CLINICAL TRIAL PROTOCOL
BNT162-17

Version: 7.0 **Date:** 28 JUN 2023

Sponsor: BioNTech SE

Trial title:	A Phase II trial to evaluate the safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines in healthy subjects
Brief title:	Safety and immunogenicity of RNA-based vaccines against SARS-CoV-2 variants in healthy participants
Trial phase:	Phase II
Indication:	Prevention of Coronavirus Disease 2019 (COVID-19)
Vaccines:	BNT162 RNA-lipid nanoparticle (RNA-LNP) vaccines: BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), BNT162b2, BNT162b2 (B.1.1.529)
Coordinating and Principal investigator:	Dr. Dr. med. Armin Schultz, CRS Clinical Research Services Mannheim GmbH, Germany (tel.: +49 621 150450)
Trial conducted by:	ICON plc, South County Business Park, Dublin 18, Ireland
Trial sites:	Approximately 40 sites worldwide including the European Union (EU) and the United States (US). For details of the trial sites and site personnel, see the Trial Master File (TMF).
Sponsor's medical representative:	Shon Remich, MD, Senior Medical Director, Clinical Development, BioNTech SE
Sponsor:	BioNTech SE, An der Goldgrube 12, 55131 Mainz, Germany
Regulatory identifiers:	EudraCT no.: 2021-003458-22; ClinicalTrials.gov ID: NCT05004181; US IND 19736
Medical Monitor:	Contact information will be provided separately.

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Amendment No. 5	04 AUG 2022	6.0	All countries
Amendment No. 6	28 JUN 2023	7.0	All countries

For details of the updates, see Section 10.9.

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT162-17

Trial title

A Phase II trial to evaluate the safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines in healthy subjects

Trial rationale

BioNTech has developed ribonucleic acid (RNA)-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The BNT162b platform uses modified RNA (modRNA). The BNT162b platform member BNT162b2 (Comirnaty, Pfizer-BioNTech COVID-19 vaccine) has received emergency use authorization or conditional/full marketing authorization in numerous countries worldwide for the prevention of Coronavirus Disease 2019 (COVID-19). As demonstrated by BNT162b2, lipid nanoparticle (LNP)-formulated RNA-based vaccines provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Mulligan et al. 2020; Rauch et al. 2018; Sahin et al. 2014; Walsh et al. 2020).

As more data about COVID-19 continue to accrue, the potential duration of protection, after SARS-CoV-2 natural infection and by vaccination, remains unknown. Further, although SARS-CoV-2 presents a mutation rate lower than that of other RNA viruses, it continues to evolve, generating new variants that arouse concern due to increased transmissibility or anticipated reduction in neutralization by antibodies generated during previous infection or vaccination. These variants include a variant with high prevalence globally, B.1.1.7 (known as Alpha) and further variants including B.1.351 (known as Beta), P.1 (known as Gamma), B.1.617.1 and B.1.617.2 (the latter known as Delta), and B.1.1.529 (Omicron) and its subvariants B.1.1.529.1 (BA.1) and B.1.1.529.5 (BA.5). BNT162b2 induces a robust immune response against SARS-CoV-2, including both humoral and multifunctional T-cell responses, and emerging vaccine effectiveness data confirm its effectiveness against COVID-19 in populations with high prevalence of those variants. If evidence emerges that particular variants do appear to influence vaccine effectiveness and prevail in different countries, it will be beneficial to be prepared to implement BNT162b2-based vaccines against variant strains able to boost memory responses against conserved SARS-CoV-2 epitopes while concurrently targeting novel neutralizing epitopes of escaping circulating strains.

On 26 November 2021, the World Health Organization (WHO) designated the SARS-CoV-2 virus variant B.1.1.529, named Omicron, a variant of concern (VOC; WHO webpage “Update on Omicron”). Initially detected in South Africa, this variant rapidly distributed across the world. The SARS-CoV-2 Omicron variant is known to have a concerning number of mutations (more than 30) in the spike protein that are associated with reduced neutralization by convalescent and vaccinee sera (Schmidt et al. 2021). The original Omicron strain has since been renamed B.1.1.529.1 (known as Omicron BA.1), with the Omicron lineage having expanded into multiple sublineages.

Reflective of the SARS-CoV-2 Omicron (BA.1) variant’s decreased sensitivity to neutralizing antibodies elicited by previous viral variants or vaccines based on those, incidence of SARS-CoV-2 infection peaked in January 2022 (WHO webpage “COVID-19 Weekly Epidemiological Update”). In

the US, prevalence of the SARS-CoV-2 Omicron (BA.1) variant reached 89.2 to 98.8% during that time frame (US Centers for Disease Control and Prevention [CDC] webpage "COVID Data Tracker – Variant Proportions", accessed 09 February 2022). Meanwhile it was confirmed that two-dose vaccination schedules with the available vaccines based on the SARS-CoV-2 wild-type strain provide lower protection against infection with the SARS-CoV-2 Omicron variant(s) compared to the previous variants or the wild-type strain. A third dose of an RNA-based vaccine appears to temporarily increase protection (UK Health Security Agency 2022), but reinfection rates with the SARS-CoV-2 Omicron variant(s) are likely higher than with the SARS-CoV-2 Delta variant (Ferguson et al. 2021).

As of 04 August 2022, no Omicron-specific variant vaccines were authorized, and there were no vaccination recommendations for subjects who experienced a breakthrough infection with the SARS-CoV-2 Omicron variant. On 31 August 2022, the US Food and Drug Administration (FDA) authorized the bivalent vaccine, BNT162b2 and BNT162b2 Omicron (B.1.1.529 sub-lineage BA.4/5), for a booster vaccination in individuals 12 years of age and older.

On 18 April 2023, the US FDA amended the BNT162b2 emergency use authorization to simplify the vaccination schedule for most individuals, including that most unvaccinated individuals may receive a single dose of a variant-modified vaccine (rather than two doses). The effectiveness of a single dose was supported by observational data from England on the effectiveness of one dose of monovalent BNT162b2, and that, among individuals 12 to 17 years of age who had received only one dose of BNT162b2, those who had evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those with no evidence of previous infection.

To combat these evolving SARS-CoV-2 strains, the sponsor has initiated clinical investigation of BNT162b2-based vaccines against variant strains as monovalent vaccines and as a multivalent vaccine (i.e., a combination of two monovalent vaccines). These BNT162b2-based vaccines are named "BNT162b2" plus the variant strain targeted by the RNA-encoded open reading frame (ORF), e.g., BNT162b2 (B.1.1.7) has an RNA that encodes the SARS-CoV-2 strain B.1.1.7 spike (S) protein. The BNT162b2-based vaccines against variant strains have the same LNP formulation and RNA components as BNT162b2 except that the RNAs differ slightly in their encoded ORF. Each RNA component leads to expression of S proteins with the amino acid changes seen in the SARS-CoV-2 strains B.1.1.7, B.1.351, B.1.617.2, and B.1.1.529.1, respectively. For further details, see Table 8.

This trial (BNT162-17) aims to investigate the safety and immunogenicity of the BNT162b2-based vaccines against variant strains, i.e., BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529) *:

- BNT162b2 (B.1.1.7 + B.1.617.2), a multivalent vaccine comprising a 1:1 mixture of BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2).
- BNT162b2 (B.1.1.7), a monovalent vaccine that expresses the full length SARS-CoV-2 Alpha S protein bearing mutations preserving neutralization-sensitive sites.
- BNT162b2 (B.1.617.2), a monovalent vaccine that expresses the full length SARS-CoV-2 Delta S protein bearing mutations preserving neutralization-sensitive sites.
- BNT162b2 (B.1.1.529), a monovalent vaccine that expresses the full length SARS-CoV-2 Omicron S protein bearing mutations preserving neutralization-sensitive sites.

* Note: In this protocol, "B.1.1.529" refers to variant B.1.1.529.1 (known as Omicron BA.1) unless stated otherwise.

The two viral strains included in the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) are selected to favor cross-reactive antibody responses and to also include dominant strains in terms of global prevalence at the time of this trial. The thorough clinical investigation of BNT162b2 (B.1.1.7 + B.1.617.2) in Parts A and B will support preparedness for the case that a multivalent BNT162b2-based vaccine against COVID-19 is needed to allow broad coverage against circulating strains at global level and to avoid the complexity of handling multiple monovalent vaccines in parallel.

To support the clinical evaluation of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), the monovalent BNT162b2 vaccines BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) will also be individually investigated clinically in Parts A and B. Data from Part B of the trial will be used to evaluate the immunogenicity of one dose of variant-modified BNT162b2 (multivalent B.1.1.7 + B.1.617.2) in vaccine-naïve seropositive individuals. To supplement real world evidence that a single dose is effective, immunogenicity results from this analysis will fill the evidence gap for use of the single dose of BNT162b2 in individuals 12 years of age and older who have not been previously vaccinated with a COVID-19 vaccine. The Alpha (B.1.1.7) and Delta (B.1.617.2) BNT162b2 variants are no longer epidemiologically relevant. Experience with other variant-modified versions of BNT162b2 is relevant because all have the same LNP formulation and RNA components except that the RNAs differ slightly in their encoded ORF and the available data has demonstrated that immune response(s) to vaccine-encoded strain(s) are similar. To provide a robust comparison, as well as assessing neutralizing titers (NTs) against Alpha and Delta, NTs against the more contemporaneous B.1.1.529.5 (Omicron BA.5) will also be assessed. Finally, to bridge to the efficacy demonstrated with the original BNT162b2 vaccine, although not encoded by the investigational vaccine in this trial, NTs against the reference strain will be compared between vaccine-naïve seropositive individuals after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) and vaccine-naïve seronegative individuals after two doses of original BNT162b2 (from trial BNT162-02 / C4591001; NCT04368728).

Part C will investigate if administration of one dose of either BNT162b2 (B.1.1.529) or BNT162b2 after previous infection with the SARS-CoV-2 Omicron variant will elicit an immune response against the SARS-CoV-2 Omicron variant in subjects who have been vaccinated with any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with a SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections). In addition, Part C (Cohort 9) will evaluate the immune response reached after infection with the SARS-CoV-2 Omicron variant.

Objectives and endpoints

Objectives and endpoints - Part A

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), given as one or two booster doses to BNT162b2-experienced subjects, or as three doses to COVID-19 vaccine-naïve subjects. To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.1.7) given as one booster dose to BNT162b2-experienced subjects. * To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.617.2), given as one booster dose to BNT162b2-experienced subjects. * To describe the safety profile of BNT162b2, given as one booster dose to BNT162b2-experienced subjects. *	For each trial treatment, in subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after each dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary objectives (Immunogenicity)		
To describe the immune response after one, two, or three doses of BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2.	For BNT162b2-experienced subjects: • GMTs at each time point. • GMFR from before vaccination to each subsequent time point after vaccination. • Seroresponse (SR) in terms of NT at each post-vaccination time point.	• Reference and VOC specific NTs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Exploratory objectives		
To comprehensively describe B-cell responses after one, two, or three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), or one booster dose of the monovalent vaccine BNT162b2 (B.1.1.7), or one booster dose of BNT162b2 (B.1.617.2), at 30 µg.	For a subset of subjects in Part A: • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells
To describe the T cell-mediated immune response after one, two, or three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), or one booster dose of the monovalent vaccine BNT162b2 (B.1.1.7), or one booster dose of BNT162b2 (B.1.617.2), at 30 µg.	For a subset of subjects in Part A: • CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and the B.1.1.7 and B.1.617.2 VOC.	• Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)
To evaluate the immune response over time to prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) and persistence of immune response in subjects with and without prior COVID-19 vaccination.	• GMC/GMT and GMFR at baseline and 1, 6, and 12 months after completion of vaccination. • Seroresponse for reference strain and B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	• For a subset of subjects, after any dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2, BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) vaccines, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data

* Note: "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.
Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; RBD = receptor binding domain; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; S = spike protein; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

