2 SYNOPSIS

Title of study	A multi-site, Phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults
Study number	BNT162-01
Protocol version	Version 9.0 (dated 05 OCT 2020); the version valid at the 23 OCT 2020 data cut-off for this report.
Type of report	Interim report (the BNT162-01 study is clinically ongoing; see the below notes)

The BNT162-01 study is clinically ongoing. This 2nd interim clinical study report (CSR) summarizes data available for the investigational medicinal products (IMP) BNT162b1 and BNT162b2 collected up until Visit 8 (the first follow-up visit at ~63 d after the second dose) in Part A of this study. Part A included younger participants (aged 18 to 55 yrs) and older participants (aged 56 to 85 yrs), therefore this CSR only describes the study conduct relevant for these participants.

This CSR differs from the 1st interim CSR in that longer post-Dose 2 reactogenicity and safety data is available for younger participants and that data from older participants is included for the first time. Immunogenicity and T-cell response data for both IMPs, but especially for BNT162b2 in younger and older participants, has been added.

The data cut-off dates are: reactogenicity, safety, disposition, and immunogenicity data (23 OCT 2020); T-cell response data (ELISpot data) data (24 NOV 2020); intracellular cytokine staining (ICS) data (17 NOV 2020 for BNT162b1) and (03 NOV 2020 for BNT162b2).

The data reported here, together with data from other sources including the study BNT162-02/C4591001 (NCT 04368728), was used to select the BNT162 vaccine and dose level for further study in the ongoing Phase II/III evaluation of efficacy.

This interim CSR will be used in support of marketing authorization applications for BNT162b2. Data not included here will be provided in later interim reports and/or the final CSR; this will include data for the other IMPs BNT162a1and BNT162c2 under investigation in this study.

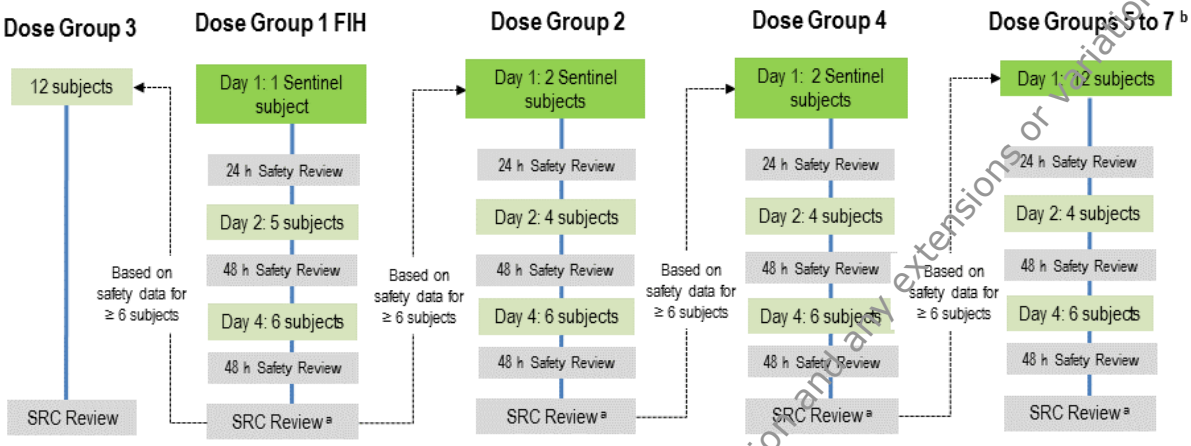
Regulatory identifiers	EudraCT no.: 2020-001038-36; ClinicalTrials.gov NCT: 04380701; WHO UTN: U1111-1249-4220
IMPs	BNT162: SARS-CoV-2 - RNA lipid nanoparticle (RNA-LNP) vaccines utilizing different RNA formats, i.e., BNT162b1 and BNT162b2.
Study sponsor	BioNTech RNA Pharmaceuticals, 55131 Mainz, Germany
Coordinating investigator	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany
Study sites	Contract research organization sites in Berlin and Mannheim, Germany
Study period	Study start / end date: 23 APR 2020 / Ongoing

Study design

This is an open-label, multi-site, Phase I/II, dose-escalation and expansion study.

The study includes the first in human dose and dose ranging groups in healthy younger participants (aged 18 to 55 years [yrs]) and older participants (aged 56 to 85 yrs). For a summary of this study as a flow diagram, see Figure 1.

Dose groups 1 to 7 with younger participants



Dose groups 8 to 10 with older participants

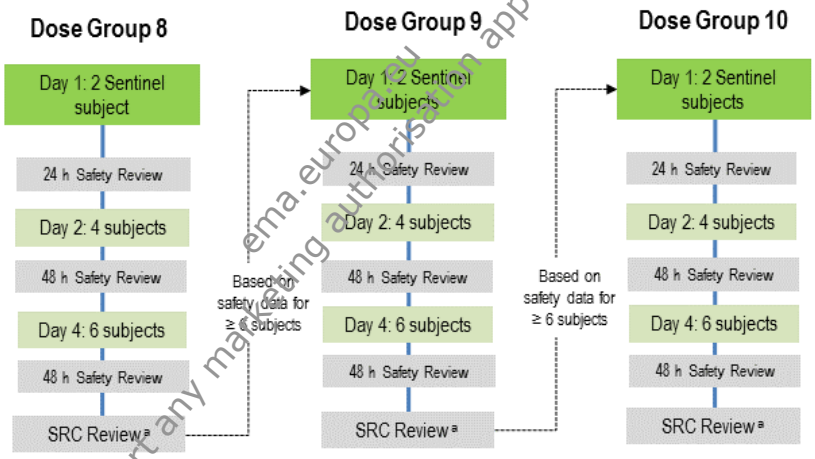


Figure 1: Dose group schema for BNT162b1 and BNT162b2 (Dose 1 and Dose 2, ~21 d apart) c

a) The data assessed by the SRC for progressing comprises 48 h data for 6 participants.

b) If these dose groups use doses lower than already tested, 12 participants may be dosed on one day in these dose groups and the dose groups may be conducted in parallel to each other / to any dose-escalation dose groups. If they use doses higher than already tested, participants were dosed using a sentinel dosing/participant (2-4-6) staggering process.

c) For the dose regimens, see the synopsis section "Study treatments".

d = day(s); FIH = first in humans; SRC = Safety Review Committee; subject = participant.

Note: This report only presents data and background information relevant for the reported Dose Groups 1 to 10.

Objectives

Only objectives and endpoints applicable for BNT162b1 and BNT162b2 are reflected in the following tabular summary of study objectives and endpoints.

