena, Italy, using the wild-type virus (SARS-CoV-2/INMI1-Isolate/2020/Italy [GenBank: MT066156]), and Alpha

(nCoV19 isolate/England/MIG457/2020), Beta (nCoV19 isolate/England ex-SA/HCM002/2021), and Delta VOC (isolated from swab, the following mutations were detected in comparison to GenBank MN908947.2 reference Spike: T19R, G142D, R158G, L452R, T478K, D614G, P681R, R682Q, D950N. DeL-156, DeL-157) specific microneutralisation assays using serum samples collected from n=59 study participants in the BNT162b2 group were collected at 1 month after the second dose. In brief, heat-inactivated serum samples from participants were serially diluted 1:2 (starting at 1:10) and incubated for 1 hour at 37°C with live SARS-CoV-2 virus to allow any antigen-specific antibodies to bind to the virus. Vero E6 cell monolayers were inoculated with the serum/virus mix in 96-well plates and incubated for 3 days (the wild-type-, Alpha-, and Beta-specific microneutralisation assay) or 4 days (Delta-specific microneutralisation assay) to allow infection by non-neutralised virus. The plates were observed under an inverted light microscope and the wells were scored as positive for SARS-CoV-2 infection (i.e., showing CPE) or negative for SARS-CoV-2 infection (i.e., cells were alive without CPE). The neutralisation titre was determined as the reciprocal of the highest serum dilution that protected more than 50% of cells from CPE and reported as the GMT of duplicate. If no neutralisation was observed, an arbitrary titre value of 5 (half of the limit of detection [LOD]) was reported.

S1-binding IgG indirect enzyme-linked immunosorbent assay (ELISA)

Anti-SARS-CoV-2 S1 IgG antibodies were determined using an indirect ELISA assay. Briefly, each test sample was 2-fold serially diluted from 1:100 to 1:51,200, and detected in 96 well plates coated with human IgG1 anti-SARS-CoV-2 Spike (S1) antibody (CR3022, Native Antigen, MAB12422-100, lot. T2013A02). Bound IgG was detected using a goat anti-human IgG-HRP conjugated secondary antibody (A80-104P, batch CV-93). Data collection was performed using an automatic plate reader (Inv. VM-E-003) to measure optical density (OD) at a wavelength of 450 nm. The cut-off value was determined through the estimation of Metrix Effect, Limit of Blank and Limit of Detection. The sample dilution corresponding to the cut-off value was the titre value. The sample titre was set to 50 if its OD was less than the cut-off at 1:100 dilution; the sample titre was set to 51,200 if its OD was greater than the cut-off value at 1:51,200 dilution.

Enzyme-linked immunosorbent spot (ELISpot) assay

Two overlapping peptide pools, representing the amino-terminal (amino acids 1–643; designated ‘S pool 1’) and the carboxy-terminal (amino acids 633–1273; designated ‘S pool 2’) portions of the SARS-CoV-2 S protein were used, as well as a CEF peptide pool (CMV, EBV, influenza virus; human leukocyte antigen (HLA) class I epitope peptide pool) and anti-CD3 pool as positive controls for T-cell response.[1] The pools were those for the original wild type COVID strain. Three replicate wells were used for positive controls (anti-CD3 and CEF) and four for the S peptide pools and negative control. The number of spot-forming cells (SFC) per 100,000 cells was determined after subtraction of the medium-only control (spot count was reset to 1 if <1). A positive T-cell response was defined as ≥55 SFC per 10^5 peripheral blood mononuclear cells and more than twice the background response for at least one of the two S peptide pools.

Reactogenicity and grading criteria

The severity of solicited local and systemic events, occurring up to 14 days after each dose, was graded according to the National Medical Products Administration (NMPA) of China criteria for grading of adverse events in vaccine clinical trials.[2] Solicited events related to the BNT162b2 vaccine (i.e., solicited reactions) occurring within 7 days after each dose were also graded according to the United States Food and Drug Administration (FDA) grading criteria.[3] NMPA and FDA grading criteria are described in the tables below. Unsolicited adverse event terms not included in the FDA list were graded according to study protocol–defined criteria. Abnormal values in thyroid function and coagulation function tests were graded according to NMPA and FDA criteria. Causality in relation to the vaccine was judged by the investigators.

Sample size calculation

Global multicentre studies have shown good efficacy and safety of vaccines, and therefore to provide both maximal protection of and benefits to subjects in the study, a ratio of active vaccine to placebo of 3:1 was chosen. The sample size was determined first by estimating the minimum sample required for statistical power to

detect between-group differences in GMT and SCR. Assuming post-immunization GMT of 157 in the vaccinated group and 10 in the placebo group, and using a one-sided test level of $\alpha = 0.025$, we estimated a total of 30 subjects in the BNT162b2 group and 10 subjects in the placebo group were needed to provide an overall power of approximately 85% and a standard deviation of 0.50 to detect a significant difference between groups in GMT for each age stratification. Assuming post-immunization SCRs of 80% in the vaccinated group and 30% in the placebo group, and using a one-sided test level of $\alpha=0.025$, we estimated that a total of 72 subjects in the BNT162b2 group and 24 subjects in the placebo group were needed to provide an overall power of approximately 85% to detect a significant between-group difference in SCR for each age stratification. Second, as per vaccine clinical development guidance in China, a minimum sample size of 300 subjects in the vaccine group is mandatory for phase 2 trials, which equates in our trial to ~150 subjects in each age stratification of the vaccine group. This exceeds the sample size we had estimated was required for statistical power. Therefore, given the 3:1 randomization ratio, and an expected 20% dropout rate, we planned to enroll 720 individuals into the BNT162b2 group and 240 into the placebo group.