Objectives and endpoints - Part B

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) given as one booster dose to BNT162b2-experienced subjects *, or as three doses to COVID-19 vaccine-naïve subjects. To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.617.2) given as one booster dose to BNT162b2-experienced subjects *.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after each dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary objectives (Immunogenicity)		
BNT162b2-experienced subjects		
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of GMT.	• GMR of B.1.1.7 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • GMR of B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.617.2) after one dose of monovalent vaccine BNT162b2 (B.1.617.2) in terms of GMT.	• GMR of B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of SR.	• The difference in SRs to B.1.1.7 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • The difference in SRs to B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific SRs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Immunogenicity)		
BNT162b2-experienced subjects		
To demonstrate the non-inferiority of immune response against VOC (B.1.617.2) after one dose of monovalent vaccine BNT162b2 (B.1.617.2) in terms of SR.	• The difference in SRs to B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific SRs
COVID-19 vaccine-naïve subjects		
To demonstrate the non-inferiority of immune response against reference strain after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response after two doses of original BNT162b2 in subjects without evidence of infection from the Phase III trial BNT162-02 / C4591001 in terms of GMT.	• GMR of reference strain NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the reference strain NT 1 month after two doses of BNT162b2 in subjects without evidence of infection.	• Reference strain NTs
To demonstrate the non-inferiority of immune response against reference strain after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response after two doses of original BNT162b2 in subjects without evidence of infection from the Phase III trial BNT162-02 / C4591001 in terms of SR.	• The difference in SRs to the reference strain NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the reference strain NT 1 month after two doses of BNT162b2 in subjects without evidence of infection.	• Reference strain NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of GMT.	• GMR of B.1.1.7 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • GMR of B.1.617.2 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs

OBJECTIVES	ESTIMANDS	ENDPOINTS
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of SR.	• The difference in SRs to B.1.1.7 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • The difference in SRs to B.1.617.2 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific SRs
Secondary objectives		
BNT162b2-experienced subjects		
To describe the immune response against the reference strain and VOCs after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) vs two doses of BNT162b2.	• GMTs and SRs of VOCs and reference strain NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) and Dose 2 of BNT162b2.	• Reference and VOC specific NTs
To describe the immune response against the reference strain and VOCs after one dose of monovalent vaccine BNT162b2 (B.1.617.2) vs two doses of BNT162b2.	• GMTs and SRs of VOCs and reference strain NT 1 month after one dose of BNT162b2 (B.1.617.2) and Dose 2 of BNT162b2.	• Reference and VOC specific NTs
COVID-19 vaccine-naïve subjects		
To describe the immune response against the reference strain and VOCs after three doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	• GMTs and SRs of VOCs and reference strain NT 1 month after Dose 2 and Dose 3 of BNT162b2 (B.1.1.7 + B.1.617.2).	• Reference and VOC specific NTs
To compare the immune response against VOCs 3 weeks after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response 1 month after one booster dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects without evidence of infection.	• GMTs and SRs of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection and 1 month after one booster dose of BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects without evidence of infection. • GMR of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the VOCs NT 1 month after one booster dose of	• VOC specific NTs (B.1.1.7, B.1.617.2, B.1.1.529.5 [Omicron BA.5])

OBJECTIVES	ESTIMANDS	ENDPOINTS
	BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • The difference in SRs to VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the VOCs NT 1 month after one booster dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection.	
To compare the immune response against VOCs 3 weeks after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response 1 month after two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects without evidence of infection.	• GMTs and SRs of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • GMR of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the VOCs NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • The difference in SRs to VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the VOCs NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection.	• VOC specific NTs (B.1.1.7, B.1.617.2, B.1.1.529.5 [Omicron BA.5])
Exploratory objectives		
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences

OBJECTIVES	ESTIMANDS	ENDPOINTS
To evaluate the immune response over time to prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2), and persistence of immune response in subjects with and without prior COVID-19 vaccination.	• GMC/GMT and GMFR at baseline and 1, 6, and 12 months after completion of vaccination. • SRs for reference strain and B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	• For a subset of subjects, after any dose of multivalent vaccine, BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccines BNT162b2 and BNT162b2 (B.1.617.2) vaccines, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data
To describe B-cell responses after one or two and three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	For a subset of Cohort 6 subjects in Part B: • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells
To describe the T cell-mediated immune response after one or two and three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	For a subset of Cohort 6 subjects in Part B: • CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and the B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)
To describe the incidence of non-S seroconversion to SARS-CoV-2 in subjects with and without prior COVID-19 vaccination who received prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2).	• Incidence of non-S-seroconversion to SARS-CoV-2 per 1,000 person-years of follow-up.	• Nucleocapsid (N)-binding antibody seroconversion in subjects with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the incidence of confirmed COVID-19 at 1 year follow-up period in subjects with and without prior COVID-19 vaccination who received prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2).	• Incidence of confirmed COVID-19 cases per 1,000 person-years of follow-up.	• Number of confirmed COVID-19 cases

* Note: "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.

Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; GMR = geometric mean ratio; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

Objectives and endpoints - Part C

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.1.529) given as one dose to RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after the last dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety profile of the monovalent vaccine BNT162b2 given as one dose to RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after the last dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary objectives (Immunogenicity)		
To describe the humoral immune response against SARS-CoV-2 variants after one dose of BNT162b2 (B.1.1.529) or after one dose of BNT162b2 in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMR and difference in SR of B.1.1.529 NT 1 month after one dose of BNT162b2 (B.1.1.529) to those at 1 month after one dose of BNT162b2 for Cohorts 7 and 8.	• VOC specific NTs • VOC specific SRs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Secondary objectives		
To describe the humoral immune response against SARS-CoV-2 variants after one dose of BNT162b2 (B.1.1.529) or after one dose of BNT162b2 or a post SARS-CoV-2 infection in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMT of VOC NT at baseline and 7 days, 1 month, and 3 months after the trial start for Cohorts 7, 8, and 9, and 6 and 12 months after the trial start for Cohorts 7 and 8.	• VOC specific NTs
Exploratory objectives		
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences
To evaluate cross-neutralization of vaccine-induced antibodies to ancestral and emerging SARS-CoV-2 variants.	• For a subset of subjects, after one dose of monovalent vaccine BNT162b2 (B.1.1.529) or BNT162b2, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data
To evaluate the immune response over time to prophylactic monovalent vaccine BNT162b2 (B.1.1.529) or BNT162b2 and persistence of immune response in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMC/GMT and GMFR at baseline, 7 days, and 1, 3, 6, and 12 months after completion of vaccination. • Seroresponse for B.1.1.529 variant strain.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate the immune response to SARS-CoV-2 in subjects.	• GMC/GMT and GMFR at baseline, 7 days, and 1, 3, 6, and 12 months after completion of vaccination.	• Nucleocapsid (N)-binding Ig levels
To describe the incidence of confirmed COVID-19 at 1 year follow-up period in subjects who received one dose of monovalent BNT162b2 (B.1.1.529) or BNT162b2.	• Incidence of confirmed COVID-19 cases per 1,000 person-years of follow-up.	• Number of confirmed COVID-19 cases
To describe the B cell- and T cell-mediated immune response to monovalent BNT162b2 (B.1.1.529) and to BNT162b2 and persistence of immune response in subjects.	For a subset of subjects in Part C: • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells • Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)

OBJECTIVES	ESTIMANDS	ENDPOINTS
	• CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and B.1.1.529 variant strain.	

Note: BNT162b2 (B.1.1.529) refers to the monovalent vaccine specific for SARS-CoV-2 Omicron subvariant BA.1, i.e., B.1.1.529.1.

Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; GMR = geometric mean ratio; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; RBD = receptor binding domain; S = spike protein; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

Trial design

This is a Phase II open-label trial.

This trial consists of three parts, Part A, Part B, and Part C, and will evaluate the safety and immunogenicity of a third booster injection of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), and the safety and immunogenicity of a third booster injection of the monovalent vaccine BNT162b2 (B.1.617.2) or BNT162b2 (B.1.1.7), in subjects who have received two doses of the parent vaccine BNT162b2 at 30 µg, at least 6 months after the second dose of BNT162b2. It will also evaluate the safety and immunogenicity of a three-dose regimen of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects who have not received prior COVID-19 vaccination. In addition, the safety and immunogenicity of BNT162b2 (B.1.1.529) or BNT162b2 given as a third or fourth vaccine dose to RNA COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection will be evaluated and contrasted with the natural immune response reached after infection with the SARS-CoV-2 Omicron variant.

Part A will describe, in parallel subject cohorts, the safety and the immunogenicity of BNT162b2 (B.1.1.7 + B.1.617.2) in relation to the corresponding monovalent vaccines BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2), and the parent vaccine BNT162b2. Comprehensive assessments of the humoral and cell-mediated immune responses in those groups will evaluate if the immunological responses to each antigen are undeterred by the addition of additional antigens in BNT162b2 (B.1.1.7 + B.1.617.2). Further, analyses of the B cell compartment, including memory B cells, will assess if BNT162b2 (B.1.1.7 + B.1.617.2) as a booster in prior vaccinated subjects elicits a qualitatively improved anamnestic response, with expansion of a diversified memory B cell population able to cross-neutralize conserved and unique strain epitopes. Part A will provide rapid information about the safety and the immunogenicity of the multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine in a previously vaccinated group and in a vaccine-naïve population, and will inform Part B in terms of dosage and sample size.

Part B will be initiated after review of reactogenicity and available immunogenicity data of Part A (Cohorts 1, 4, 6) by the Safety Review Committee (SRC). Part B will compare the immune response after one dose or after two doses of the multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine against the variant strains or after one dose of multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine against the reference strain vs the immune response after two doses of BNT162b2 against the reference strain observed in subjects from the Phase III BNT162-02 / C4591001 (NCT04368728) trial. Part B will also compare the immune response after one dose of the monovalent vaccine BNT162b2 (B.1.617.2) against the variant strain vs the immune response after

two doses of BNT162b2 against the reference strain observed in subjects from the Phase III BNT162-02 / C4591001 trial. Part B will further include the same assessments of the B cell and T cell compartments as described in Part A in a pre-defined sample size of the cohort population.

Based on data from Part A, the dosage, sample size and trial groups planned in Part B may be adjusted via a protocol amendment.

Part C will include healthy subjects who were previously vaccinated with two or three doses of any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with a SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections). Part C will compare immune responses against the SARS-CoV-2 Omicron variant after one dose of 30 µg monovalent BNT162b2 (B.1.1.529) vaccine vs the immune response after one dose of 30 µg BNT162b2. In addition, Part C (Cohort 9) will evaluate the immune response reached after infection with the SARS-CoV-2 Omicron variant.

Part A

Part A consists of six parallel cohorts of approximately n = 20 subjects each, which will enroll subjects 18 to 55 years of age (Cohorts 1 to 6).

Cohorts 1 to 5 will enroll subjects who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose in the following five cohorts:

- **Cohort 1**: Subjects will receive one dose of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) on Day 1 (baseline in this trial), consisting of a 1:1 mixture of two BNT162b2 monovalent vaccines: 15 µg BNT162b2 (B.1.1.7) and 15 µg BNT162b2 (B.1.617.2).
- **Cohort 2**: Subjects will receive two doses of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and on Day 56 (8 weeks apart).
- **Cohort 3**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.1.7) on Day 1.
- **Cohort 4**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.617.2) on Day 1.
- **Cohort 5**: Subjects will receive one dose of 30 µg BNT162b2 on Day 1.

Cohort 6 will enroll subjects who have not received any prior prophylactic vaccine against COVID-19.

- **Cohort 6**: Subjects will receive three doses of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 21 and the third dose ~6 months after the second dose.

Part B

Part B will be initiated after review of reactogenicity and available immunogenicity data of Part A (Cohorts 1, 4, 6) by the SRC.

Part B consists of three cohorts of n = 300 subjects each (~375 subjects will be enrolled in each cohort to ensure there are 300 evaluable subjects), which will enroll subjects 18 to 85 years old; ~60% of these subjects should be 18 to 55 years old and ~40% should be 56 to 85 years old:

- **Cohort 1** will enroll subjects from the trial BNT162-02 / C4591001 who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose. Subjects will receive on Day 1 one dose of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).

- **Cohort 4** will enroll subjects from the trial BNT162-02 / C4591001 who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose. Subjects will receive on Day 1 one dose of 30 µg monovalent vaccine BNT162b2 (B.1.617.2).
- **Cohort 6** will enroll subjects who have not received any prior prophylactic vaccine against COVID-19. Subjects will receive 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 21 and the third dose ~6 months after the second dose. Approximately 15 subjects at preselected sites in Part B will be evaluated in terms of cell-mediated immunity.