Objectives	Endpoints [a]
Primary objective	
(All dose groups) To describe the safety and tolerability profiles in healthy adults after Dose 1 only or after Dose 1 and Dose 2.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each dose (study days 8 and 29). • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7 d after each dose (study days 8 and 29). • The proportion of subjects with at least 1 unsolicited treatment-emergent adverse event (TEAE) occurring up to 21 d after Dose 1 (study day 22) and 28 d after Dose 2 (study day 50).
Secondary objectives	
(All dose groups) To describe the immune response in healthy adults after Dose 1 only or after Dose 1 and Dose 2 measured by a functional antibody titer, e.g., virus neutralization test (VNT) or an equivalent assay available by the time of study conduct.	As compared to baseline at 7 and 21 d after Dose 1 (study days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after Dose 2 (study days 5 to 9): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.
Exploratory objectives	
(All dose groups) To describe the immune response in healthy adults after Dose 1 only or after Dose 1 and Dose 2 measured by an antibody binding assay, e.g., enzyme-linked immunosorbent assay (ELISA) or an equivalent assay available by the time of study conduct.	As compared to baseline at 7 and 21 d after Dose 1 (study days 8 and 22) and at 7, 14 [b], 21, 28, 63, and 162 d after the Dose 2 (study days 8 to 184). • Antibody responses measured (concentrations/titers). • Fold increase in antibody (concentrations/titers). • Number of subjects with seroconversion defined as a minimum of 4-fold increase of antibody concentrations/titers.
(All dose groups) To describe the cell-mediated immune (CMI) responses.	• At baseline and at 28 d after Dose 1 (study day 29): CMI responses measured, e.g., by enzyme-linked immuno-spot (ELISpot) and ICS.

a) The given days are approximate; the respective schedule of activities defines assessment windows.

b) Only dose groups starting dose 1 after approval of amendment 09.

Note: To harmonize data reporting across BNT162 clinical studies, several terms, e.g., the terms “prime” and “boost” were replaced with “Dose 1” and “Dose 2”, respectively. For further details, see the Section 4 of this report.

The additional exploratory objectives apply for subjects included in the expansion dose groups in addition to all primary, secondary, and exploratory endpoints defined for other study subjects.

Study treatments

Name:	BNT162 vaccines - Antiviral RNA vaccines against COVID-19.
IMP and dose levels:	Younger participants aged 18 to 55 yrs: BNT162b1: 1 µg, 3 µg, 10 µg, 20 µg, 30 µg, 50 µg, and 60 µg. BNT162b2: 1 µg, 3 µg, 10 µg, 20 µg, 30 µg. Older participants aged 56 to 85 yrs: BNT162b1: 10 µg, 20 µg, and 30 µg. BNT162b2: 10 µg, 20 µg, and 30 µg.
Regimen:	Two injections ~21 d apart. Injection volumes were up to 1.5 mL.
Dosing route:	Intramuscular (IM); upper arm, musculus deltoideus.
Batch Nr.	BNT162b1: E220195-0001L, E220195-0004L, E220195-0014L, E220195-0017L, E220195-0019L, E220195-0020L. BNT162b2: E220195-0004L, E220195-0017L, E220195-0018L, E220195-0022L, E220195-0024L.

This was an open-label study. There was no randomization to treatment groups.

Study population

Healthy participants aged 18 to 55 yrs (Dose Groups 1 to 7; younger participants) and healthy participants aged 56 to 85 yrs (Dose Groups 8 to 10). There were no protocol waivers or exemptions to the defined inclusion/exclusion criteria.

Methodology

Study participants were selected based on their reported background and the outcomes of assessments performed at up to 30 d before Day 1. Study participants meeting all inclusion/exclusion criteria were allocated to study treatment and dosed with IMP at Visits 1 and 4, i.e., with ~21 d between doses.

There are 9 planned visits in this study, starting with Visit 1 (the day of administration of the first IMP dose, Dose 1). Visit 7 on Day 50 (i.e., at Dose 2 + 28 d) was the end of treatment (EoT) visit.

Assessments for safety (physical examination, vital signs, blood/urine clinical laboratory assessments) were performed at baseline (pre-dose on Day 1) and thereafter at predefined times until Visit 7. Unsolicited TEAEs reported were recorded from after the first IMP dose until Visit 7. Solicited local reactions/systemic reactions were recorded continuously using participant diaries from after the first IMP until Visit 7. The primary reactogenicity endpoints focus on data recorded up to 7±1 d (Day 8) after each IMP dosing. The primary safety endpoint focuses on unsolicited TEAE occurring up to 21±2 d after Dose 1 (Day 22) and 28±4 d after Dose 2 (Day 50).

Assessments of binding antibodies, functional antibody titers (neutralizing antibodies), and cell-mediated immunity (antigen-specific T-cells) were performed at baseline (pre-dose on Day 1) and thereafter at predefined times until Visit 8 (follow-up visit at 63 d after Dose 2).

Two follow-up visits are planned, one at 63 d after Dose 2 and one at 162 d after Dose 2.

Statistical methods

No formal sample size calculations were performed. The inclusion of 12 participants per dose group was considered to be adequate for a safety assessment of each IMP per dose level. The

probability to observe a particular TEAE with incidence of 15% at least once in 12 participants per dose group is 85.8%.

There is no formal statistical hypothesis under test.

In general, data were summarized by dose groups and groups were combined as appropriate. Continuous variables were summarized by dose group using descriptive statistics. Categorical variables were summarized by dose group presenting absolute and relative frequencies (n and %) of participants in each category.

Baseline was defined as last available value prior to first dose of IMP.

In general, TEAEs were analyzed by dose group (i.e., by IMP and dose level), for each dose, and each observation interval, e.g., Day 1 to 21 (pre-Dose 2). Additionally, TEAEs were summarized for all dose levels combined for each type.

For each analysis, the number and percentage of participants reporting at least one AE was summarized by preferred term (PT) nested within system organ class (SOC) for predefined adverse event (AE) types: any AE, any AE excluding AEs based on solicited reporting via participant diaries, any related AE, Grade ≥3 AEs, related Grade ≥3 AEs, any treatment-emergent serious AEs (TESAE), and related TESAEs. Moreover, the number and percentage of participants with any AE were summarized by worst grade by PT nested within SOC.

Local reactions and systemic reactions were graded using criteria based on the guidance given in US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

For each dose, the number and percentage of participants reporting at least one local reaction or systemic reaction (i.e., solicited data collected using participant diaries) were summarized for predefined reaction types.