FDA Toxicity Grading Table for Prophylactic Vaccine Clinical Trials

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Local				
Injection site pain	Does not interfere with daily activities	Interferes with daily activities	Hinders daily activities	Severe pain requiring emergency room visit or hospitalisation
Redness	2.5 to 5.0 cm	>5.0 to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling	2.5 to 5.0 cm	>5.0 to 10.0 cm	>10 cm	Necrosis
Systemic				
Vomiting	1–2 times within 24 h	>2 times within 24 h	IV infusion required	Hypotensive shock requiring emergency room visit or hospitalisation
Diarrhoea	Loose stools 2–3 times within 24 h	Loose stools 4–5 times within 24 h	Loose stools ≥6 times within 24 h	Severe diarrhoea requiring emergency room visit or hospitalisation
Headache	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe headache requiring emergency room visit or hospitalisation
Fatigue/ asthenia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe fatigue requiring emergency room visit or hospitalisation
Chills	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe chills requiring emergency room visit or hospitalisation
New or worsening myalgia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	New or worsening myalgia requiring emergency room visit or hospitalisation
New or worsening arthralgia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	New or worsening arthralgia requiring emergency room visit or hospitalisation
Fever	38.0–38.4°C	38.5–38.9°C	39.0–40.0°C	>40.0°C

h, hour; IV, intravenous

NMPA Adverse Event Grading Scale for Preventive Vaccine Clinical Trial Guidelines

	Grade 1	Grade 2	Grade 3	Grade 4
Local				
Injection site pain	No or slight influence on limb movement	Influence on limb movement	Influence on daily life	Loss of basic self-care ability, or hospitalisation
Redness, blush	2.5 to <5.0 cm in diameter, with no or slight influence on daily life	5.0 to <10.0 cm in diameter or interferes with daily life	≥10 cm in diameter or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or significant impact on daily life	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue
Induration, swelling	2.5 to <5.0 cm in diameter, with no or slight influence on daily life	5.0 to <10.0 cm in diameter or interferes with daily life	≥10 cm in diameter or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or significant impact on daily life	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue
Systemic				
Vomiting	1–2 times per 24 h without influence on activities	3–5 times within 24 h or limited activities	≥6 episodes within 24 h or need for IV hydration	Shock due to hypotension requiring hospitalisation or other routes of nutrition
Diarrhoea	Mild or transient, 3–4 times/day, abnormal stool appearance, or mild diarrhoea lasting less than 1 week	Moderate or persistent, 5–7 times/day, abnormal stool appearance, or diarrhoea for >1 week	>7 times/day, abnormal stool appearance, or haemorrhagic diarrhoea, orthostatic hypotension, electrolyte imbalance, requiring >2L IV fluids	Hypotensive shock, needs to be hospitalised
Headache	No influence on daily activities, no treatment required	Transient, slight influence on daily activities, may require treatment or intervention	Significant disruption of daily activity requiring treatment or intervention	Intractable, requiring emergency room visit or hospitalisation
Fatigue/ asthenia	No influence on daily activities	Influences normal daily activities	Seriously influences daily activities and cannot work	Requiring emergency room visit or hospitalisation
Chills	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe chills requiring emergency room visit or hospitalisation
Myalgia (non-vaccination site)	No influence on daily activities	Slight influence on daily activities	Severe muscle pain, severe interference with daily activities	Requiring emergency room visit or hospitalisation
Arthralgia	Mild pain, no interference with function	Moderate pain; pain requiring analgesics and/or pain preventing function but not influencing daily activities	Severe pain; requiring analgesics and/or pain influencing daily activities	Disabling pain
Fever	37.3 to <38.0°C	38.0 to <38.5°C	38.5 to <39.5°C	≥39.5°C for more than 3 days

h, hour; IV, intravenous

Tables

Table S1.

Baseline demographic and clinical characteristics by comorbidity status in the intent-to-treat population (aged 18–85 years).

Characteristic	At-Risk Participants[1]		Non-Risk Participants	
	BNT162b2	Placebo	BNT162b2	Placebo
No. of participants	115	35	605	204
Sex – no. (%)				
Male	81 (70.4)	19 (54.3)	287 (47.4)	104 (51.0)
Female	34 (29.6)	16 (45.7)	318 (52.6)	100 (49.0)
Age at vaccination – years				
Mean (standard deviation)	54.0 (12.2)	51.2 (11.9)	52.6 (11.7)	52.5 (12.3)
Median (range)	57.0 (25–79)	55.0 (25–71)	54.0 (19–84)	53.0 (18–80)
Body mass index – kg/m^2				
Mean (standard deviation)	30.0 (3.3)	31.0 (3.2)	24.9 (2.6)	25.0 (2.6)
Median (range)	30.6 (22.0–40.5)	30.9 (20.5–37.2)	25.0 (17.9–29.9)	25.2 (19.0–29.9)
Body mass index ⩾30.0 kg/m2 (obese) – no. (%)	83 (72.2)	28 (80.0)	0	0
Subjects with Charlson comorbidity – no. (%)				
Diabetes	28 (24.3)	9 (25.7)	0	0
Chronic pulmonary disease	2 (1.7)	0	0	0
Cerebrovascular disease	7 (6.1)	3 (8.6)	0	0
Rheumatic disease	1 (0.9)	1 (2.9)	0	0
Peptic ulcer disease	1 (0.9)	0	0	0
Any Charlson Comorbidity Index condition	37 (32.2)	12 (34.3)	0	0

[1] At-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese.

Table S2.

Neutralising antibody response at 1 week, 1 month and 6 months after the second vaccine dose presented in World Health Organization standard units.

Endpoint	BNT162b2		
	Participants 18–55 Years of Age	**Participants 56–85 Years of Age**	**Total**
No. of participants	389	331	720
Neutralising antibodies (95% CI), IU/mL			
1 week	1226.50 (1136.25 to 1324.00)	1224.38 (1114.50 to 1345.06)	1225.56 (1154.63 to 1300.81)
1 month	2027.19 (1907.13 to 2154.81)	1642.19 (1532.75 to 1759.38)	1840.25 (1757.06 to 1927.44)
6 months	127.19 (119.50 to 135.37)	108.31 (100.94 to 116.12)	118.12 (112.75 to 123.81)

CI, confidence interval; IU/mL, international units per milliliter.