Part C

Part C consists of n = ~225 subjects who previously received two or three injections of any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with SARS-CoV-2 infection from January 2022 onwards (limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections).

Subjects in Part C will be randomized in a 2:2:1 ratio into three cohorts; ~90 subjects each in Cohorts 7 and 8 (to ensure ~80 evaluable subjects in each cohort after 11% dropout) and 45 subjects in Cohort 9. Randomization will be stratified by age group (18 to 55 years of age or 56 to 85 years of age) and by number of prior doses of COVID-19 RNA-based vaccine (two or three doses).

The sponsor may terminate the enrollment into Cohort 9 at any time in case the evolving COVID-19 epidemiology and/or the recommendations issued in the context of national vaccination campaigns no longer support enrollment of the trial population in a realistically feasible time.

Cohorts 7 to 9 will enroll subjects 18 to 85 years old; ~60% of these subjects should be 18 to 55 years old and ~40% should be 56 to 85 years old:

- **Cohort 7**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.1.529) on Day 1.
- **Cohort 8**: Subjects will receive one dose of 30 µg BNT162b2 on Day 1.
- **Cohort 9**: No vaccination will be given to Cohort 9 subjects within 3 months after Visit 1. After the 3-month follow-up period, subjects in Cohort 9 will be offered a BNT162b2 vaccination, depending on the epidemiological situation, local regulatory authority recommendations, and/or variant vaccine authorization status.

Approximately 25 subjects at preselected sites in each cohort of Part C will be evaluated in terms of cell-mediated immunity.

For further trial design background, see Section 4.1.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2. For the planned assessments and visits, see the Schedule of Activities (SoA) in Section 1.3.

Duration of all trial periods

Depending on the cohort, the planned trial duration for a subject in this trial is up to ~61 weeks (for the cohort with the longest duration: ≤1 week of screening, 8 weeks between IMP doses, and ~52 weeks-follow-up after the last IMP dose).

The estimated planned trial start (first subject first visit) and trial end (last subject last visit) are Q3-2021 and Q3-2023.

Trial population

This trial will enroll healthy volunteers:

i. Part A: Who are 18 to 55 years old.

ii. Part B: Who are 18 to 85 years old (~60% should be 18 to 55 years old and ~40% 56 to 85 years old).

iii. Part C: Who are 18 to 85 years old (~60% should be 18 to 55 years old and ~40% 56 to 85 years old).

iv. For Cohorts 1 to 5: In Part A, who have received the BNT162b2 vaccine (30 µg, two-dose regimen) in either a clinical trial or as part of the governmental vaccination programs at least 6 months before Visit 0. Subjects who are currently enrolled in the Phase III trial BNT162-02 / C4591001, have already been unblinded, and have previously received two doses of BNT162b2 with Dose 2 at least 6 months earlier can be included (for Cohorts 1 and 4 in Part B, prior enrollment and dosing in the trial BNT162-02 / C4591001 is mandatory). At enrollment into Part B of this trial, their participation in the trial BNT162-02 / C4591001 will be terminated. Subjects should have not experienced COVID-19 based on medical history.

v. For Cohort 6: Who are COVID-19 vaccine-naïve and have not experienced COVID-19 based on their medical history.

vi. For Part C, Cohorts 7, 8, and 9: Who have received two or three documented doses of any authorized COVID-19 RNA-based vaccine (e.g., BNT162b2 [Comirnaty] or the Moderna vaccine [Spikevax]) prior to being diagnosed with SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections) that is documented with a result from a nucleic acid amplification-based test (NAAT) for SARS-CoV-2.

Planned enrollment is ~1,470 subjects; ~120 in Part A (~20 in each of the six cohorts), ~1,125 in Part B (~375 in each of the three cohorts), and ~225 in Part C (~80 in each of Cohort 7 and Cohort 8 and ~45 in Cohort 9).

Trial treatments

IMP name:	• BNT162b2 • BNT162b2 (B.1.1.7 + B.1.617.2) • BNT162b2 (B.1.1.7) • BNT162b2 (B.1.617.2) • BNT162b2 (B.1.1.529)
Type:	Vaccine (BNT162 RNA-LNP vaccine utilizing modRNA).
Use:	Experimental
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. The same arm may be used for both immunizations. The non-dominant arm is preferred.
Dosing regimen:	**Part A:** • Cohort 1: One dose of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2), consisting of a 1:1 mixture of 15 µg BNT162b2 (B.1.1.7) and 15 µg BNT162b2 (B.1.617.2), given on Day 1. • Cohort 2: Two doses of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 56. • Cohort 3: One dose of 30 µg BNT162b2 (B.1.1.7) on Day 1. • Cohort 4: One dose of 30 µg BNT162b2 (B.1.617.2) on Day 1. • Cohort 5: One dose of 30 µg BNT162b2 on Day 1. • Cohort 6: Three doses (on Day 1, Day 21, and the third dose ~6 months after the second dose) of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). **Part B:** • Cohort 1: One (on Day 1) dose of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). • Cohort 4: One (on Day 1) dose of 30 µg BNT162b2 (B.1.617.2). • Cohort 6: Three doses (on Day 1, Day 21, and the third dose ~6 months after the second dose) of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). **Part C:** • Cohort 7: One dose of 30 µg BNT162b2 (B.1.1.529) on Day 1. • Cohort 8: One dose of 30 µg BNT162b2 on Day 1. • Cohort 9: No IMP injection within 3 months of Visit 1.

Note: BNT162b2 (B.1.1.529) refers to the monovalent vaccine specific for SARS-CoV-2 Omicron subvariant BA.1, i.e., B.1.1.529.1.

1.2 Schema (graphical representation of the trial)

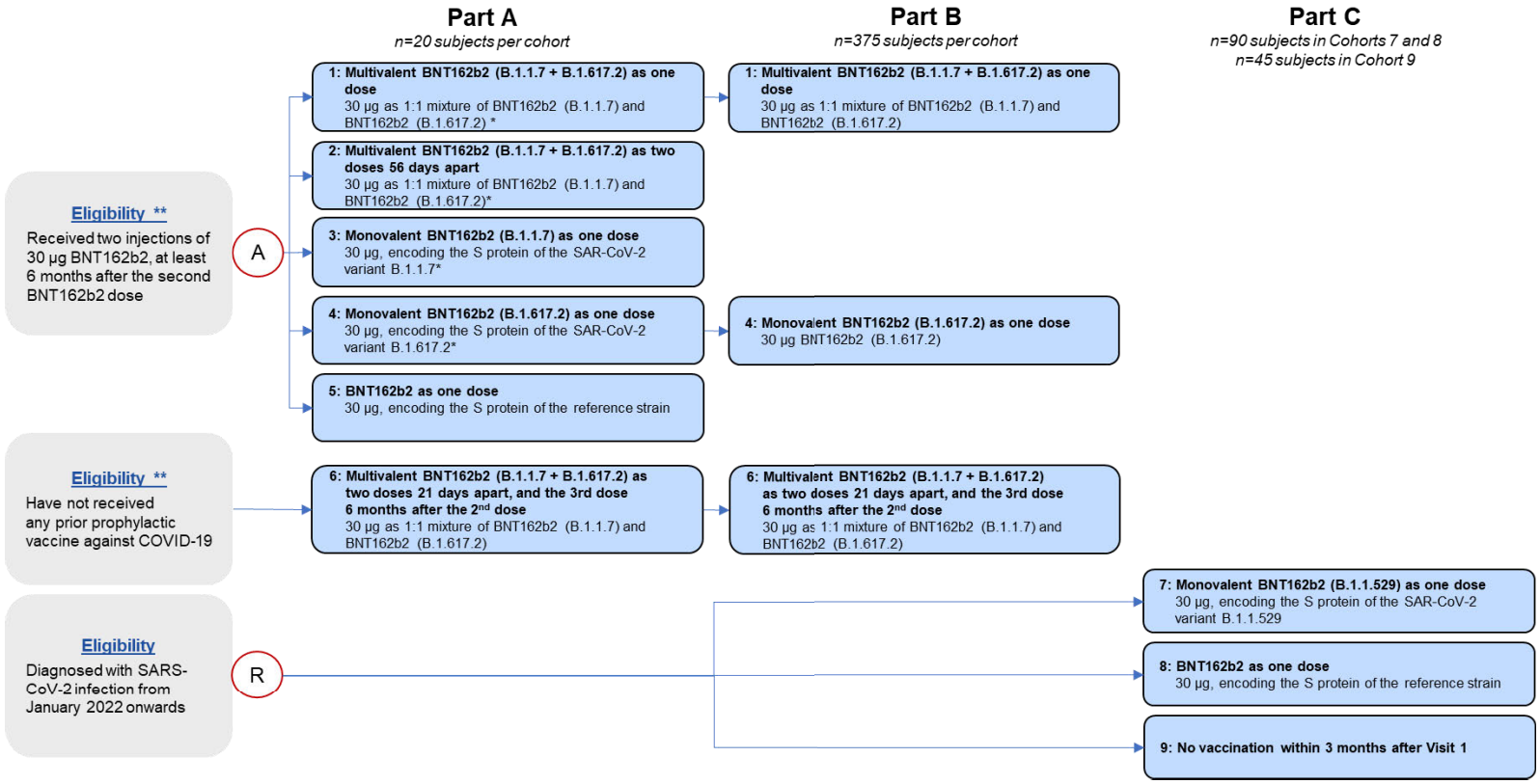

Figure 1: Schema - Safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines in healthy subjects

"A" = assignment to cohort; "R" = randomization.

* An optional additional lower dose level may be tested in each of the cohorts in up to 20 additional subjects per cohort.

** No history of COVID-19 and/or clinical or evidence of prior infection with SARS-CoV-2 at screening (Visit 0).

1.3 Schedule of activities

The SoAs provide an overview of the trial visits and procedures. The investigator may schedule unplanned visits in addition to those listed in the SoAs, in order to conduct evaluations or assessments required to protect the wellbeing of the trial subjects (subjects).

Table 1: Schedule of events for Part A, Cohorts 1, 3, 4, and 5; one dose of either BNT162b2 (B.1.1.7 + B.1.617.2), or BNT162b2 (B.1.1.7), or BNT162b2 (B.1.617.2), or BNT162b2 in BNT162b2-experienced subjects

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	3 wk Post-Vax FU	1 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8+2	21±3	29±3	180±10	360±10		
Collect informed consent	X								
Assess inclusion/exclusion criteria compliance	X	X (review)							
Collect demographic and medical history	X	X (update)							
12-lead ECG	X	X [g]	X						
Perform clinical assessment (includes 15 mL blood draw and urine collection at Visit 0) [a]	X	X							
Record (concomitant) medication [j]	X	X	X	X	X	X [l]	X [l]	X [l]	X [l]
Perform urine pregnancy test for WOCBP	X	X							
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]							
Allocation to IMP		X							
IMP injection		X							
Assess acute reactions for ≥30 minutes after IMP injection		X							
Measure oral body temperature		X [c]	X	X	X				
Issue/train and collect e-diary		Issue/train	Collect					Collect	

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	3 wk Post-Vax FU	1 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8+2	21±3	29±3	180±10	360±10		
Subjects report daily reactogenicity (incl. oral body temperature) for 7 days after dosing using an e-diary		Start after Vax	End					End	
Review e-diary data		Start	End					End	
Record any AEs, AESIs, or SAEs since last visit [h]		X	X	X	X	X [f]	X [f]	X [f]	X [f]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (20 mL)		X	X	X	X	X	X	X	X [i]
Blood draws for T- and B-cell responses (120 mL)		X	X		X [e]	X	X		X [i]
Blood draw for explorative research (25 mL) [k]				X					
Record pregnancies		Start	=>	=>	=>	=>	End	End	

Notes: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects. "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.

a At Visit 0: complete physical examination including body weight, vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]), blood and urine clinical laboratory tests; at Visit 1: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e 5 mL blood will be taken from this sample for genetics (human leukocyte antigen typing).