Study performance

This study is ongoing clinically. There were 5 protocol amendments implemented at the data cut-off for this CSR. There were no investigator-reported protocol deviations considered by the sponsor to have impacted either GCP compliance, participant safety, or the statistical analyses.

Summary of results

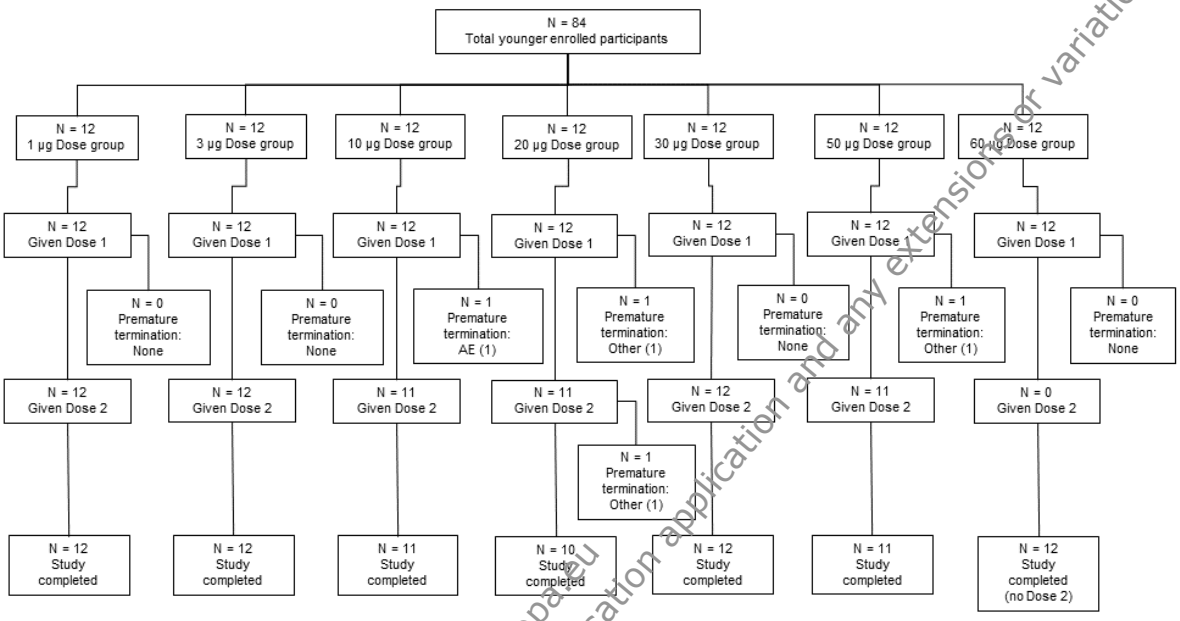
Demographics

All participants met the inclusion criteria for age, weight, and body mass index (BMI).

In total 120 younger and older participants were treated with BNT162b1 and included in the Safety Set. All participants met the inclusion criteria for age, weight, and BMI. Across the dose groups, the mean (SD) age was 46.53 (15.94) yrs, the mean (SD) participant weight was 74.28 (12.57) kg, and the mean (SD) participant BMI was 25.10 (2.70) kg/m^2. Of these participants, 57 (48%) were male and 63 (53%) were female, 117 (98%) participants were White (there were 2 Asian and 1 Black participants), and 118 (98%) participants were not of Hispanic or Latino origin.

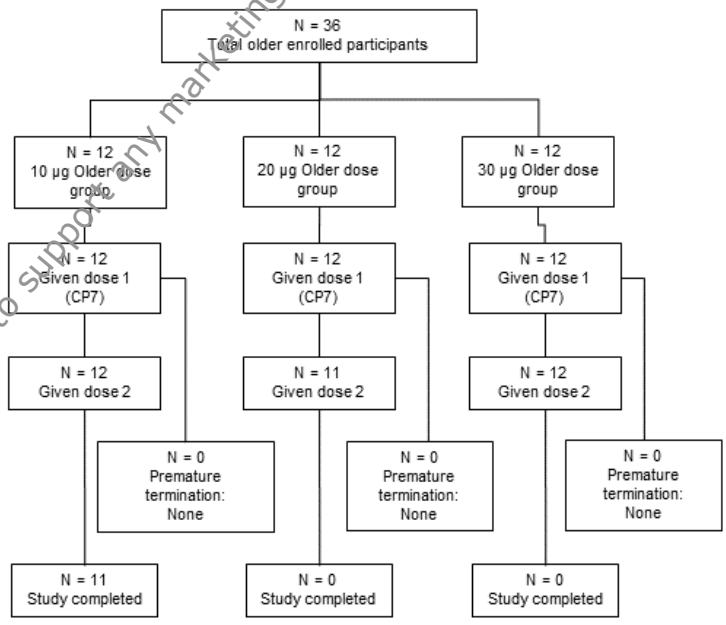
In total 96 younger and older participants were treated with BNT162b2 and included in the Safety Set. All participants met the inclusion criteria for age, weight, and BMI. Across the dose groups, the mean (SD) participant age was 49.56 (15.01) yrs, the mean (SD) weight was 76.77 (11.15) kg, and the mean (SD) participant BMI was 25.40 (2.38) kg/m^2. Of the older participants, 44 (46%) were male and 52 (54%) were female, 96 (100%) participants were White, and 96 (100%) participants were not of Hispanic or Latino origin.

Participant disposition



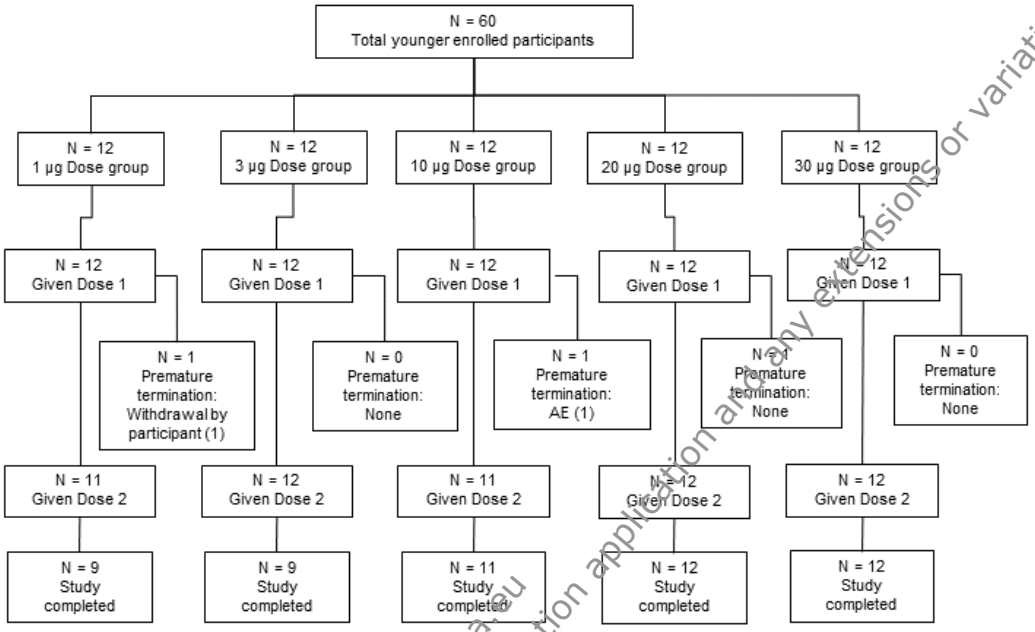
Disposition of younger participants – BNT162b1