The results in this table were calculated from Table 2 according to the World Health Organization international standard (NIBSC code 20/136), using the following formula: IU/mL = geometric mean titer/0.16.

Table S3

Immunogenicity by comorbidity status in the intent-to-treat population (aged 18–85 years).

Endpoint	At-Risk Participants[1]			Non-Risk Participants		
	BNT162b2	**Placebo**	**BNT162b2 vs Placebo**	**BNT162b2**	**Placebo**	**BNT162b2 vs Placebo**
No. of participants	115	35		605	204	
Neutralising antibody geometric mean titre (95% CI)[2,3]			**Geometric mean ratio (95% CI)**[4]			**Geometric mean ratio (95% CI)**[4]
Baseline (pre-dose)						–
1 week	160.50 (137.06 to 187.94)	5.00 (5.00 to 5.00)	32.10† (24.10 to 42.75)	203.53 (190.90 to 217.00)	5.00 (5.00 to 5.00)	40.71† (36.45 to 45.46)
1 month	274.13 (244.79 to 306.98)	5.00 (5.00 to 5.00)	54.83† (44.65 to 67.33)	298.40 (283.63 to 313.94)	5.00 (5.00 to 5.00)	59.68† (54.69 to 65.12)
Neutralising antibody geometric mean fold rise (95% CI)[2]						
1 week	32.10 (27.41 to 37.59)	1.00 (1.00 to 1.00)	32.10† (24.10 to 42.75)	40.71 (38.18 to 43.40)	1.00 (1.00 to 1.00)	40.71† (36.45 to 45.46)
1 month	54.83 (48.96 to 61.40)	1.00 (1.00 to 1.00)	54.83† (44.65 to 67.33)	59.68 (56.73 to 62.79)	1.00 (1.00 to 1.00)	59.68† (54.69 to 65.12)
Neutralising antibody seroconversion rate, n (%) (95% CI)[2]			**Difference in seroconversion rate, % (95% CI)**[5]			**Difference in seroconversion rate, % (95% CI)**[5]
1 week	111 (9.11) (95.13 to 99.98)	0 (0 to 10.28)	99.11† (88.85 to 99.84)	596 (99.00) (97.84 to 99.63)	0 (0 to 1.80)	99.00† (97.13 to 99.54)
1 month	112 (100.00) (96.76 to 100.00)	0 (0 to 10.28)	100.00† (89.79 to 100.00)	598 (99.67) (98.80 to 99.96)	0 (0 to 1.80)	99.67† (97.80 to 99.91)

CI, confidence interval.

†P<0.0001 vs placebo

[1]At-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as body mass index ≥30 kg/m^2).

[2]Values missing for 3, 1, 3 and 1 participants at 1 week in the BNT162b2 at-risk, placebo at-risk, BNT162b2 non-risk, and placebo non-risk groups, respectively, as well as for 3, 1, 5 and 1 participants at 1 month, respectively.

[3] Data are functional 50% SARS-CoV-2 neutralising geometric mean titre (ID_{50} GMT). An arbitrary titre of 5 (half the lower limit of quantitation) is given if no neutralisation reaction was observed at the initial serum dilution (1:10).

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

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

Table S4.

Cross-neutralisation antibody titres from post-BNT162b2 immunisation sera collected 1 month after dose 2 (n=59) tested against wild-type strain (reference) and Alpha, Beta, and Delta variants of concern[1]

Individual Participant, Anonymised ID number	VNT_{50}				VNT_{50} ratio		
	Wild-type	Alpha	Beta	Delta	Alpha to Wild-type	Beta to Wild-type	Delta to Wild-type
1	160	80	28	80	0.5	0.18	0.5
2	40	28	10	28	0.7	0.25	0.7
3	113	113	20	28	1	0.18	0.25
4	56	80	20	20	1.43	0.36	0.36
5	113	56	40	56	0.50	0.35	0.50
6	80	160	14	40	2	0.18	0.5
7	452	320	113	160	0.71	0.25	0.35
8	80	80	7	40	1	0.09	0.5
9	56	80	20	40	1.43	0.36	0.71
10	80	40	10	56	0.5	0.13	0.7
11	80	80	14	40	1	0.18	0.5
12	160	113	20	56	0.71	0.13	0.35
13	80	80	14	14	1	0.18	0.18
14	80	56	10	20	0.7	0.13	0.25
15	226	160	14	40	0.71	0.06	0.18
16	160	160	20	80	1	0.13	0.5
17	160	226	40	80	1.41	0.25	0.5
18	226	160	40	113	0.71	0.18	0.5
19	113	226	5	20	2	0.04	0.18
20	40	160	20	40	4	0.5	1
21	56	56	14	40	1	0.25	0.71
22	320	80	28	80	0.25	0.09	0.25
23	226	160	40	113	0.71	0.18	0.5
24	113	56	10	20	0.50	0.09	0.18
25	56	40	5	40	0.71	0.09	0.71
26	452	226	40	113	0.5	0.09	0.25
27	56	80	40	40	1.43	0.71	0.71
28	160	56	40	80	0.35	0.25	0.5
29	226	160	40	80	0.71	0.18	0.35
30	320	80	20	40	0.25	0.06	0.13
31	226	160	80	160	0.71	0.35	0.71
32	226	113	14	40	0.5	0.06	0.18
33	226	226	113	160	1	0.5	0.71
34	113	80	28	40	0.71	0.25	0.35
35	226	160	20	40	0.71	0.09	0.18
36	56	40	5	10	0.71	0.09	0.18
37	56	56	10	20	1	0.18	0.36
38	320	226	40	56	0.71	0.13	0.18
39	113	80	14	56	0.71	0.12	0.50
40	113	80	14	28	0.71	0.12	0.25
41	226	160	40	80	0.71	0.18	0.35
42	226	320	56	113	1.42	0.25	0.5
43	113	160	28	56	1.42	0.25	0.50
44	113	56	14	20	0.50	0.12	0.18
45	226	113	14	113	0.5	0.06	0.5
46	160	113	40	56	0.71	0.25	0.35
47	40	20	5	14	0.5	0.125	0.35
48	10	10	5	5	1	0.5	0.5
49	226	113	14	160	0.5	0.06	0.71
50	160	80	56	80	0.5	0.35	0.5
51	160	160	28	80	1	0.18	0.5
52	20	20	5	5	1	0.25	0.25
53	28	56	5	14	2	0.18	0.5
54	160	160	40	56	1	0.25	0.35