f For any visits >1 month after IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h For subjects rolling over from the trial BNT162-02 / C4591001 (NCT04368728), the recording will start from IMP allocation during Visit 1 (after eligibility is confirmed and the subject is withdrawn from the trial BNT162-02 / C4591001).

i If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤120 mL for T-cell and B-cell response assessments and one 20 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

j Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

k For consenting subjects.

l For any visits >1 month after IMP injection, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 2: Schedule of events for Part A, Cohort 2; two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax 1 (except IMP injection)	1 wk Post-Vax 1 FU	3 wk Post-Vax 1 FU	1 mon Post-Vax 1 FU	Pre-Vax 2 (except IMP injection)	1 wk Post-Vax 2 FU	1 mon Post-Vax 2 FU	6 mon Post-Vax 2 FU	1 yr Post-Vax 2 FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8±2	21±3	29±3	56±3	63±2	86±3	238±10	421±10		
Collect informed consent	X											
Assess inclusion/exclusion criteria compliance	X	X (review)										
Collect demographic and medical history	X	X (update)										
12-lead ECG	X	X [g]	X			X	X					
Perform clinical assessment (includes 15 mL blood draw; urine collection at Visit 0) [a]	X	X				X						
Record (concomitant) medication [j]	X	X	X	X	X	X	X	X	X [l]	X [l]	X [l]	X [l]
Perform urine pregnancy test for WOCBP	X	X				X						
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]										
Allocation to IMP		X										
IMP injection and assess acute reactions for ≥30 minutes after IMP injection		X				X						
Measure oral body temperature		X [c]	X	X	X	X	X	X				
Issue/train and collect e-diary		Issue/train					Collect				Collect	

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax 1 (except IMP injection)	1 wk Post-Vax 1 FU	3 wk Post-Vax 1 FU	1 mon Post-Vax 1 FU	Pre-Vax 2 (except IMP injection)	1 wk Post-Vax 2 FU	1 mon Post-Vax 2 FU	6 mon Post-Vax 2 FU	1 yr Post-Vax 2 FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8±2	21±3	29±3	56±3	63±2	86±3	238±10	421±10		
Subjects report daily reactogenicity (incl. oral body temperature) for 7 days after dosing using an e-diary		Start after Vax 1	End			Start after Vax 2	End				End	
Review e-diary data		Start	End			Start	End				End	
Record any AEs, AESIs, or SAEs since last visit [h]		X	X	X	X	X	X	X	X [f]	X [f]	X [f]	X [f]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (20 mL)		X	X	X	X	X	X	X	X	X	X	X [i]
Blood draws for T- and B-cell responses (Visit 5 50 mL; other visits 120 mL)		X	X		X [e]	X	X	X	X	X		X [i]
Blood draw for explorative research (25 mL) [k]				X								
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	=>	End	End	

Notes: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects. "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.

a At Visit 0: complete physical examination including body weight, vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]), blood and urine clinical laboratory tests; at Visit 1 and Visit 5: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from the Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e 5 mL blood will be taken from this sample for genetics (human leukocyte antigen typing).

f For any visits >1 month after each IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h For subjects rolling over from the trial BNT162-02 / C4591001 (NCT04368728), the recording will start from IMP allocation during Visit 1 (after eligibility is confirmed and the subject is withdrawn from the trial BNT162-02 / C4591001).

i If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤120 mL for T-cell and B-cell response assessments and one 20 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

j Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

k For consenting subjects.

l For any visits >1 month after each IMP injection, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 3: Schedule of events for Part A, Cohort 6; three doses of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [j]	Visit 8 [j]	Visit 9/ EOT	Early term.	COVID-19
Visit description	**Screening**	**Pre-Vax 1 [i]**	**1 wk Post-Vax 1 FU**	**Pre-Vax 2 [i]**	**1 wk Post-Vax 2 FU**	**1 mon Post-Vax 2 FU**	**6 mon Post-Vax 2 FU + Pre-Vax 3 [i]**	**1 wk Post-Vax 3 FU**	**1 mon Post-Vax 3 FU**	**1 yr Post-Vax 2 FU or 6 mon Post-Vax 3 FU**		***Ad hoc***
Day (relative to Visit 1 on Day 1)	**-7 to -1**	**1**	**8+2**	**21±3**	**29+3**	**51±3**	**203±10**			**386±10**		
Day (relative to Visit 6)								**8+3**	**29±3**	**180±10**		
Collect informed consent	X											
Assess inclusion/exclusion criteria compliance	X	X (review)										
Collect demographic and medical history	X	X (update)										
12-lead ECG	X	X [g]	X	X	X		X	X				
Perform clinical assessment (includes 15 mL blood draw and urine collection at Visit 0) [a]	X	X		X			X					
Record (concomitant) medication [k]	X	X	X	X	X	X	X [l]	X	X	X [l]	X [l]	X [l]
Perform urine pregnancy test for WOCBP	X	X		X			X					
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]										
Allocation to IMP		X										
IMP injection and assess acute reactions for ≥30 minutes after IMP injection		X		X			X					

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [j]	Visit 8 [j]	Visit 9/ EOT	Early term.	COVID-19
Visit description	Screening	Pre-Vax 1 [i]	1 wk Post-Vax 1 FU	Pre-Vax 2 [i]	1 wk Post-Vax 2 FU	1 mon Post-Vax 2 FU	6 mon Post-Vax 2 FU + Pre-Vax 3 [i]	1 wk Post-Vax 3 FU	1 mon Post-Vax 3 FU	1 yr Post-Vax 2 FU or 6 mon Post-Vax 3 FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8+2	21±3	29+3	51±3	203±10			386±10		
Day (relative to Visit 6)								8+3	29±3	180±10		
Measure oral body temperature		X [c]	X	X	X	X	X	X	X			
Issue/train and collect e-diary		Issue/ train			Collect		Issue/ train	Collect			Collect	
Subjects report daily reactogenicity (incl. oral body temperature) for 7 days after dosing using an e-diary		Start after Vax 1	End	Start after Vax 2	End		Start after Vax 3	End			End	
Review e-diary data		Start	End	Start	End		Start	End			End	
Record any AEs, AESIs, or SAEs since last visit		X	X	X	X	X	X [f]	X	X	X [f]	X [f]	X [f]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (20 mL)		X	X	X	X	X	X	X	X	X	X	X [h]
Blood draws for T- and B-cell responses (50 mL for Visit 3; other visits 120 mL)		X		X	X [e]	X	X	X	X	X		X [h]
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	=>	End	End	

Note: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

a At Visit 0: complete physical examination including body weight, vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]), blood and urine clinical laboratory tests; at Visit 1, Visit 3, and Visit 6: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e 5 mL blood will be taken from this sample for genetics (human leukocyte antigen typing).

f For any visits >1 month after each IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤120 mL for T-cell and B-cell response assessments and one 20 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

i Except IMP injection, i.e., all procedures should be performed before IMP administration. The third injection can be administered earlier than 6 months post-Dose 2 if supported by local legislation. For subjects who are not administered Dose 3, only the following activities will be done: record concomitant medications, AEs, and pregnancies, and take oral swabs and blood draws.

j Visit 7 and Visit 8 are planned visits only for subjects who receive the third vaccination.

k Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

l For any visits >1 month after each IMP injection, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 4: Schedule of events for Part B, Cohort 1 with one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects and Cohort 4 with one dose of BNT162b2 (B.1.617.2) in BNT162b2-experienced subjects

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	1 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8±2	29±3	180±10	360±10		
Collect informed consent	X							
Assess inclusion/exclusion criteria compliance	X	X (review)						
Collect demographic and medical history	X	X (update)						
12-lead ECG	X	X [g]	X					
Perform clinical assessment (includes 15 mL blood draw and urine collection at Visit 0) [a]	X	X						
Record (concomitant) medication [i]	X	X	X	X	X [k]	X [k]	X [k]	X [k]
Perform urine pregnancy test for WOCBP	X	X						
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]						
Allocation to IMP		X						
IMP injection and assess acute reactions for ≥30 minutes after IMP injection		X						
Measure oral body temperature		X [c]	X	X				
Issue/train and collect e-diary or help to delete the application		Issue/train	Collect				Collect	
Subjects report daily reactogenicity (incl. oral body temperature) for 7 days after dosing using an e-diary		Start after Vax	End				End	
Review e-diary data		Start	End				End	
Record any AEs, AESIs, or SAEs since last visit [h]		X	X	X	X [e]	X [e]	X [e]	X [e]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	1 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8+2	29±3	180±10	360±10		
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (20 mL) [f]		X	X	X	X	X	X	X [j]
Record pregnancies		Start	=>	=>	=>	End	End	

Notes: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects. "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.

a At Visit 0: complete physical examination including body weight, vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]), blood and urine clinical laboratory tests; at Visit 1: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e For any visits >1 month after each IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

f Serum samples will be stored and may be analyzed retrospectively for additional clinical parameters (troponin, cytokine).

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h The recording will start from IMP allocation during Visit 1 (after eligibility is confirmed and the subject is withdrawn from the trial BNT162-02 / C4591001 [NCT04368728]).

i Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

j If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be one 20 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

k For any visits >1 month after each IMP injection, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; SAE = serious AE;

SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 5: Schedule of events for Part B, Cohort 6; three doses of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [i]	Visit 8 [i]	Visit 9/ EOT	Early term.	COVID-19
Visit description	**Screening**	**Pre-Vax 1 [h]**	**1 wk Post-Vax 1 FU**	**Pre-Vax 2 [h]**	**1 wk Post-Vax 2 FU**	**1 mon Post-Vax 2 FU**	**6 mon Post-Vax 2 FU & Pre-Vax 3 [h]**	**1 wk Post-Vax 3 FU**	**1 mon Post-Vax 3 FU**	**1 yr Post-Vax 2 FU [m] or 6 mon Post-Vax 3 FU**		***Ad hoc***
Days relative to last dose	**-7 to -1**	**1**	**8+2**	**21±3**	**8+2**	**29±3**	**182±10**			**365±10**		
Day (relative to Visit 6)								**8+2**	**29±3**	**180±10**		
Collect informed consent	X											
Assess inclusion/exclusion criteria compliance	X	X (review)										
Collect demographic and medical history	X	X (update)										
12-lead ECG	X	X [g]	X	X	X		X	X				
Perform clinical assessment (includes 15 mL blood draw and urine collection at Visit 0) [a]	X	X		X			X					
Record (concomitant) medication [j]	X	X	X	X	X	X	X [o]	X	X	X [o]	X [o]	X [o]
Perform urine pregnancy test for WOCBP	X	X		X			X					
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]										
Allocation to IMP		X										
IMP injection and assess acute reactions for ≥30 minutes after		X		X			X					

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [i]	Visit 8 [i]	Visit 9/ EOT	Early term.	COVID-19
Visit description	**Screening**	**Pre-Vax 1 [h]**	**1 wk Post-Vax 1 FU**	**Pre-Vax 2 [h]**	**1 wk Post-Vax 2 FU**	**1 mon Post-Vax 2 FU**	**6 mon Post-Vax 2 FU & Pre-Vax 3 [h]**	**1 wk Post-Vax 3 FU**	**1 mon Post-Vax 3 FU**	**1 yr Post-Vax 2 FU [m] or 6 mon Post-Vax 3 FU**		***Ad hoc***
Days relative to last dose	**-7 to -1**	**1**	**8+2**	**21±3**	**8+2**	**29±3**	**182±10**			**365±10**		
Day (relative to Visit 6)								**8+2**	**29±3**	**180±10**		
IMP injection												
Measure oral body temperature		X [c]	X	X	X	X	X	X	X			
Issue/train and collect e-diary		Issue/ train			Collect		Issue/ train	Collect			Collect	
Subjects report daily reactogenicity using (incl. oral body temperature) for 7 day after each dose using an e-diary		Start after Vax 1	End	Start after Vax 2	End		Start after Vax 3	End			End	
Review e-diary data		Start	End	Start	End		Start	End			End	
Record any AEs, AESIs, or SAEs since last visit		X	X	X	X	X	X [e]	X	X	X [e]	X [e]	X [e]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (20 mL) [f]		X	X	X	X	X	X	X	X	X	X	X [l]

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [i]	Visit 8 [i]	Visit 9/ EOT	Early term.	COVID-19
Visit description	Screening	Pre-Vax 1 [h]	1 wk Post-Vax 1 FU	Pre-Vax 2 [h]	1 wk Post-Vax 2 FU	1 mon Post-Vax 2 FU	6 mon Post-Vax 2 FU & Pre-Vax 3 [h]	1 wk Post-Vax 3 FU	1 mon Post-Vax 3 FU	1 yr Post-Vax 2 FU [m] or 6 mon Post-Vax 3 FU		*Ad hoc*
Days relative to last dose	-7 to -1	1	8+2	21±3	8+2	29±3	182±10			365±10		
Day (relative to Visit 6)								8+2	29±3	180±10		
Blood draws for T- and B-cell responses (50 mL for Visit 3; other visits 120 mL) [n]		X		X	X [k]	X	X	X	X	X		X [l]
Record pregnancies		Start	=>	=>	=>	=>	=>	=>	=>	End	End	

Note: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

a At Visit 0: complete physical examination including body weight, vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]), blood and urine clinical laboratory tests; at Visit 1, Visit 3, and Visit 6: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e For any visits >1 month after each IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

f Blood samples will be stored and may be analyzed retrospectively for additional clinical parameters (troponin, cytokine).