AE = adverse; N = number of participants; study completed = have completed Visit 7 (the end of treatment visit).
Source: Based on data from Listing 16.2.3-2.1-1.



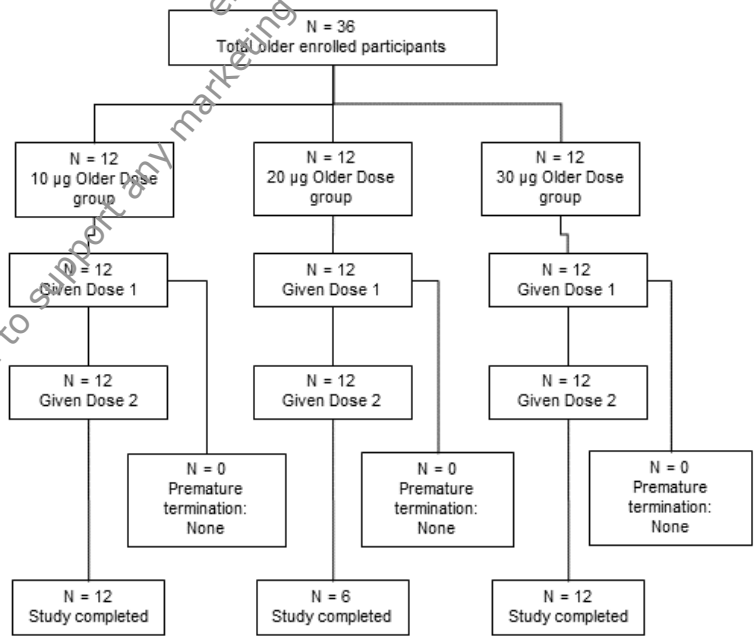
Disposition of older participants – BNT162b1

AE = adverse; N = number of participants; study completed = have completed Visit 7 (the end of treatment visit).
Source: Based on data from Listing 16.2.3-2.1-1.



Disposition of younger participants – BNT162b2

N = number of participants; study completed = have completed Visit 7 (the end of treatment visit).
Source: Based on data from Listing 16.2.3-2.1-3.



Disposition of older participants – BNT162b2

N = number of participants; study completed = have completed Visit 7 (the end of treatment visit).
Source: Based on data from Listing 16.2.3-2.1-3.

Safety

Primary endpoints – Solicited local reactions – BNT162b1

Summary of solicited local reactions – BNT162b1 (SAF)

Time interval		Younger participants							
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	50 µg (N=12)	60 µg (N=12)	Total (N=84)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	12	12	84
	Any local reaction n (%)	6 (50)	5 (42)	10 (83)	12 (100)	11 (92)	12 (100)	12 (100)	68 (81)
	Any grade >= 3 local reaction n (%)	0 (0)	0 (0)	1 (8)	2 (17)	4 (33)	2 (17)	1 (8)	10 (12)
Dose 2 up to Day 7 after Dose 2	nn	12	6	11	10	12	11	N/A	69
	Any local reaction n (%)	7 (58)	5 (42)	10 (91)	11 (100)	11 (92)	11 (100)	N/A	55 (80)
	Any grade >= 3 local reaction n (%)	2 (17)	0 (0)	0 (0)	0 (0)	2 (17)	3 (27)	N/A	7 (10)

Time interval		Older participants				All Total (N=120)
		10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	120
	Any local reaction n (%)	7 (58)	11 (92)	11 (92)	29 (81)	97 (81)
	Any grade >= 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	10 (8)
Dose 2 up to Day 7 after Dose 2	nn	12	11	12	35	104
	Any local reaction n (%)	8 (67)	9 (82)	9 (75)	26 (74)	81 (78)
	Any grade >= 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	7 (7)

All = all is the sum of younger and older participants; N = number of participants in the analysis set; n = number of participants with the respective reactions; nn = number of participants with any information on reactions available; N/A = not available, SAF = Safety Set.
Source: Table 14.3.1-1.1-1.

Solicited local reactions – BNT162b1 – Younger participants

In the younger participants group, in the combined time interval, after both doses, the majority of the participants experienced mild (n=72, 86%) followed by moderate (n=45, 54%) solicited local reactions. While few participants experienced severe (n=15, 18%) solicited local reactions.

- The most frequent severe solicited local reactions were reported in 30 µg (5 participants [42%]), 50 µg (4 participants [33%]), 20 µg (2 participants [17%]), 60 µg and 10 µg (1 participant each [8%], respectively) dose groups.

The most frequently reported solicited local reactions of any severity were tenderness (n=70, 83%) and pain (n=67, 80%). The remaining symptom terms were infrequently described.

- Only mild and moderate reactions were reported for erythema and induration.
- For pain and tenderness each symptom was assessed as severe in ≤14% of participants.
- No clear pattern of dose dependency was seen across the symptom terms for mild reactions in 10 µg and above dose groups. However, a possible dose dependency for moderate local reactions between the 10 µg group (5 participant) and the 20 µg and 30 µg groups (6 and 11 participants) was seen.

Solicited local reactions – BNT162b1 (SAF) – Older participants and all (younger and older) participants

In the older participants group, in the combined time interval, after both doses, the majority of the participants experienced mild (n=30, 83%) followed by moderate (n=15, 42%) solicited local reactions, while no older participants experienced severe solicited local reactions.

The most frequently reported solicited local reactions of any severity were tenderness (n=28, 78%) and pain (n=27, 75%). The remaining symptom terms were infrequently described.

- Only mild reactions were reported for erythema and induration.
- For pain and tenderness each symptom was assessed as moderate in <40% of participants.