55	320	452	80	80	1.41	0.25	0.25
56	56	56	5	28	1	0.09	0.5
57	226	226	40	80	1	0.18	0.35
58	14	14	7	5	1	0.5	0.36
59	160	113	28	80	0.71	0.18	0.5

[1] The wild-type strain identity is SARS-CoV-2/INMI1-Isolate/2020/Italy GenBank: MT066156; the identity of the variants of concern are: Alpha, nCoV19 isolate/England/MIG457/2020; Beta, nCoV19 isolate/England ex-SA/HCM002/2021; and Delta, isolated from a swab (the following mutations were detected in comparison to a GenBank MN908947.2 reference spike protein: T19R, G142D, R158G, L452R, T478K, D614G, P681R, R682Q, D950N. DeL-156, DeL-157). The VNT_{50} was determined as described in the **Supplementary Methods**.

ID, identity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VNT_{50}, 50% virus neutralisation titre

Table S5.

T-cell response one week after the second dose in the intent-to-treat population

	BNT162b2			Placebo
	Participants 18–55 Years of Age (N=44)	**Participants 56–85 Years of Age (N=30)**	**Total (N=74)**	**Total (N=24)**
Positive Response,[1,2] n (%) [95% confidence interval, %][3]	37/44 (84.1) [69.93 to 93.36]	21/29 (72.4) [52.76 to 87.27]	58/73 (79.5) [68.38 to 88.02]	1/24 (4.2) [0.11 to 21.12]

[1] A positive T-cell response was defined as ≥55 spot-forming cells per 10^5 peripheral blood mononuclear cells and more than twice the background response for at least one of the two S peptide pools (see **Supplementary Methods** for description of peptide pools).

[2] Data were missing for one participant in the BNT162b2 group aged 56–85 years.

[3] The confidence interval was calculated using the Clopper-Pearson method.

Table S6.

Solicited local and systemic events and unsolicited adverse events reported in the at-risk and non-risk safety analysis population (aged 18–85 years).

	At-Risk Participants[1]				Non-Risk Participants			
	BNT162b2		Placebo		BNT162b2		Placebo	
	Events	Participants	Events	Participants	Events	Participants	Events	Participants
No. of participants		115		35		605		204
Solicited Events, n (%)	296	79 (68.7)	4	3 (8.6)	2115	455 (75.2)	45	28 (13.7)
Local Events	166	72 (62.6)	2	2 (5.7)	986	413 (68.3)	14	11 (5.4)
Pain	108	70 (60.9)	2	2 (5.7)	659	407 (67.3)	12	11 (5.4)
Swelling	35	28 (24.4)	0	0 (0)	183	139 (23.0)	2	2 (1.0)
Redness	23	20 (17.4)	0	0 (0)	144	110 (18.2)	0	0 (0)
Systemic Events	130	57 (49.6)	2	2 (5.7)	1129	350 (57.9)	31	22 (10.8)
Fever	52	44 (38.3)	1	1 (2.9)	351	280 (46.3)	9	8 (3.9)
Fatigue	22	21 (18.3)	1	1 (2.9)	210	173 (28.6)	8	8 (3.9)
Chills	20	19 (16.5)	0	0 (0)	209	174 (28.8)	1	1 (0.5)
Headache	15	15 (13.0)	0	0 (0)	169	141 (23.3)	5	5 (2.5)
New or worsening muscle pain	12	12 (10.4)	0	0 (0)	97	84 (13.9)	3	2 (1.0)
New or worsening arthralgia	6	6 (5.2)	0	0 (0)	63	55 (9.1)	2	2 (1.0)
Diarrhoea	3	3 (2.6)	0	0 (0)	18	18 (3.0)	3	3 (1.5)
Vomiting	0	0 (0)	0	0 (0)	12	11 (1.8)	0	0 (0)
Unsolicited Adverse Events, n (%)	10	6 (5.2)	3	3 (8.6)	101	73 (12.1)	18	16 (7.8)

[1]At-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as body mass index ≥30 kg/m^2).

Table S7.

Unsolicited adverse events reported between receipt of the first dose and 1 month after the second dose in the safety analysis population.

	BNT162b2						Placebo	
	18–55 years (N=389)		56–85 years (N=331)		18–85 years (N=720)		18–85 years (N=239)	
	Events	Participants	Events	Participants	Events	Participants	Events	Participants
Any TEAEs (solicited events not included)	82	56 (14.4)	29	23 (7.0)	111	79 (11.0)	21	19 (8.0)
TEAEs related to study intervention[1]	60	41 (10.5)	19	17 (5.1)	79	58 (8.1)	10	9 (3.8)
TEAEs Grade ≥3 by NMPA criteria	2	2 (0.5)	4	3 (0.9)	6	5 (0.7)	1	1 (0.4)
TEAEs related to study intervention Grade ≥3 by NMPA criteria	0	0	0	0	0	0	0	0
TEAEs related to study intervention Grade ≥3 by FDA criteria	0	0	0	0	0	0	0	0
TEAEs resulting in treatment discontinuation[2]	2	2 (0.5)	2	2 (0.6)	4	4 (0.6)	2	2 (0.8)
TEAEs related to study intervention[1] and resulting in withdrawal	0	0	0	0	0	0	0	0
TEAEs of special interest	0	0	0	0	0	0	0	0
TEAEs related to study intervention[1] and of special interest	0	0	0	0	0	0	0	0
SAE	2	2 (0.5)	3	3 (0.9)	5	5 (0.7)	1	1 (0.4)
SAEs related to study intervention[1]	0	0	0	0	0	0	0	0

All data are n (%).