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h Except IMP injection, i.e., all procedures should be performed before IMP administration. The third injection can be administered earlier than 6 months post-Dose 2 if supported by local legislation. For subjects who are not administered Dose 3, only the following activities will be done: record concomitant medications, AEs, and pregnancies, and take oral swabs and blood draws.

i Visit 7 and Visit 8 are planned visits only for subjects who receive the third vaccination.

j Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response at the early termination visit.

k 5 mL blood will be taken from this sample for genetics (human leukocyte antigen typing).

l If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤120 mL for T-cell and B-cell response assessments and one 20 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

m One-year FU (386±10 days) will only apply for subjects who for any reason do not receive the third IMP injection.

n ~15 subjects at preselected sites in Part B will be evaluated in terms of cell-mediated immunity.

o For any visits >1 month after each IMP injection, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 6: Schedule of events for Part C, Cohorts 7 and 8; one dose of BNT162b2 (B.1.1.529) or BNT162b2 in subjects who received two or three doses of any COVID-19 RNA-based vaccine prior to a SARS-CoV-2 infection from January 2022 onwards

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	1 mon Post-Vax FU	3 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8±2	29±3	85±5	180±10	360±10		
Collect informed consent	X								
Assess inclusion/exclusion criteria compliance	X	X (review)							
Collect demographic and medical history	X	X (update)							
12-lead ECG	X	X [g]	X						
Perform physical examination (incl. body weight) and vital signs [a]	X	X							
Blood (15 mL) and urine collection for clinical assessments	X								
Record (concomitant) medication [l]	X	X	X	X	X [m]	X [m]	X [m]	X [m]	X [m]
Perform urine pregnancy test for WOCBP	X	X							
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]							
Randomization		X							
IMP injection and assess acute reactions for ≥30 minutes after IMP injection		X							
Measure oral body temperature		X [c]	X	X					
Issue/train and collect e-diary		Issue/train	Collect					Collect	

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6/ EOT	Early termination	COVID-19
Visit description	Screening	Pre-Vax (except IMP injection)	1 wk Post-Vax FU	1 mon Post-Vax FU	3 mon Post-Vax FU	6 mon Post-Vax FU	1 yr Post-Vax FU		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8+2	29±3	85±5	180±10	360±10		
Subjects report daily reactogenicity (incl. oral body temperature) for 7 days after dosing using an e-diary		Start after Vax	End						
Review e-diary data		Start	End						
Record any AEs, AESIs, or SAEs since last visit [h]		X	X	X	X [e]	X [e]	X [e]	X [e]	X [e]
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X	X	X
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (30 mL) [f]		X	X	X	X	X	X	X	X [j]
SARS-CoV-2 N-binding antibodies assessment (5 mL) [n]	X								
Blood draws for T- and B-cell responses (135 mL) [i]		X	X	X	X	X	X		X [j]
Blood draw for HLA		X [k]							
Record pregnancies		Start	=>	=>	=>	=>	End	End	

Note: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

a At Visit 0: complete physical examination including body weight and vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]); at Visit 1: symptom-orientated physical examination.

b If the result from an oral swab for NAAT-based SARS-CoV-2 is not older than 24 h at the planned time of IMP injection, availability of the test result from Visit 1 on Day 1 is optional.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e For any visits >1 month after each IMP injection, only IMP-related AEs, trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

f Blood samples will be stored and may be analyzed retrospectively for additional clinical parameters (troponin, cytokine).

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h prior to the planned IMP dose.

h The recording will start from IMP allocation during Visit 1 (after eligibility is confirmed).

i Biomarker/PBMC subgroup (~25 subjects in each cohort).

j If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤135 mL for T-cell and B-cell response assessments and one 30 mL sample for serological testing for SARS-CoV-2 N-binding antibodies and humoral immunogenicity assessments.

k A 5 mL blood sample will be taken for genetics (HLA typing) within the biomarker/PBMC subgroup (~25 subjects in each cohort).

l Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

m For any visits >1 month after each IMP injection, only prohibited medications should be recorded.

n SARS-CoV-2 N-binding antibodies assessment only to be done by local lab when no historic NAAT result is available to prove prior SARS-CoV-2 infection.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; e-diary = electronic diary or an equivalent application; EOT = end of trial; FU = follow-up; h = hour(s); HLA = human leukocyte antigen; IMP = investigational medicinal product; mon = month(s); N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; PBMC = peripheral blood mononuclear cell; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; Vax = vaccination (i.e., IMP injection); wk = week(s); WOCBP = women of childbearing potential; yr = year(s).

Table 7: Schedule of events for Part C, Cohort 9; no vaccination (within 3-month period) in subjects who received two or three doses of any COVID-19 RNA-based vaccine prior to a SARS-CoV-2 infection from January 2022 onwards

Activity	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4/ EOT	Early termination	COVID-19
Visit description	Screening	Day 1	1 wk	1 mon	3 mon		*Ad hoc*
Day (relative to Visit 1 on Day 1)	-7 to -1	1	8±2	29±3	85±5		
Collect informed consent	X						
Assess inclusion/exclusion criteria compliance	X	X (review)					
Collect demographic and medical history	X	X (update)					
12-lead ECG	X	X [g]					
Perform physical examination (incl. body weight) and vital signs [a]	X	X					
Blood (15 mL) and urine collection for clinical assessments	X						
Record (concomitant) medication [e]	X	X	X	X	X [m]	X [m]	X [m]
Perform urine pregnancy test for WOCBP	X	X					
Oral swabs for NAAT-based SARS-CoV-2 for screening	X	X [b]					
Randomization		X					
Measure oral body temperature		X [c]	X	X			
Oral swabs for NAAT-based SARS-CoV-2 for surveillance			X	X	X	X	X
Oral swabs for SARS-CoV-2 sequencing [d]	X	X	X	X	X	X	X
Record any AEs, AESIs, or SAEs since last visit [h]		X	X	X	X [l]	X [l]	X [l]
SARS-CoV-2 N-binding antibodies assessment (5 mL) [b]	X						
Blood draws for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity assessments (30 mL) [f]		X	X	X	X		
Blood draws for T- and B-cell responses (135 mL) [i]		X	X	X	X		X [j]
Blood draw for HLA		X [k]					
Record pregnancies		Start	=>	=>	End	End	

Note: The SoA allows for *ad hoc* visits for SARS-CoV-2 testing for symptomatic or asymptomatic subjects.

a At Visit 0: complete physical examination including body weight and vital signs (oral body temperature, heart rate, blood pressure [systolic and diastolic]); at Visit 1: symptom-orientated physical examination.

b SARS-CoV-2 N-binding antibodies assessment only to be done by local lab when no historic NAAT result is available to prove prior SARS-CoV-2 infection.

c Issue thermometer or other measuring device for subjects to measure their oral body temperature each day and if they experience flu-like symptoms.

d All swabs will be analyzed, even if no COVID-19 symptoms are shown.

e Subjects who receive non-trial SARS-CoV-2 vaccinations will be discontinued, resulting in an early termination visit. For subjects who receive non-trial SARS-CoV-2 vaccinations, there will be no blood sampling for humoral immunogenicity or T-cell and B-cell response assessments at the early termination visit.

f Blood samples will be stored and may be analyzed retrospectively for additional clinical parameters (troponin, cytokine).

g The 12-lead ECG at Visit 1 can be skipped if the 12-lead ECG from Visit 0 was performed within 24 h of Visit 1.

h The recording will start during Visit 1 (after eligibility is confirmed).

i Biomarker/PBMC subgroup (~25 subjects).

j If an *ad hoc* visit occurs in combination with a planned visit, blood sampling will only be ≤135 mL for T-cell and B-cell response assessments.

k A 5 mL blood sample will be taken for genetics (HLA typing) within the biomarker/PBMC subgroup (~25 subjects).

l For any visits >1 month after Visit 1, only trial procedure-related AEs, AESIs, any SAEs. In addition, all AEs linked to confirmed COVID-19 cases will be recorded.

m For any visits >1 month after Visit 1, only prohibited medications should be recorded.

Abbreviations: AE = adverse event; AESI = AE of special interest; ECG = electrocardiogram; EOT = end of trial; h = hour(s); mon = month(s); HLA = human leukocyte antigen; N-binding = nucleocapsid-binding; NAAT = nucleic acid amplification-based test; PBMC = peripheral blood mononuclear cell; SAE = serious AE; SARS-CoV-2 = the virus leading to COVID-19; SoA = schedule of activities; wk = week(s); WOCBP = women of childbearing potential.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS/TERMS

Abbreviation	Explanation
~	Approximately
AE	Adverse Event
AESI	Adverse Event of Special Interest
BNT162b2 (B.1.1.529)	Monovalent vaccine specific for SARS-CoV-2 Omicron subvariant BA.1, i.e., B.1.1.529.1
BNT162b2 (B.1.1.7)	Monovalent vaccine specific for SARS-CoV-2 Alpha variant
BNT162b2 (B1.617.2)	Monovalent vaccine specific for SARS-CoV-2 Delta variant
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CD	Cluster of differentiation, e.g., CD4, CD8, glycoproteins that serves as a co-receptor for T-cell receptors
CDC	US Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Contract research organization
ddPCR	Digital drop polymerase chain reaction
DNA	Deoxyribonucleic acid
e-diary(ies)	Electronic diary(ies)
ECG	Electrocardiogram
EDC	Electronic Data Capture (system)
ELISA	Enzyme-linked immunosorbent assay
Enrolled	Subjects are enrolled if they have given informed consent by signing and dating the informed consent form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
h	Hour(s)
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IEC/IRB	Independent Ethics Committee/Independent Review Board
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
ISF	Investigator's Site File
LNP	Lipid nanoparticle
mRNA	Messenger RNA

Abbreviation	Explanation
NAAT	Nucleic Acid Amplification-based Test
NT	Neutralizing titer
ORF	Open reading frame
PCR	Polymerase chain reaction
PT	Preferred Term
RBD	Receptor Binding Domain
RNA	Ribonucleic acid
RNA-LNP	RNA-lipid nanoparticle
S protein	SARS-CoV-2 spike protein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2, the virus leading to COVID-19
SR	Seroresponse
SoA	Schedule of Activities
SRC	Safety Review Committee
Subject(s)	Otherwise called trial participant(s) or trial subject(s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
Trial subjects	Otherwise called trial participant(s) or subject(s)
US(A)	United States (of America)
VOC	Variant(s) Of Concern
WOCBP	Women Of Childbearing Potential
WHO	World Health Organization

NOTES FOR THE READER

When the term “must” is used, the action/item is always mandatory. Non-compliance with this instruction constitutes a protocol deviation. When the term “should” is used, the action/item is recommended but not mandatory. Non-compliance with this instruction does not constitute a protocol deviation.

The BNT162b platform member BNT162b2 is also referred to as Comirnaty or Pfizer-BioNTech COVID-19 vaccine.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of the disease

Considering the increase in the number of variants of concern (VOC), as well as the number of new mutations in the S protein in these variants, resulting in a lower efficacy of some of the current vaccines, there is an urgent need for the development of variant-specific prophylactic vaccines targeting novel neutralizing epitopes.