Primary endpoints – Solicited local reactions – BNT162b2

Summary of solicited local reactions – BNT162b2 (SAF)

Time interval		Younger participants					
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=60)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	60
	Any local reaction n (%)	6 (50)	9 (75)	12 (100)	12 (100)	10 (83)	49 (82)
	Any grade >= 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dose 2 up to Day 7 after Dose 2	nn	11	12	11	12	12	58
	Any local reaction n (%)	4 (36)	8 (67)	10 (91)	10 (83)	11 (92)	43 (74)
	Any grade >= 3 local reaction n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Time interval		Older participants				All Total (N=96)
		10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	96
	Any local reaction n (%)	7 (58)	9 (75)	9 (75)	25 (69)	74 (77)
Dose 2 up to Day 7 after Dose 2	nn	12	12	12	36	94
	Any local reaction n (%)	7 (58)	8 (67)	10 (83)	25 (69)	68 (72)
	Any grade >= 3 local reaction n (%)	1 (8)	0 (0)	1 (8)	2 (6)	2 (2)

All = all is the sum of younger and older participants; N = number of participants in the analysis set; n = number of participants with the respective reactions; nn = number of participants with any information on reactions available; - = not estimable; SAF = Safety Set.
Source: Table 14.3.1-1.1-3.

Solicited local reactions – BNT162b2 (SAF) – Younger participants

In younger participants, in the combined time interval, after both doses, the majority of the participants experienced mild (n=52, 87%) solicited local reactions. A few participants experienced moderate (n=21, 35%) solicited local reactions.

- The most frequent, moderate grade solicited local reactions were reported in 10 µg and 20 µg (7 participants each [58%], respectively) dose groups, followed by 30 µg (3 participants [25%]) dose group.

- The most frequently reported solicited local reactions of any severity was mild tenderness (n=45, 75%) and mild pain (n=45, 75%). The remaining symptom terms were infrequently described.
- Only mild reactions were reported for erythema and induration.
- Pain was assessed as moderate in ≤10% of participants.
- No clear pattern of dose dependency was seen across the symptom terms for mild or moderate reactions.

Solicited local reactions – BNT162b2 – Older participants and all (younger and older) participants

In older participants, in the combined time interval, after both doses, the majority of the participants experienced mild (n=28, 78%) solicited local reactions. A few participants experienced moderate (n=13, 36%) solicited local reactions.

- The most frequent, moderate grade solicited local reactions were reported in 30 µg (n=6, 50%) followed by 20 µg (n=4, 33%) and 10 µg (n=3, 25%) dose groups.
- The most frequently reported solicited local reactions of any severity was mild tenderness (n=24, 67%) followed by mild pain (n=22, 61%). The remaining symptom terms were infrequently described.
- One participant had a moderate reaction of erythema and only mild reactions were reported for induration.
- Pain was assessed as moderate in ≤11% of participants.
- No clear pattern of dose dependency was seen across the symptom terms for mild or moderate reactions.

Primary endpoints – Solicited systemic reactions – BNT162b1

Summary of solicited systemic reactions – BNT162b1 (SAF)

Time interval		Younger participants							
		1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	50 µg (N=12)	60 µg (N=12)	Total (N=84)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	12	12	84
	Any systemic reaction n (%)	9 (75)	8 (67)	8 (67)	11 (92)	11 (92)	12 (100)	12 (100)	71 (85)
	Any grade >= 3 systemic reaction n (%)	0 (0)	0 (0)	1 (8)	2 (17)	3 (25)	5 (42)	8 (67)	19 (23)
Dose 2 up to Day 7 after Dose 2	nn	12	12	11	11	12	11	N/A	69
	Any systemic reaction n (%)	7 (58)	7 (58)	9 (82)	10 (91)	11 (92)	11 (100)	N/A	55 (80)
	Any grade >= 3 systemic reaction n (%)	3 (25)	1 (8)	5 (45)	5 (45)	6 (50)	5 (45)	N/A	25 (36)

Time interval		Older participants				All Total (N=120)
		10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	120
	Any systemic reaction n (%)	9 (75)	11 (92)	11 (92)	31 (86)	102 (85)
	Any grade >= 3 systemic reaction n (%)	1 (8)	1 (8)	2 (17)	4 (11)	23 (19)
Dose 2 up to Day 7 after Dose 2	nn	12	11	12	35	104
	Any systemic reaction n (%)	8 (67)	10 (91)	12 (100)	30 (86)	85 (82)
	Any grade >= 3 systemic reaction n (%)	2 (17)	2 (18)	4 (33)	8 (23)	33 (32)

The denominator for the percentage calculation is nn. N = number of participants in the analysis set; n = number of participants with the respective systemic reactions; nn = number of participants with any information on systemic reactions available; N/A = not available; SAF = Safety Set.

Source: Table 14.3.1-2.1-1.

Solicited systemic reactions – BNT162b1 (SAF) – Younger participants

Overall, in the combined time interval, after both doses, the majority of the participants experienced mild (n=76, 90%) followed by moderate (n=62, 74%) solicited systemic reactions. A few participants experienced severe (n=37, 44%) solicited systemic reactions.

- The most frequent severe systemic reactions were reported in 50 µg and 60 µg groups (8 participants each [67%]) followed by 10 µg and 30 µg (6 participants each [50%]) groups.
- The most frequently reported solicited systemic reactions of any severity were fatigue (n=68, 81%), headache (n=66, 79%), myalgia (n=51, 61%), malaise (n=50, 60%), and chills (n=47, 56%). The remaining symptom terms were infrequently described.
- For nausea, vomiting, diarrhoea, myalgia, arthralgia and fever each symptom was assessed as severe in ≤10% of participants.
- A possible dose dependency for both severe headache and chills was seen with 2 participants at 10 µg vs. 6 participants at 50 µg and 3 participants at 10 µg vs. 5 participants at 50 µg, respectively. A possible dose dependency for both severe fatigue and loss of appetite was seen with each 1 case at 10 µg vs. 4 participants at 50 µg, respectively.
- No clear pattern of dose dependency was seen across the symptom terms for mild or moderate reactions, with the exception of moderate intensity malaise which was reported for 25% of participants receiving 10 µg and 75% of participants with 30 µg dose.

Older participants and all (younger and older) participants

Overall, in the combined time interval, after both doses, the majority of the participants experienced mild (n=32, 89%) followed by moderate (n=22, 61%) solicited systemic reactions. A few participants experienced severe (n=10, 28%) solicited systemic reactions.