AE, adverse event; FDA, Food and Drug Administration (USA); NMPA, National Medical Products Administration (China); SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[1]"Related" means "possibly related", "probably related" or "definitely related" to study intervention.

[2]All TEAEs resulting in treatment discontinuation were considered unrelated to study intervention.

Table S8.

Treatment-emergent unsolicited adverse events after each dose.

	BNT162b2			Placebo		
	N[1]	Events	Participants, n (%)	N[1]	Events	Participants, n (%)
Any unsolicited event	720	111	79 (11.0)	239	21	19 (8.0)
Dose 1 Vaccination	720	71	57 (7.9)	239	15	13 (5.4)
Dose 2 Vaccination	715	40	33 (4.6)	237	6	6 (2.5)
General disorders and administration site conditions	720	52	40 (5.6)	239	3	3 (1.3)
Dose 1 Vaccination	720	28	24 (3.3)	239	0	0
Dose 2 Vaccination	715	24	22 (3.1)	237	3	3 (1.3)
Respiratory, thoracic and mediastinal disorders	720	14	13 (1.8)	239	6	5 (2.1)
Dose 1 Vaccination	720	11	10 (1.4)	239	6	5 (2.1)
Dose 2 Vaccination	715	3	3 (0.4)	237	0	0
Nervous system disorders	720	13	12 (1.7)	239	4	4 (1.7)
Dose 1 Vaccination	720	9	9 (1.3)	239	4	4 (1.7)
Dose 2 Vaccination	715	4	4 (0.6)	237	0	0
Gastrointestinal disorders	720	6	6 (0.8)	239	3	3 (1.3)
Dose 1 Vaccination	720	5	5 (0.7)	239	2	2 (0.8)
Dose 2 Vaccination	715	1	1 (0.1)	237	1	1 (0.4)
Infections and infestations	720	5	5 (0.7)	239	1	1 (0.4)
Dose 1 Vaccination	720	3	3 (0.4)	239	1	1 (0.4)
Dose 2 Vaccination	715	2	2 (0.3)	237	0	0
Skin and subcutaneous tissue disorders	720	7	5 (0.7)	239	0	0
Dose 1 Vaccination	720	5	4 (0.6)	239	0	0
Dose 2 Vaccination	715	2	2 (0.3)	237	0	0
Musculoskeletal and connective tissue disorders	720	4	4 (0.6)	239	1	1 (0.4)
Dose 1 Vaccination	720	2	2 (0.3)	239	1	1 (0.4)
Dose 2 Vaccination	715	2	2 (0.3)	237	0	0
Cardiac disorders	720	1	1 (0.1)	239	1	1 (0.4)
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	0	0	237	1	1 (0.4)
Hepatobiliary disorders	720	2	2 (0.3)	239	0	0
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	1	1 (0.1)	237	0	0
Injury, poisoning and procedural complications	720	1	1 (0.1)	239	1	1 (0.4)
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	0	0	237	1	1 (0.4)
Vascular disorders	720	2	2 (0.3)	239	0	0
Dose 1 Vaccination	720	2	2 (0.3)	239	0	0
Dose 2 Vaccination	715	0	0	237	0	0
Investigations	720	0	0	239	1	1 (0.4)
Dose 1 Vaccination	720	0	0	239	1	1 (0.4)

	BNT162b2			Placebo		
Dose 2 Vaccination	715	0	0	237	0	0
Metabolism and nutrition disorders	720	1	1 (0.1)	239	0	0
Dose 1 Vaccination	720	0	0	239	0	0
Dose 2 Vaccination	715	1	1 (0.1)	237	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	720	1	1 (0.1)	239	0	0
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	0	0	237	0	0
Psychiatric disorders	720	1	1 (0.1)	239	0	0
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	0	0	237	0	0
Renal and urinary disorders	720	1	1 (0.1)	239	0	0
Dose 1 Vaccination	720	1	1 (0.1)	239	0	0
Dose 2 Vaccination	715	0	0	237	0	0

[1]N is the number of participants in the corresponding safety population; the incidence is calculated with N as the denominator.
'Dose 1 Vaccination' captured events from the time of the first dose up to the time of the second dose (i.e., 21 days), and 'Dose 2 Vaccination' captured events from the time of the second dose up to 28 days after the second dose.
Unsolicited events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.1.

Table S9.

Treatment-emergent serious adverse events by System Organ Class and Preferred Term between receipt of the first dose and 6 months after the second dose in the safety analysis population.