Since the SARS-CoV-2 viral sequence was first determined, it continues to evolve in humans (through recombination, suboptimal immune control, etc.), resulting in a variety of SARS-CoV-2 variant strains, including VOCs and variants of interest (VOI). An overview of the key SARS-CoV-2 variant strains tracked by the WHO as VOCs and VOIs is provided in Table 8.

Table 8: SARS-CoV-2 variant strains tracked by the WHO

Variant of concern or interest	WHO label	Pango lineage	GISAID clade / lineage	Nextstrain clade
VOC	Alpha	B.1.1.7	GRY	20I (V1)
VOC	Beta	B.1.351	GH/501Y.V2	20H (V2)
VOC	Gamma	P.1	GR/501Y.V3	20J (V3)
VOC	Delta	B.1.617.2	G/478K.V1	21A
VOC	Omicron	B.1.1.529	GRA/484A	21K, 21L 21M, 22A, 22B, 22C
VOI	Lambda	C.37	GR/452Q.V1	21G
VOI	Mu	B.1.621	GH	21H

VOC = A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: Increase in transmissibility or detrimental change in COVID-19 epidemiology; or increase in virulence or change in clinical disease presentation; or Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

VOI = A SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

Abbreviations: GISAID = Global Initiative on Sharing Avian Influenza Data; VOC = variant of concern; VOI = variant of interest; WHO = World Health Organization.

Source: WHO webpage https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/, accessed 26 JUL 2022.

In addition to mutations, additions or deletions near the receptor binding domain (RBD) of the S protein, which is responsible for attaching to the human angiotensin cell receptor 2 and resulting in host infection, and/or other key changes (e.g., deletions) circumventing antibody detection (e.g., around Y144 in the N terminal domain) are increasingly recognized. More specifically, newer mutations of the S protein not only provide the virus with greater transmissibility and affinity/avidity for cellular attachment but may also render the variant strains less susceptible to virus neutralization, thus allowing increases in overall infection rates.

Because successful prophylactic COVID-19 vaccines are designed to primarily work by inducing neutralizing antibodies, an increased sense of urgency has again risen to anticipate and combat SARS-CoV-2 evolution through numerous tactics. These tactics include characterization of evolving variant sequences of SARS-CoV-2 with respect to vaccine-induced immune response breadth and other key functional immune response parameters.

2.1.2 Introduction to the trial treatment

The development of an RNA-based vaccine encoding a viral antigen that is translated to protein by the vaccinated organism to induce a protective immune response provides significant advantages over more conventional vaccine approaches. RNA-based vaccines have some advantages over DNA, protein subunit, inactivated or live attenuated virus vaccines. First, safety: The RNA is degraded by normal cellular processes, is non-infectious, non-integrating, and poses no risk of insertional mutagenesis. Second, efficiency: Delivery of RNA results in transient translation that can be controlled by modifications in the untranslated regions, cap, poly(A) tail, and coding sequences. These modifications can make the RNA more stable and highly translatable. Efficient *in vivo* delivery can be achieved by formulating RNA into carrier LNPs that promote rapid uptake and enable RNA expression in the cytoplasm. Third, production: Manufacturing of conventional protein subunits, inactivated virus or replication-defective virus vaccines is time consuming and involves multiple pieces of manufacturing equipment. Protein vaccine production and purification require optimization for each mammalian or insect cell culture system. In addition, each production system introduces the potential for improper folding and altered glycosylation patterns of the protein, particularly when produced in insect cells. In contrast, RNA-based vaccine production does not require individualized cell culture systems and unique purification systems for each vaccine antigen. Uniformly optimized transcription and purification techniques can be used to produce any RNA sequence. Furthermore, because RNA sequences are processed *in vivo* as would occur during viral infection, glycosylation patterns of the antigens are similar to those seen after natural infection.

As demonstrated by the SARS-CoV-2 RNA-LNP-based vaccine BNT162b2, LNP-formulated RNA-based vaccines provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2 (Mulligan et al. 2020; Rauch et al. 2018; Sahin et al. 2014; Walsh et al. 2020). BNT162b2 (Comirnaty, Pfizer-BioNTech COVID-19 vaccine) received emergency use authorization or conditional/full marketing authorization in numerous countries worldwide for the prevention

of COVID-19. Administration of BNT162b2 to millions of individuals in the post-authorization setting has confirmed the benefit-risk profile seen in clinical trials.

The BNT162b2-based vaccines against variant strains, BNT162b2 (B.1.1.7), BNT162b2 (B.1.351), BNT162b2 (B.1.617.2), BNT162b2 (B.1.1.7 + B.1.617.2), and BNT162b2 (B.1.1.529), have the same LNP formulation and RNA components as BNT162b2 except that the RNAs differ slightly in their encoded ORF. Each RNA component leads to expression of S proteins with the amino acid changes seen in the respective SARS-CoV-2 strains B.1.1.7, B.1.351, B.1.617.2, and B.1.1.529. For further details, see Table 8.

The BNT162b2-based vaccines against variant strains are named by combining the parent vaccine name “BNT162b2” with the name of the SARS-CoV-2 strain from which the S protein encoded by the RNA originates, e.g., BNT162b2 (B.1.1.7) has an RNA that encodes the SARS-CoV-2 strain B.1.1.7 S protein.

For further details on the BNT162 family of RNA-based vaccines, see the current BNT162 investigator’s brochure (IB).

2.2 Trial rationale

Efficacy and immunogenicity data from clinical studies have demonstrated that the BNT162b2 (30 µg) two-dose regimen induces a strong immune response and high vaccine efficacy and protection against COVID-19 across a spectrum of individuals ≥12 years of age: those with or without prior exposure to SARS-CoV-2 and those in higher risk categories based on age, race, ethnicity, and/or comorbidity. The sponsor has accumulated significant experience on the safety of BNT162b2 in the BNT162-02 / C4591001 trial (NCT04368728), which was the basis of the BNT162b2 authorization for emergency use and the conditional/full marketing authorizations given in numerous countries worldwide for the prevention of COVID-19 (Feldman et al. 2019; Polack et al. 2020). Administration of BNT162b2 to millions of individuals in the post-authorization setting has confirmed its favorable benefit-risk profile. For details, see the current BNT162 IB.

As more data about COVID-19 continue to accrue, the potential duration of protection, after SARS-CoV-2 natural infection and by vaccination, remains unknown. Further, although SARS-CoV-2 presents a mutation rate lower than that of other RNA viruses, it continues to evolve, generating new variants that arouse concern due to increased transmissibility or anticipated reduction in neutralization by antibodies generated during previous infection or vaccination (Dan et al. 2021, Abdool Karim and de Oliveira 2021). These variants include a variant with high prevalence globally, B.1.1.7 (known as Alpha) and further variants including B.1.351 (known as Beta), P.1 (known as Gamma), B.1.617.1 and B.1.617.2 (the latter known as Delta), and B.1.1.529 (Omicron) and its subvariants B.1.1.529.1 (BA.1) and B.1.1.529.5 (BA.5). BNT162b2 induces a robust immune response against SARS-CoV-2, including both humoral and multifunctional T-cell responses, and emerging *in vitro* cross-neutralization data and vaccine effectiveness data confirm its effectiveness against COVID-19 in populations with high prevalence of those variants (Liu et al. 2021, Abu-Raddad et al. 2021). If evidence emerges that particular variants do appear to influence vaccine effectiveness and prevail in different countries, it will be

beneficial to be prepared to implement BNT162b2-based vaccines against variant strains able to boost memory responses against conserved SARS-CoV-2 epitopes while concurrently targeting novel neutralizing epitopes of escaping circulating strains.

On 26 November 2021, the WHO designated the SARS-CoV-2 virus variant B.1.1.529, named Omicron, a VOC (WHO webpage "Update on Omicron"). Initially detected in South Africa, this variant rapidly distributed across the world. The SARS-CoV-2 Omicron variant is known to have a concerning number of mutations (more than 30) in the spike protein that are associated with reduced neutralization by convalescent and vaccinee sera (Schmidt et al. 2021). The original Omicron strain has since been renamed B.1.1.529.1 (known as Omicron BA.1), with the Omicron lineage having expanded into multiple sublineages.

Reflective of the SARS-CoV-2 Omicron (BA.1) variant's decreased sensitivity to neutralizing antibodies elicited by previous viral variants or vaccines based on those, incidence of SARS-CoV-2 infection peaked in January 2022 (WHO webpage "COVID-19 Weekly Epidemiological Update"). In the US, prevalence of the SARS-CoV-2 Omicron variant reached 89.2 to 98.8% during that time frame (CDC webpage "COVID Data Tracker – Variant Proportions", accessed 09 February 2022). Meanwhile it was confirmed that two-dose vaccination schedules with the available vaccines based on the SARS-CoV-2 wild-type strain provide lower protection against infection with the SARS-CoV-2 Omicron variant(s) compared to the previous variants or the wild-type strain. A third dose of an RNA-based vaccine appears to temporarily increase protection (UK Health Security Agency 2022), but reinfection rates with the SARS-CoV-2 Omicron variant(s) are likely higher than with the SARS-CoV-2 Delta variant (Ferguson et al. 2021).

As of 04 August 2022, no Omicron-specific variant vaccines were authorized, and there were no vaccination recommendations for subjects who experienced a breakthrough infection with the SARS-CoV-2 Omicron variant. On 31 August 2022, the US FDA authorized the bivalent vaccine, BNT162b2 and BNT162b2 Omicron (B.1.1.529 sub-lineage BA.4/5), for a booster vaccination in individuals 12 years of age and older.

On 18 April 2023, the US FDA amended the BNT162b2 emergency use authorization to simplify the vaccination schedule for most individuals, including that most unvaccinated individuals may receive a single dose of a variant-modified vaccine (rather than two doses). The effectiveness of a single dose was supported by observational data from England on the effectiveness of one dose of monovalent BNT162b2, and that, among individuals 12 to 17 years of age who had received only one dose of BNT162b2, those who had evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those with no evidence of previous infection.

To combat these evolving SARS-CoV-2 strains, the sponsor has initiated clinical investigation of BNT162b2-based vaccines against variant strains as monovalent vaccines and as a multivalent vaccine (i.e., a combination of two monovalent vaccines). These BNT162b2-based vaccines are named "BNT162b2" plus the variant strain targeted by the RNA-encoded ORF, e.g., BNT162b2 (B.1.1.7) has an RNA that encodes the SARS-CoV-2 strain B.1.1.7 spike (S) protein. The BNT162b2-based vaccines against variant strains have the same LNP formulation and RNA components as BNT162b2 except that the

RNAs differ slightly in their encoded ORF. Each RNA component leads to expression of S proteins with the amino acid changes seen in the SARS-CoV-2 strains B.1.1.7, B.1.351, B.1.617.2, and B.1.1.529.1, respectively. For further details, see Table 8.

The safety and immunogenicity of a monovalent BNT162b2-based vaccine, BNT162b2 (B.1.351), is under evaluation in the BNT162-02 / C4591001 trial. This approach will allow an evaluation of immunogenicity of the monovalent vaccine BNT162b2 (B.1.351) against the reference ancestral SARS-CoV-2 strain (Wuhan-Hu-1/USA-WA1) and the selected B.1.351 variant strain, using immunobridging to the immune response after two doses of BNT162b2 as a primary vaccination series.

This trial (BNT162-17) aims to investigate the safety and immunogenicity of the BNT162b2-based vaccines against variant strains BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529) *:

- BNT162b2 (B.1.1.7 + B.1.617.2), a multivalent vaccine comprising a 1:1 mixture of BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2).
- BNT162b2 (B.1.1.7), a monovalent vaccine that expresses the full length SARS-CoV-2 Alpha S protein bearing mutations preserving neutralization-sensitive sites.
- BNT162b2 (B.1.617.2), a monovalent vaccine that expresses the full length SARS-CoV-2 Delta S protein bearing mutations preserving neutralization-sensitive sites.
- BNT162b2 (B.1.1.529), a monovalent vaccine that expresses the full length SARS-CoV-2 Omicron S protein bearing mutations preserving neutralization-sensitive sites.

* Note: In this protocol, “B.1.1.529” refers to variant B.1.1.529.1 (known as Omicron BA.1) unless stated otherwise.