- The most frequent severe systemic reactions were reported in the 30 µg group (5 participants, 42%) followed by 20 µg (3 participants, 25%) and 10µg (2 participants, 17%) groups.
- The most frequently reported solicited systemic reactions of any severity were headache (n=29, 81%), fatigue (n=27, 75%), and myalgia (n=18, 50%). The remaining symptom terms were infrequently described.

- No clear pattern of dose dependency was seen across the symptom terms for mild, moderate, or severe reactions.

Primary endpoints – Solicited systemic reactions – BNT162b2

Summary of solicited systemic reactions – BNT162b2 (SAF)

Time interval		Younger participants 1 µg (N=12)	3 µg (N=12)	10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=60)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	12	12	60
	Any systemic reaction n (%)	9 (75)	9 (75)	12 (100)	9 (75)	9 (75)	48 (80)
	Any grade >= 3 systemic reaction n (%)	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	1 (2)
Dose 2 up to Day 7 after Dose 2	nn	11	12	11	12	12	58
	Any systemic reaction n (%)	4 (36)	2 (17)	7 (64)	10 (83)	10 (83)	33 (57)
	Any grade >= 3 systemic reaction n (%)	0 (0)	0 (0)	1 (9)	1 (8)	3 (25)	5 (9)

Time interval		Older participants 10 µg (N=12)	20 µg (N=12)	30 µg (N=12)	Total (N=36)	All Total (N=96)
Dose 1 up to Day 7 after Dose 1	nn	12	12	12	36	96
	Any systemic reaction n (%)	3 (25)	4 (33)	9 (75)	16 (44)	64 (67)
	Any grade >= 3 systemic reaction n (%)	1 (8)	0 (0)	0 (0)	1 (3)	2 (2)
Dose 2 up to Day 7 after Dose 2	nn	12	12	12	36	94
	Any systemic reaction n (%)	4 (33)	8 (67)	11 (92)	23 (64)	56 (60)
	Any grade >= 3 systemic reaction n (%)	1 (8)	0 (0)	2 (17)	3 (8)	8 (9)

The denominator for the percentage calculation is nn.

All = all is the sum of younger and older participants; N = number of participants in the analysis set; n = number of participants with the respective systemic reactions; nn = number of participants with any information on systemic reactions available; - = not estimable; SAF = Safety Set.

Source: Table 14.3.1-2.1-3.

Younger participants

Overall, in the combined time interval after both doses, the majority of the younger participants experienced mild (n=53, 88%) followed by moderate (n=23, 38%) solicited systemic reactions. A few participants experienced severe (n=6, 10%) solicited systemic reactions.

- Severe grade systemic reactions were reported in 30 µg (3 participants [25%]), 20 µg (2 participants [17%]), and 10 µg (1 participant [8%]) dose groups.
- The most frequently reported solicited systemic reactions of any severity were fatigue (n=40, 67%), followed by headache (n=32, 53%), malaise (n=24, 40%), and myalgia (n=23, 38%). The remaining symptom terms were infrequently described.
- Most symptom terms reported were predominantly at mild intensity with a ratio of mild to moderate reports of between 3:1 and 2:1.
- Only mild reactions were reported for diarrhoea and fever.

- For nausea, headache, fatigue, myalgia, chills, arthralgia and malaise each symptom was assessed as severe in <10% of participants.
- A possible dose dependency for both severe fatigue and arthralgia was seen with 0 participants at 10 µg vs. 2 participants at 30 µg, and 0 participants at 10 µg vs. 3 participants at 30 µg, respectively.
- Similarly, no clear pattern of dose dependency was seen across the symptom terms for mild reactions or moderate reactions, with the exception of moderate intensity malaise which was reported for 1 participant receiving 10 µg and 6 participants with 30 µg dose.
- For the 30 µg dose selected for further development, there were consistently slightly higher rates of reporting systemic reactions than for the next lowest 20 µg level for every individual symptom term except headache, diarrhoea, fatigue, and fever. The difference is pronounced for malaise 33% (20 µg) vs. 58% (30 µg) and arthralgia 17% (20 µg) vs. 50% (30 µg).
- No major differences were noted between the pattern seen for the combined time intervals and the individual reporting period.

Older participants and all (younger and older) participants

Overall, in the combined time interval after both doses, the majority of the older participants experienced mild (n=25, 69%) followed by moderate (n=13, 36%) solicited systemic reactions. A few participants experienced severe (n=4, 11%) solicited systemic reactions.

- Severe grade systemic reactions were reported in 30 µg (2 participants [17%]) and 10 µg (2 participants [17%]) dose groups.
- The most frequently reported solicited systemic reactions of any severity were fatigue (n=20, 56%), followed by headache (n=17, 47%), malaise (n=12, 33%), and myalgia (n=12, 33%). The remaining symptom terms were infrequently described.
- Most symptom terms reported were predominantly at mild intensity with a ratio of mild to moderate reports of between 3:1 and 2:1.
- Only mild reactions were reported for diarrhoea and fever.
- All symptoms were assessed as severe in <10% of participants.
- For the 30 µg dose selected for further development, there were consistently slightly higher rates of reporting systemic reactions than for the next lowest 20 µg level for every individual symptom term. The difference is pronounced for malaise 17% (20 µg) vs. 58% (30 µg).
- No major differences were noted between the pattern seen for the combined time intervals and the individual reporting period.

Note: For BNT162b1, a summary of TEAEs without AEs based on solicited reporting via diaries is given using Safety Dose 2 set (SAFB), because the decision was made not to give the second 60 µg dose (Dose 2).

Primary endpoints – Unsolicited TEAEs after BNT162b1 dosing

Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Younger participants (SAF)

Time interval		1 µg (N=12) n (%) E	3 µg (N=12) n (%) E	10 µg (N=12) n (%) E	20 µg (N=12) n (%) E	30 µg (N=12) n (%) E	50 µg (N=12) n (%) E	60 µg (N=12) n (%) E	Total (N=84) n (%) E
Dose 1 up to Dose 2 or Day 28 after Dose 1 (whatever comes first)	Any TEAE	1 (8) 6	0 (0) 0	4 (33) 11	3 (25) 4	4 (33) 5	3 (25) 4	6 (50) 9	21 (25) 39
	Related TEAE	1 (8) 1	0 (0) 0	3 (25) 7	3 (25) 4	3 (25) 3	1 (8) 1	6 (50) 8	17 (20) 24
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
Dose 1 up to Day 28 after Dose 2 or after Dose 1 (if no Dose 2)	Any TEAE	6 (50) 21	0 (0) 0	7 (58) 16	5 (42) 12	6 (50) 8	8 (67) 17	6 (50) 9	38 (45) 83
	Related TEAE	4 (33) 10	0 (0) 0	6 (50) 10	4 (33) 9	4 (33) 4	6 (50) 10	6 (50) 8	30 (36) 51
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	2 (17) 4	0 (0) 0	0 (0) 0	0 (0) 0	2 (2) 4
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	1 (8) 3	0 (0) 0	0 (0) 0	0 (0) 0	1 (1) 3
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

The denominator for the percentage calculation is N.

AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAF = Safety Set.

Source: modified from Table 14.3.1-3.1.3-1.

Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b1 – Younger participants (SAFB)

Time interval		1 µg (N=12) n (%) E	3 µg (N=6) n (%) E	10 µg (N=11) n (%) E	20 µg (N=11) n (%) E	30 µg (N=12) n (%) E	50 µg (N=11) n (%) E	Total (N=63) n (%) E
Dose 2 up to Day 28 after Dose 2	Any TEAE	6 (50) 15	0 (0) 0	4 (36) 5	3 (27) 8	3 (25) 4	6 (55) 13	22 (32) 45
	Related TEAE	4 (33) 9	0 (0) 0	3 (27) 3	2 (18) 5	2 (17) 2	5 (45) 9	16 (23) 28
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	2 (18) 4	0 (0) 0	0 (0) 0	2 (3) 4
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	1 (9) 3	0 (0) 0	0 (0) 0	1 (1) 3
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

The denominator for the percentage calculation is N.

AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; N/A = not available; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAFB = Safety Dose 2 set (Safety Boost Set).

Source: modified from Table 14.3.1-3.1.3-1.

Primary endpoints – Unsolicited TEAEs after BNT162b2 dosing

Summary of TEAEs without AEs based on solicited reporting via diaries – BNT162b2 – Younger participants (SAF)

Time interval		1 µg (N=12) n (%) E	3 µg (N=12) n (%) E	10 µg (N=12) n (%) E	20 µg (N=12) n (%) E	30 µg (N=12) n (%) E	Total (N=60) n (%) E
Dose 1 up to Dose 2 or Day 28 after Dose 1 (whatever comes first)	Any TEAE	2 (17) 3	6 (50) 10	5 (42) 7	1 (8) 1	4 (33) 5	18 (30) 26
	Related TEAE	0 (0) 0	2 (17) 2	0 (0) 0	0 (0) 0	0 (0) 0	2 (3) 2
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	1 (8) 1	0 (0) 0	0 (0) 0	1 (2) 1
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
Dose 2 up to Day 28 after Dose 2	Any TEAE	4 (33) 4	5 (42) 12	4 (33) 4	1 (8) 2	1 (8) 3	15 (25) 25
	Related TEAE	1 (8) 1	0 (0) 0	1 (8) 1	1 (8) 2	1 (8) 3	4 (7) 7
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
Dose 1 up to Day 28 after Dose 2 or after Dose 1 (if no Dose 2)	Any TEAE	5 (42) 7	7 (58) 22	7 (58) 11	2 (17) 3	5 (42) 8	26 (43) 51
	Related TEAE	1 (8) 1	2 (17) 2	1 (8) 1	1 (8) 2	1 (8) 3	6 (10) 9
	Grade >=3 TEAE	0 (0) 0	0 (0) 0	1 (8) 1	0 (0) 0	0 (0) 0	1 (2) 1
	Related grade >=3 TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Any TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
	Related TESAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

The denominator for the percentage calculation is N.

AE = adverse event; E = number of events; N = number of participants in the analysis set; n = number of participants with the specified characteristic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SAF = Safety Set.

Source: Table 14.3.1-3.1.3-3.

Secondary endpoints – Functional antibody titer data

Functional antibody titer data is available up until Day 43 for BNT162b1-dosed younger participants aged 18 to 55 yrs dosed with 1, 10, 30, 50, and 60 µg on Day 1 (all dose levels) and Day 22 (all dose levels except 60 µg) (n=12 per group).

For BNT162b2-dosed participants, data is available for younger participants aged 18 to 55 yrs dosed with 1, 3, 10, 20, and 30 µg, and older participants aged 56 to 85 yrs dosed with 20 µg on Days 1 and 22 (n=12 per group). Functional antibody data for younger participants is available up until Day 50 for dose groups 1 µg and 3 µg, and up until Day 85 for dose groups 10, 20, and 30 µg. For the BNT162b2-dosed older participants, data is available up until Day 29.

Participants dosed with BNT162b1 showed a strong dose-dependent antibody response. On Day 22, at 21 d after Dose 1, virus neutralizing antibody geometric mean titers (neutralizing GMTs) increased in a dose-dependent manner for the 1, 10, 30, and 50 µg dose groups. At 7 d after Dose 2 (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In

the 60 µg dose group, which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titers.

On Day 43 (21 d after Dose 2 BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 human convalescent serum (HCS) panel.

Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected after Dose 1 and showed a substantial booster response by 7 d after Dose 2 (Day 29) for dose level groups ≥3 µg. Day 29 neutralizing GMTs were comparable between the younger and older participants in the 20 µg dose groups.

On Day 43 (21 d after the second dose of BNT162b2), virus neutralizing GMTs in the younger adult cohorts decreased for the 3, 20, and 30 µg dose levels. Thereafter, neutralizing GMTs remained stable up to Day 85 (63 d after the boost) for younger participant dose groups 10, 20, and 30 µg, and were 1.3-fold to 1.9-fold those of a COVID-19 HCS panel.

All participants dosed with Dose 1 at ≥30 µg BNT162b1 or BNT162b2 seroconverted either by 7 d or 21 d after Dose 2 (Days 29 or 43). All participants immunized with 30 µg BNT162b2 remained seropositive throughout the follow-up until Day 85.

Exploratory endpoints – Binding antibody concentrations

Binding antibody concentration data is available up until Day 43 for BNT162b1-dosed younger participants aged 18 to 55 yrs dosed with 1, 10, 30, 50, and 60 µg on Day 1 (all dose levels) and Day 22 (all dose levels except 60 µg) (n=12 per group).

For BNT162b2-dosed participants, data is available for younger participants aged 18 to 55 yrs dosed with 1, 3, 10, 20, and 30 µg, and older adults aged 56 to 85 yrs dosed with 20 µg on Days 1 and 22 (n=12 per group). Binding antibody data for younger adult participants is available up until Day 50 for the 1 µg and 3 µg dose groups, and up until Day 85 for the 10, 20, and 30 µg dose groups. For the BNT162b2-dosed older participants, data is available up until Day 29.