	BNT162b2						Placebo	
	18–55 years (N=389)		56–85 years (N=331)		18–85 years (N=720)		18–85 years (N=239)	
	Events	Participants	Events	Participants	Events	Participants	Events	Participants
Total	4	4 (1.0)	26	13 (3.9)	30	17 (2.4)	9	8 (3.4)
Hepatobiliary disorders	1	1 (0.3)	0	0	1	1 (0.1)	1	1 (0.4)
Cholecystitis acute	1	1 (0.3)	0	0	1	1 (0.1)	0	0
Drug-induced liver injury	0	0	0	0	0	0	1	1 (0.4)
Injury, poisoning and procedural complications	2	2 (0.5)	7	2 (0.6)	9	4 (0.6)	0	0
Extradural haematoma	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Foot fracture	1	1 (0.3)	0	0	1	1 (0.1)	0	0
Limb traumatic amputation	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Lower limb fracture	1	1 (0.3)	0	0	1	1 (0.1)	0	0
Meniscus injury	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Rib fracture	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Skull fracture	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Subdural haematoma	0	0	1	1 (0.3)	1	1 (0.1)	0	0
VIIth nerve injury	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	6	2 (0.6)	6	2 (0.3)	2	1 (0.4)
Intestinal adenocarcinoma	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Lung carcinoma cell type unspecified stage 0	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Metastases to abdominal wall	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Metastases to liver	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Metastases to ovary	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Ovarian germ cell teratoma	0	0	0	0	0	0	1	1 (0.4)
Rectal cancer	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Uterine leiomyoma	0	0	0	0	0	0	1	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	2	2 (0.6)	2	2 (0.3)	0	0
Arthralgia	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Osteonecrosis	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Metabolism and nutrition disorders	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Diabetic ketoacidosis	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Renal and urinary disorders	0	0	2	1 (0.3)	2	1 (0.1)	0	0
Renal hydrocele	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Ureterolithiasis	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Nervous system disorders	0	0	6	5 (1.5)	6	5 (0.7)	3	3 (1.3)
Cerebral infarction	0	0	4	3 (0.9)	4	3 (0.4)	2	2 (0.8)

Diabetic neuropathy	0	0	1	1 (0.3)	1	1 (0.1)	1	1 (0.4)
Dizziness	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Infections and infestations	0	0	1	1 (0.3)	1	1 (0.1)	2	2 (0.8)
Pneumonia	0	0	1	1 (0.3)	1	1 (0.1)	1	1 (0.4)
Appendicitis	0	0	0	0	0	0	1	1 (0.4)
Reproductive system and breast disorders	1	1 (0.3)	0	0	1	1 (0.1)	0	0
Epididymal cyst	1	1 (0.3)	0	0	1	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1	1 (0.3)	1	1 (0.1)	0	0
Interstitial lung disease	0	0	1	1 (0.3)	1	1 (0.1)	0	0
SOC unencoded	0	0	0	0	0	0	1	1 (0.4)
PT unencoded	0	0	0	0	0	0	1	1 (0.4)

All data are n (%).

PT, preferred term; SOC, system organ class.

Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) v23.1.

Table S10.

Selected haematology parameters in a subgroup of subjects in the safety population, i.e. participants with laboratory test data taken at relevant time points.

Haematology parameters	Time & statistical descriptor	BNT162b2			Placebo	P-Value BNT162b2 vs placebo[b]
		18–55 years (N[a]=83)	56–85 years (N[a]=30)	All ages (18–85 years) (N[a]=113)	All ages (18–85 years) (N[a]=37)	All ages (18–85 years)
Lymphocytes (10^9/L)	Baseline[c], n	83	30	113	37	
	Mean (SD)	1.863 (0.472)	1.752 (0.474)	1.834 (0.473)	2.038 (0.627)	**0.0377**
	Median (range)	1.820 (1.04–3.29)	1.790 (1.02–2.97)	1.820 (1.02–3.29)	1.940 (0.75–4.67)	
	Change from baseline at Day 1–3 after Dose 1, n	83	30	113	37	
	Mean (SD)	–0.525 (0.349)	–0.394 (0.510)	–0.490 (0.400)	0.175 (0.357)	**<0.0001**
	Change from baseline at 1 week after Dose 1, n	83	30	113	37	
	Mean (SD)	0.130 (0.292)	0.089 (0.416)	0.120 (0.328)	0.061 (0.458)	0.3980
	Before Dose 2, n	83	29	112	37	
	Mean (SD)	1.865 (0.455)	1.790 (0.490)	1.846 (0.464)	2.131 (0.622)	**0.0036**
	Median (range)	1.860 (1.06–2.98)	1.740 (1.01–3.26)	1.830 (1.01–3.26)	1.950 (1.21–4.40)	
	Change from baseline at 1 week after Dose 2, n	83	29	112	37	
	Mean (SD)	–0.040 (0.337)	–0.213 (0.352)	–0.085 (0.348)	–0.061 (0.402)	0.7356
	1 week after Dose 2, n	83	29	112	37	
	Mean (SD)	1.823 (0.502)	1.532 (0.361)	1.748 (0.485)	1.977 (0.678)	**0.0267**
Platelets (10^9/L)	Baseline[c], n	83	30	113	37	
	Mean (SD)	212.0 (51.2)	197.6 (54.1)	208.2 (52.1)	219.8 (57.7)	**0.2552**
	Median (range)	204.0 (126–357)	185.0 (113–307)	202.0 (113–357)	207.0 (143–426)	
	Change from baseline at Day 1–3 after Dose 1, n	83	30	113	37	
	Mean (SD)	–15.8 (16.0)	–17.9 (18.0)	–16.4 (16.5)	5.5 (16.4)	**<0.0001**
	Change from baseline at 1 week after Dose 1, n	83	30	113	37	
	Mean (SD)	10.9 (29.3)	6.8 (23.1)	9.8 (27.8)	12.1 (22.9)	0.6516
	Before Dose 2, n	83	29	112	37	
	Mean (SD)	211.1 (54.7)	184.3 (50.3)	204.2 (54.6)	224.0 (56.5)	0.0597
	Median (range)	210.0 (90–350)	180.0 (92–293)	194.5 (90–350)	213.0 (123–396)	

Change from baseline at 1 week after Dose 2, n	83	29	112	37	
Mean (SD)	7.7 (32.4)	–15.0 (27.0)	1.8 (32.6)	0.2 (32.6)	0.7941
1 week after Dose 2, n	83	29	112	37	
Mean (SD)	219.7 (49.7)	179.1 (49.6)	209.2 (52.6)	220.0 (56.9)	0.2915

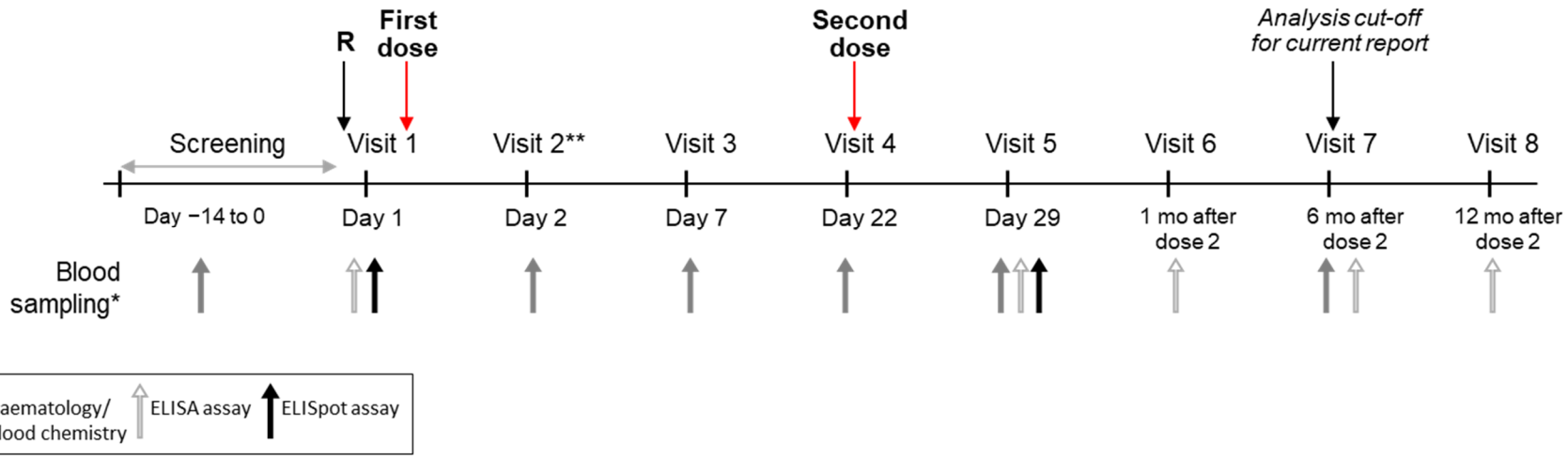
[a]n= total number of subjects with at least one result for the given laboratory test after study vaccination.

[b]t-tests were used to establish the between-group difference in mean (SD) values.

[c]Baseline was defined as the last non-missing value prior to dose 1.

Figures

***Figure S1.*Time points for study procedures**



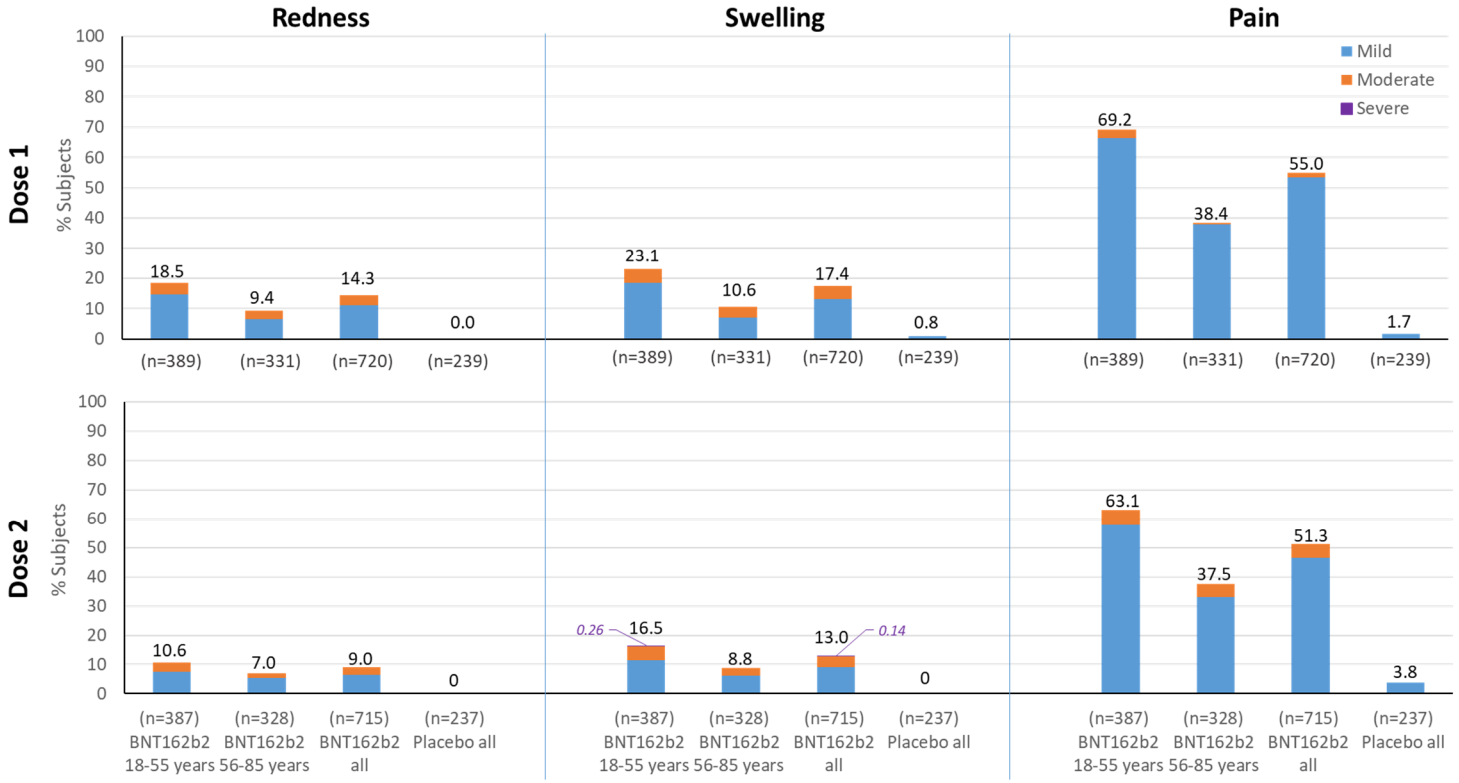
*Blood samples for hematology and blood chemistry testing was collected only from the first 150 subjects, as follows: at visits 0, 2, 3, 4, and 5 for routine safety laboratory tests, at visits 0, 2, and 5 for coagulation function tests, and visits 0, 2, 5 and 7 for thyroid function tests. Blood samples for ELISpot testing (cellular immunoassay) were collected from the first ~100 subjects.