Participants dosed with BNT162b1 showed a strong dose-dependent antibody response against the SARS-CoV-2 spike (S) protein S1 subunit and receptor binding domain (RBD) at 21 d after Dose 1 (Day 22). At 7 d after Dose 2 (Day 29), S1- and RBD-binding immunoglobulin (IgG) GMCs showed a strong, dose-dependent booster response. In the 60 µg dose group, which was only dosed once, S1- and RBD-binding IgG GMCs remained at a lower level, indicating that a booster dose is necessary to increase antibody concentrations.

At 21 d after the second BNT162b1 dose (Day 43), S1- and RBD-binding IgG GMCs decreased (with exception of the 1 µg dose group), but were clearly above those of a COVID-19 HCS panel for all dose levels tested.

BNT162b2 dosed participants showed a strong BNT162b2-induced S1- and RBD-binding IgG response at 21 d after Dose 1 (Day 22) with evidence of a dose-dependent response only between the 1 µg and 10 µg dose levels. S1- and RBD-binding IgG GMCs showed a substantial booster response by 7 d after Dose 2 (Day 29). Day 29 S1- and RBD-binding IgG GMCs were comparable between the younger and older adult 20 µg dose level cohorts. Across all dose level cohorts, antibody levels decreased over time, but with S1- and RBD-binding antibody GMCs well above that observed in a COVID 19 HCS panel at Day 85 (63 d after Dose 2; 10 µg to 30 µg dose level).

Independent of age, all participants dosed with Dose 1 at ≥20 µg BNT162b1 and or BNT162b2 seroconverted either by 7 d or 21 d after Dose 2 (Day 29 or Day 43).

Exploratory endpoints – SARS-CoV-2 -specific CD4$^+$ and CD8$^+$ T-cell responses

In both younger and older participants, two doses of BNT162b1 and BNT162b2 induced strong SARS-CoV-2 RBD-specific CD4$^+$ and CD8$^+$ T-cell responses in ≥95.5% and ≥96.6% of dosed participants, respectively. The T-cell responses elicited by BNT162b2 were directed against additional epitopes of the S antigen outside RBD, indicating the induction of multi-epitopic responses by BNT162b2 in both age groups. The magnitude of the T-cell responses did not show clear dose dependency. Dosing twice with BNT162b1 or BNT162b2 led to a substantial increase in incidence and magnitude of T-cell responses, especially for dose levels of 10 µg or higher. For BNT162b2, the participants with the strongest CD4$^+$ T-cell responses had more than 10-fold of the memory responses observed in the same participants against immunodominant peptides from Cytomegalovirus, Epstein Barr virus, Influenza virus, and tetanus toxoid. Also, strong CD8$^+$ T-cell responses were seen for the majority of participants and were comparable with memory responses against the above mentioned viral antigens in the same participants.

Exploratory endpoints – Functional and pro-inflammatory CD4$^+$/CD8$^+$ T-cell responses

De novo induction of SARS-CoV-2 S protein or RBD protein directed T-cells was confirmed using ICS. IFNγ-producing CD4$^+$ and CD8$^+$ T-cells against SARS-CoV-2 S protein or RBD were induced robustly by both BNT162b1 and BNT162b2. No clear dose dependency was observed for both IMPs. The cytokine responses elicited after dosing with either BNT162b1 or BNT162b2 in older participants was mostly identical in response pattern and intensity with that in younger participants.

BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory CD4$^+$/CD8$^+$ T-cell responses in almost all participants. The detection of interferon (IFN)γ, interleukin (IL)-2 but not IL-4 indicates a favorable Th1 profile and the absence of a potentially deleterious Th2 immune response. No notable age-related differences were observed.

Conclusions

- The majority of events reported were reactogenicity symptoms compared to TEAEs which were anticipated for IM-administered vaccines. The observed reactogenicity was mild or moderate in severity. The results of this study show that BNT162b1 and BNT162b2 are well tolerated and have an acceptable safety profile in younger participants 18 to 55 yrs of age.
- The frequency of local and systemic reactogenicity was generally lower for BNT162b2 compared to BNT162b1. BNT162b2 generally had a milder and therefore more favorable reactogenicity profile than BNT162b1 across dose levels.
- Participants dosed with BNT162b1 (1 to 50 µg) showed a strong, IMP- and dose-dependent antibody response in a SARS-CoV-2 neutralization assay by Day 22 (at 21 d after Dose 1). This response increased further by Day 29 (at 7 d after Dose 2), and the second dose elicited a booster effect. By Day 43 (21 d after Dose 2), the observed responses decreased for most dose levels. For participants dosed at ≥10 µg BNT162b1, Day 43 neutralizing GMTs were comparable or even superior to those of a COVID-19 HCS panel.
- Independent of age, participants dosed with BNT162b2 (1 to 30 µg) showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected after Dose 1 and showed a substantial booster response by 7 d after Dose 2 (Day 29) for dose level groups ≥3 µg. On Day 43, neutralizing GMTs in the younger participant doe groups decreased for the 3, 20, and 30 µg dose levels. Thereafter, GMTs remained stable up to Day 85 (63 d after dose 2) for younger adult dose groups 10, 20, and 30 µg BNT162b2 and were comparable or even superior to those of a COVID-19 HCS panel.

- After dosing with ≥30 µg BNT162b1 and BNT162b2, all participants showed GMC - and GMT-based seroconversion by either 7 d or 21 d after the second dose (Day 29 or Day 43). All participants immunized with 30 µg BNT162b2 remained seropositive throughout the follow-up until Day 85.
- The observed kinetics of the BNT162b1 and BNT162b2 induced neutralizing antibody response is typical of antigen-activated B cells going through over proliferation, followed by rebound contraction with a gradual decline in numbers before stabilization of the immune response.
- Two doses of BNT162b1 and BNT162b2 induced strong SARS-CoV-2-RBD-specific $CD4^+$ and $CD8^+$ T-cell responses in ≥95% and ≥76% of dosed participants, respectively. The T-cell responses elicited by BNT162b2 were directed against additional epitopes of the S antigen outside RBD, indicating the induction of multi-epitopic responses by BNT162b2. The magnitude of the T-cell responses did not show clear dose dependency.
- BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory $CD4^+$/$CD8^+$ T-cell responses in almost all participants. The detection of IFNγ and IL-2, but no or only minor IL-4 production, indicates a favorable Th1 profile. No notable age-related differences were observed.
- The favorable tolerability profile was the major driver for choosing BNT162b2 for entry into Phase II/III. At the time of finalization of this report, applications for marketing authorization of BNT162b2 is ongoing in numerous countries. The dosing regimen proposed is two 30 µg BNT162b2 doses given ~21 d apart.