**Visit 2 applied only to participants in the early safety monitoring group.

ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; mo, month; R, randomization

Figure S2.

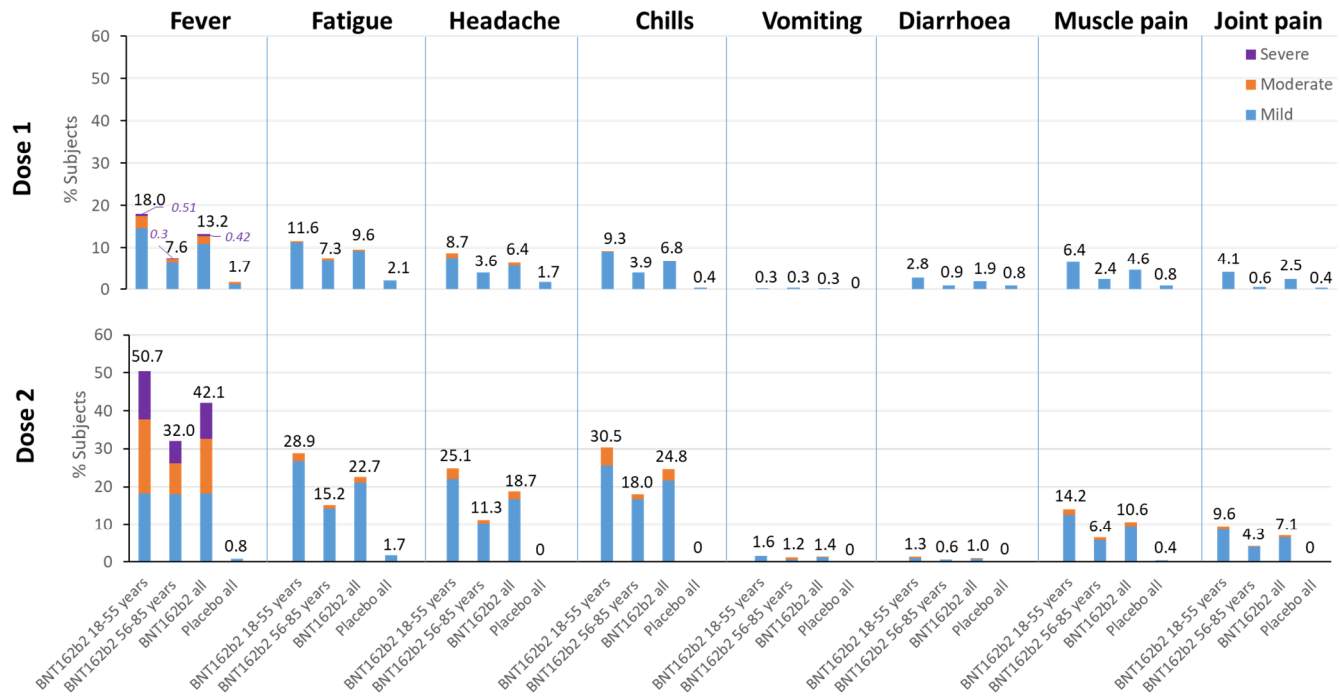
The incidence of solicited local events considered treatment related, occurring within 14 days after each dose of BNT162b2 30 µg or placebo, by maximum severity.



The number above each column is the overall incidence (grade 1–3). Data are for subsets of the safety population by doses received: the safety population for dose 1 included recipients of the first dose (n=959) and for dose 2, recipients of both doses (n=952). Grade 1 events are labelled mild, grade 2 moderate and grade 3 severe. Grading was per the National Medical Products Administration of China.

Figure S3.

The incidence of solicited systemic events considered related to treatment, occurring within 14 days after each dose of BNT162b2 30 µg or placebo, by maximum severity.



	BNT162b2 18-55 years	BNT162b2 56-85 years	BNT162b2 all	Placebo all
Dose 1, n	389	331	720	239
Dose 2, n	387	328	715	237

The number above each column is the overall incidence (grade 1–3) of the adverse event. Data are for subsets of the safety population by doses received: the safety population for dose 1 included recipients of the first dose (n=959) and for dose 2, recipients of both doses (n=952). Grade 1 adverse events are labelled mild, grade 2 moderate, and grade 3 severe. Grading of systemic reactions was per the National Medical Products Administration of China.

References

1. Li J, Hui A, Zhang X, et al. Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. *Nat Med.* 2021;**27**(6):1062-1070.

2. National Medical Products Administration China. Guidelines for the Grading of Adverse Events in Preventive Vaccine Clinical Trials (in Chinese). https://www.nmpa.gov.cn/yaopin/ypggtg/ypqtgg/20191231111901460.html. (Accessed 23 September, 2021.)

3. United States Food and Drug Administration.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical. (Accessed 23 September, 2021.)