The two viral strains included in the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) are selected to favor cross-reactive antibody responses and to also include dominant strains in terms of global prevalence at the time of this trial. The thorough clinical investigation of BNT162b2 (B.1.1.7 + B.1.617.2) in Parts A and B will support preparedness for the case that a multivalent BNT162b2-based vaccine against COVID-19 is needed to allow broad coverage against circulating strains at global level and to avoid the complexity of handling multiple monovalent vaccines in parallel.

To support the clinical evaluation of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), the monovalent BNT162b2 vaccines BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) will also be individually investigated clinically in Parts A and B. Data from Part B of the trial will be used to evaluate the immunogenicity of one dose of variant-modified BNT162b2 (multivalent B.1.1.7 + B.1.617.2) in vaccine-naïve seropositive individuals. To supplement real world evidence that a single dose is effective, immunogenicity results from this analysis will fill the evidence gap for use of the single dose of BNT162b2 in individuals 12 years of age and older who have not been previously vaccinated with a COVID-19 vaccine. The Alpha (B.1.1.7) and Delta (B.1.617.2) BNT162b2 variants are no longer epidemiologically relevant. Experience with other

BNT162b2 variants is relevant because all BNT162b2 variants have the same LNP formulation and RNA components except that the RNAs differ slightly in their encoded ORF and the available data has demonstrated that immune response(s) to vaccine-encoded strain(s) are similar. To provide a robust comparison, as well as assessing NTs against Alpha and Delta, NTs against the more contemporaneous B.1.1.529.5 (Omicron BA.5) will also be assessed. Finally, to bridge to the efficacy demonstrated with the original BNT162b2 vaccine, although not encoded by the investigational vaccine in this trial, NTs against the reference strain will be compared between vaccine-naïve seropositive individuals after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) and vaccine-naïve seronegative individuals after two doses of original BNT162b2 (from trial BNT16202 / C4591001; NCT04368728).

Part C will investigate if administration of one dose of either BNT162b2 (B.1.1.529) or BNT162b2 after previous infection with the SARS-CoV-2 Omicron variant will elicit an immune response against the SARS-CoV-2 Omicron variant in subjects who have been vaccinated with any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with a SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections). In addition, Part C (Cohort 9) will evaluate the immune response reached after infection with the SARS-CoV-2 Omicron variant.

2.3 Benefit/risk assessment

Typically, healthy trial volunteers participating in clinical trials can expect no direct health benefits; however, subjects in this trial may be offered doses of BNT162b2, for which extensive clinical and post-authorization data have been collected. Trial subjects may also receive BNT162b2-based monovalent or multivalent vaccines, or different schedules of BNT162b2, for which efficacy and safety may have not been demonstrated yet (see Section 2.3.2). This trial is also designed to minimize the risks to trial subjects while maximizing the potential value of knowledge it is designed to provide.

For further information on the expected benefits and risks for injection with BNT162b2, including the reference safety information, see the current BNT162 IB.

2.3.1 Risk assessment

General risks of vaccines:

- The vaccines used in this trial may have side effects, some of which are listed below. Note that these lists do not include all individual side effects ever seen with these vaccines. The more serious or common side effects with a known or possible relationship to the vaccine are listed.
- Rarely, a vaccine may cause allergic reactions such as rash or difficulty breathing. Allergic reactions may be life-threatening. All trial subjects will be queried for a history of reactions to vaccines and this vaccine’s excipients.

- Side effects seen from giving a vaccine by injection into the muscle include local reactions at the injection site such as redness, itchiness, tenderness, pain, and swelling.
- All vaccines can cause fever, chills, rash, aches and pains in the muscles or joints, nausea and loss of appetite, headache, dizziness, and feeling tired. Most people are still able to do their planned activities after getting a vaccine. Rarely, people experience side effects that limit their normal activities or make them go to their doctor.
- Very rarely, a vaccine may cause an autoimmune disease in a person or may make an autoimmune disease worse.

Risks related to BNT162b2, BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529):

- BNT162b2 has received temporary authorization for emergency use, conditional marketing authorization approval, and/or full authorization in more than 100 countries globally. Full approval of a two-dose regimen of BNT162b2 30 µg in individuals ≥16 years of age was granted by the US FDA on 23 AUG 2021. The safety profile of BNT162b2 based on available data in the ongoing Phase II/III trial BNT162-02 / C4591001 is favorable. The US FDA has also authorized emergency use of BNT162b2 as first booster dose and second booster dose in various populations. Since its first marketing authorization in December 2020, BNT162b2 has been administered to hundreds of millions of individuals worldwide.
- The safety of BNT162b2 after two doses was evaluated in subjects 5 years of age and older. The trial BNT162-02 / C4591001 enrolled ~46,000 subjects 12 years of age or older. The trial BNT162-07 / C4591007 (NCT048166443) enrolled ~4,500 (data cutoff date of 29 OCT 2021) subjects 5 through less than 12 years of age. Additionally, 306 existing Phase III subjects at least 18 through 55 years of age in the trial BNT162-02 / C4591001 received a booster dose (third dose) of BNT162b2 ~6 months after the second dose (data cutoff date of 17 JUN 2021). The overall safety profile for the booster dose (third dose) was similar to that seen after two doses.

- The safety of BNT162b2 was evaluated in subjects 16 years of age and older after two doses. In the trial BNT162-02 / C4591001, a total of 22,026 subjects 16 years of age or older received at least one dose of BNT162b2 and a total of 22,021 subjects 16 years of age or older received placebo (as of the data cutoff date of 13 MAR 2021). The most frequent adverse reactions in subjects 16 years of age and older that received two doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A lower frequency of reactogenicity events was associated with greater age. The safety profile in 545 subjects receiving BNT162b2, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population. The trial BNT162-02 / C4591001 also included 200 subjects with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the subjects receiving BNT162b2 (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.
- The safety of BNT162b2 was evaluated in subjects 18 years of age and older after booster dose (third dose). A subset from trial BNT162-02 / C4591001 Phase II/III subjects of 306 adults at least 18 through 55 years of age who completed the primary BNT162b2 two-dose course, received a booster dose (third dose) of BNT162b2 ~6 months (range of 4.8 to 8.0 months) after receiving Dose 2. The most frequent adverse reactions in subjects 18 through 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).
- The most common adverse reactions (seen ≥1/10) were headache, diarrhea, arthralgia, myalgia, injection site pain, fatigue, chills, pyrexia, and injection site swelling, and (seen ≥1/100 to <1/10) were vomiting, nausea, and injection site redness.
- Special warnings and precautions for use have been defined for anaphylaxis, myocarditis and pericarditis, acute severe febrile illness, coagulation disorders, for immunocompromised individuals, and for stress-related responses associated with the process of vaccination itself. For details see the current BNT162 IB.
- Hypersensitivity to the BNT162b2 active substance and/or to any of the excipients is a contraindication.
- Although not seen to date, it cannot yet be ruled out that the trial IMPs could make a later COVID-19 illness more severe.
- Since BNT162b2 and the vaccines BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529) use the same RNA platform and LNP formulation, they are expected to share the same formulation-based risks.

- BNT162b2 and the vaccines BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529) differ slightly in the RNA-encoded ORF. Despite this difference, the safety and immunogenicity of the vaccine variants is not anticipated to be any different than for the parent vaccine BNT162b2.

Risks associated with trial-specific procedures:

- There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site. To minimize this risk, only appropriately qualified personnel will draw blood.
- The volume of blood drawn at any visit is kept to the amounts required to support the objectives of this trial.

Mitigations for vaccine-related and trial risks:

- In general, the listed risks of IM injection can be managed using routine symptom-driven standard of care. Treatment of these events is dependent on the discretion of the investigators. As the parent vaccine BNT162b2 has been authorized for emergency use or been given conditional/full marketing authorization in numerous countries worldwide, and use since then has confirmed the favorable benefit-risk profile, procedures routine for monitoring Phase I trials are not planned.
- All trial-specific procedures will be performed by qualified trial site personnel.
- Trial subjects will be observed at the site for at least 30 minutes after each IMP injection.
- Equipment to treat anaphylaxis will be readily available.
- 12-lead electrocardiogram (ECG) will be recorded before and at 7 days after each IMP injection and at any time point if clinically indicated.
- Volunteers with any current or history of cardiovascular diseases, e.g., myocarditis, pericarditis, myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias, are specifically excluded from this trial.
- To minimize the risk to trial subjects, the Medical Monitor and the SRC will regularly review and evaluate the safety data including any emerging SAEs or AESIs. For details, see Section 10.1.5.
- Human reproductive safety data are limited for BNT162b2. Therefore, although human teratogenicity is not suspected based on the intended pharmacology of the compound, the use of contraception is required in this trial (see Section 10.4). For further details, see in the current BNT162 IB.

The risks and mitigations linked to the COVID-19 pandemic while participating in the trial include the following:

- The risk of becoming SARS-CoV-2 infected or unknowingly spreading the virus during participation in the trial; therefore, trial subjects will continue to be required to practice social distancing and infection prevention practices, i.e., to follow any local laws or guidance.
- Provision of site contact numbers for subjects to contact the trial site during their participation should they require guidance or experience symptoms suggestive of SARS-CoV-2 infection.
- If the subject reports symptoms of illness, e.g., enhanced respiratory disease or flu-like symptoms, the subject will be asked to return to the site for diagnostic measures. More specifically, respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 3 days, i.e., symptom kinetics that are inconsistent with SARS-CoV-2 RNA immunization, will trigger diagnostic measures, i.e., antigen and diagnostic nucleic acid SARS-CoV-2 testing.

2.3.2 Benefit assessment

The parent vaccine BNT162b2 has been authorized for emergency use or been given conditional/full marketing authorization in numerous countries worldwide. Since then, pharmacovigilance data after BNT162b2 administration to hundreds of millions of individuals worldwide has confirmed the favorable benefit-risk profile. Thus, subjects in this trial administered BNT162b2 will have access to vaccination with a vaccine proven to be safe and effective protection against COVID-19.

Although not yet proven in clinical trials, the BNT162b2 vaccine variants are also expected to provide a safe and effective protection against COVID-19, therefore subjects in this trial administered the BNT162b2-based vaccine variants are expected to have access to a safe and effective protection against COVID-19 caused by new variants of the SARS-CoV-2 variants.

Participation in this trial could also help the trial subject indirectly. The clinical laboratory tests, physical examinations, and other safety assessments performed while participating in this trial could uncover previously undiagnosed health problems. The trial subject will have access to real-time SARS-CoV-2 diagnostic testing. Also, by participating in this trial, trial subjects may better understand how vaccines can help protect against COVID-19.

2.3.3 Overall benefit/risk conclusion

Overall, based on all available data, the sponsor considers the benefit/risk ratio for this trial to be acceptable.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints - Part A

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), given as one or two booster doses to BNT162b2-experienced subjects, or as three doses to COVID-19 vaccine-naïve subjects. To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.1.7) given as one booster dose to BNT162b2-experienced subjects. * To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.617.2), given as one booster dose to BNT162b2-experienced subjects. * To describe the safety profile of BNT162b2, given as one booster dose to BNT162b2-experienced subjects. *	For each trial treatment, in subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after each dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary objectives (Immunogenicity)		
To describe the immune response after one, two, or three doses of BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2.	For BNT162b2-experienced subjects: • GMTs at each time point. • GMFR from before vaccination to each subsequent time point after vaccination. • Seroresponse (SR) in terms of NT at each post-vaccination time point.	• Reference and VOC specific NTs
Exploratory objectives		
To comprehensively describe B-cell responses after one, two, or three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), or one booster dose of the monovalent vaccine BNT162b2 (B.1.1.7), or one booster dose of BNT162b2 (B.1.617.2), at 30 µg.	<u>For a subset of subjects in Part A:</u> • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells

OBJECTIVES	ESTIMANDS	ENDPOINTS
To describe the T cell-mediated immune response after one, two, or three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), or one booster dose of the monovalent vaccine BNT162b2 (B.1.1.7), or one booster dose of BNT162b2 (B.1.617.2), at 30 µg.	For a subset of subjects in Part A: • CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and the B.1.1.7 and B.1.617.2 VOC.	• Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)
To evaluate the immune response over time to prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) and persistence of immune response in subjects with and without prior COVID-19 vaccination.	• GMC/GMT and GMFR at baseline and 1, 6, and 12 months after completion of vaccination. • Seroresponse for reference strain and B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	• For a subset of subjects, after any dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2, BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) vaccines, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data

* Note: "BNT162b2-experienced" is defined as subjects who have previously received two injections of 30 µg BNT162b2.

Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; RBD = receptor binding domain; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; S = spike protein; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

Objectives and endpoints – Part B

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) given as one booster dose to BNT162b2-experienced subjects *, or as three doses to COVID-19 vaccine-naïve subjects. To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.617.2) given as one booster dose to BNT162b2-experienced subjects *.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after each dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary objectives (Immunogenicity)		
BNT162b2-experienced subjects		
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of GMT.	• GMR of B.1.1.7 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • GMR of B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.617.2) after one dose of monovalent vaccine BNT162b2 (B.1.617.2) in terms of GMT.	• GMR of B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of SR.	• The difference in SRs to B.1.1.7 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • The difference in SRs to B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific SRs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Immunogenicity)		
BNT162b2-experienced subjects		
To demonstrate the non-inferiority of immune response against VOC (B.1.617.2) after one dose of monovalent vaccine BNT162b2 (B.1.617.2) in terms of SR.	• The difference in SRs to B.1.617.2 NT 1 month after one dose of BNT162b2 (B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific SRs
COVID-19 vaccine-naïve subjects		
To demonstrate the non-inferiority of immune response against reference strain after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response after two doses of original BNT162b2 in subjects without evidence of infection from the Phase III trial BNT162-02 / C4591001 in terms of GMT.	• GMR of reference strain NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the reference strain NT 1 month after two doses of BNT162b2 in subjects without evidence of infection.	• Reference strain NTs
To demonstrate the non-inferiority of immune response against reference strain after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response after two doses of original BNT162b2 in subjects without evidence of infection from the Phase III trial BNT162-02 / C4591001 in terms of SR.	• The difference in SRs to the reference strain NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the reference strain NT 1 month after two doses of BNT162b2 in subjects without evidence of infection.	• Reference strain NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of GMT.	• GMR of B.1.1.7 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2. • GMR of B.1.617.2 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	• Reference and VOC specific NTs
To demonstrate the non-inferiority of immune response against VOC (B.1.1.7 and B.1.617.2) after two doses of	• The difference in SRs to B.1.1.7 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to	• Reference and VOC specific SRs

OBJECTIVES	ESTIMANDS	ENDPOINTS
multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in terms of SR.	the reference strain NT 1 month after two doses of BNT162b2. • The difference in SRs to B.1.617.2 NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference strain NT 1 month after two doses of BNT162b2.	
Secondary objectives		
BNT162b2-experienced subjects		
To describe the immune response against the reference strain and VOCs after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) vs two doses of BNT162b2.	• GMTs and SRs of VOCs and reference strain NT 1 month after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) and Dose 2 of BNT162b2.	• Reference and VOC specific NTs
To describe the immune response against the reference strain and VOCs after one dose of monovalent vaccine BNT162b2 (B.1.617.2) vs two doses of BNT162b2.	• GMTs and SRs of VOCs and reference strain NT 1 month after one dose of BNT162b2 (B.1.617.2) and Dose 2 of BNT162b2.	• Reference and VOC specific NTs
COVID-19 vaccine-naïve subjects		
To describe the immune response against the reference strain and VOCs after three doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	• GMTs and SRs of VOCs and reference strain NT 1 month after Dose 2 and Dose 3 of BNT162b2 (B.1.1.7 + B.1.617.2).	• Reference and VOC specific NTs
To compare the immune response against VOCs 3 weeks after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response 1 month after one booster dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects without evidence of infection.	• GMTs and SRs of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection and 1 month after one booster dose of BNT162b2 (B.1.1.7 + B.1.617.2) in BNT162b2-experienced subjects without evidence of infection. • GMR of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the VOCs NT 1 month after one booster dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • The difference in SRs to VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the VOCs NT 1 month after one booster dose of	• VOC specific NTs (B.1.1.7, B.1.617.2, B.1.1.529.5 [Omicron BA.5])

OBJECTIVES	ESTIMANDS	ENDPOINTS
	BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection.	
To compare the immune response against VOCs 3 weeks after one dose of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection to the immune response 1 month after two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects without evidence of infection.	• GMTs and SRs of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • GMR of VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection to the VOCs NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection. • The difference in SRs to VOCs NT 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects with evidence of prior infection and to the VOCs NT 1 month after two doses of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects without evidence of infection.	• VOC specific NTs (B.1.1.7, B.1.617.2, B.1.1.529.5 [Omicron BA.5])
Exploratory objectives		
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences
To evaluate the immune response over time to prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2), and persistence of immune response in subjects with and without prior COVID-19 vaccination.	• GMC/GMT and GMFR at baseline and 1, 6, and 12 months after completion of vaccination. • SRs for reference strain and B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	• For a subset of subjects, after any dose of multivalent vaccine, BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccines BNT162b2 and BNT162b2 (B.1.617.2) vaccines, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data

OBJECTIVES	ESTIMANDS	ENDPOINTS
To describe B-cell responses after one or two and three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	For a subset of Cohort 6 subjects in Part B: • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells
To describe the T cell-mediated immune response after one or two and three doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).	For a subset of Cohort 6 subjects in Part B: • CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and the B.1.1.7 and B.1.617.2 variant strains.	• Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)
To describe the incidence of non-S seroconversion to SARS-CoV-2 in subjects with and without prior COVID-19 vaccination who received prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2).	• Incidence of non-S-seroconversion to SARS-CoV-2 per 1,000 person-years of follow-up.	• Nucleocapsid (N)-binding antibody seroconversion in subjects with no serological or virological evidence of past SARS-CoV-2 infection or confirmed COVID-19
To describe the incidence of confirmed COVID-19 at 1 year follow-up period in subjects with and without prior COVID-19 vaccination who received prophylactic multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) or monovalent vaccine BNT162b2 (B.1.617.2).	• Incidence of confirmed COVID-19 cases per 1,000 person-years of follow-up.	• Number of confirmed COVID-19 cases

* Note: “BNT162b2-experienced” is defined as subjects who have previously received two injections of 30 µg BNT162b2.

Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; GMR = geometric mean ratio; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

Objectives and endpoints - Part C

OBJECTIVES	ESTIMANDS	ENDPOINTS
Primary objectives (Safety)		
To describe the safety profile of the monovalent vaccine BNT162b2 (B.1.1.529) given as one dose to RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after the last dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To describe the safety profile of the monovalent vaccine BNT162b2 given as one dose to RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	In subjects receiving at least one dose of IMP, the percentage of subjects reporting: • Local reactions at the injection site up to 7 days after each dose. • Systemic events up to 7 days after each dose. • AEs from Dose 1 up to 1 month after the last dose. • SAEs from Dose 1 up to 6 months after the last dose.	• Local reactions (pain, tenderness, erythema/redness, induration/swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, nausea, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Primary objectives (Immunogenicity)		
To describe the humoral immune response against SARS-CoV-2 variants after one dose of BNT162b2 (B.1.1.529) or after one dose of BNT162b2 in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMR and difference in SR of B.1.1.529 NT 1 month after one dose of BNT162b2 (B.1.1.529) to those at 1 month after one dose of BNT162b2 for Cohorts 7 and 8.	• VOC specific NTs • VOC specific SRs
Secondary objectives		
To describe the humoral immune response against SARS-CoV-2 variants after one dose of BNT162b2 (B.1.1.529) or after one dose of BNT162b2 or a post SARS-CoV-2 infection in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMT of VOC NT at baseline and 7 days, 1 month, and 3 months after the trial start for Cohorts 7, 8, and 9, and 6 and 12 months after the trial start for Cohorts 7 and 8.	• VOC specific NTs

OBJECTIVES	ESTIMANDS	ENDPOINTS
Exploratory objectives		
To evaluate SARS-CoV-2 viral sequences in subjects.	• SARS-CoV-2 S antigen sequences or whole viral genome sequencing of interest.	• Viral sequences
To evaluate cross-neutralization of vaccine-induced antibodies to ancestral and emerging SARS-CoV-2 variants.	• For a subset of subjects, after one dose of monovalent vaccine BNT162b2 (B.1.1.529) or BNT162b2, measured cross-neutralization of other SARS-CoV-2 variants (e.g., using VNT or pVNT).	• NT data
To evaluate the immune response over time to prophylactic monovalent vaccine BNT162b2 (B.1.1.529) or BNT162b2 and persistence of immune response in RNA-based COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection.	• GMC/GMT and GMFR at baseline, 7 days, and 1, 3, 6, and 12 months after completion of vaccination. • Seroresponse for B.1.1.529 variant strain.	• Reference and VOC specific NTs • RBD and full length S-binding or S1-binding Ig levels
To evaluate the immune response to SARS-CoV-2 in subjects.	• GMC/GMT and GMFR at baseline, 7 days, and 1, 3, 6, and 12 months after completion of vaccination.	• Nucleocapsid (N)-binding Ig levels
To describe the incidence of confirmed COVID-19 at 1 year follow-up period in subjects who received one dose of monovalent BNT162b2 (B.1.1.529) or BNT162b2.	• Incidence of confirmed COVID-19 cases per 1,000 person-years of follow-up.	• Number of confirmed COVID-19 cases
To describe the B cell- and T cell-mediated immune response to monovalent BNT162b2 (B.1.1.529) and to BNT162b2 and persistence of immune response in subjects.	For a subset of subjects in Part C: • Characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes. • CMI responses including CD4 and CD8 T-cell responses to S and RBD antigens of the reference strain and B.1.1.529 variant strain.	• Frequency and phenotypic characterization of SARS-CoV-2 spike-specific B cells • Reference and VOC specific CD4 and CD8 T-cell responses (e.g., using ELISpot, ICS)

Note: BNT162b2 (B.1.1.529) refers to the monovalent vaccine specific for SARS-CoV-2 Omicron subvariant BA.1, i.e., B.1.1.529.1.

Abbreviations: AE = adverse event; CD = cluster of differentiation (e.g., CD4, CD8); CMI = cell-mediated immunity; ELISpot = enzyme-linked immunospot; GMC = geometric mean concentration; GMFR = geometric mean fold rises; GMT = geometric mean titer; GMR = geometric mean ratio; ICS = intracellular cytokine staining; Ig = immunoglobulin; NT = neutralizing titers; pVNT = pseudo-virus neutralization test; RBD = receptor binding domain; S = spike protein;

SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SR = seroresponse; VNT = virus neutralization test; VOC = variant(s) of concern.

4 TRIAL DESIGN

4.1 Overall design

This is a Phase II open-label trial.

This trial consists of three parts, Part A, Part B, and Part C, and will evaluate the safety and immunogenicity of a third booster injection of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), and the safety and immunogenicity of a third booster injection of the monovalent vaccine BNT162b2 (B.1.617.2) or BNT162b2 (B.1.1.7), in subjects who have received two doses of the parent vaccine BNT162b2 at 30 µg, at least 6 months after the second dose of BNT162b2. It will also evaluate the safety and immunogenicity of a three-dose regimen of BNT162b2 (B.1.1.7 + B.1.617.2) in subjects who have not received prior COVID-19 vaccination. In addition, the safety and immunogenicity of BNT162b2 (B.1.1.529) or BNT162b2 given as a third or fourth vaccine dose to RNA COVID-19 vaccine-experienced subjects with history of SARS-CoV-2 infection will be evaluated and contrasted with the natural immune response reached after infection with the SARS-CoV-2 Omicron variant.

Part A will describe, in parallel subject cohorts, the safety and the immunogenicity of BNT162b2 (B.1.1.7 + B.1.617.2) in relation to the corresponding monovalent vaccines BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2), and the parent vaccine BNT162b2. Comprehensive assessments of the humoral and cell-mediated immune responses in those groups will evaluate if the immunological responses to each antigen is undeterred by the addition of additional antigens in BNT162b2 (B.1.1.7 + B.1.617.2). Further, analyses of the B cell compartment, including memory B cells, will assess if BNT162b2 (B.1.1.7 + B.1.617.2) as a booster in prior vaccinated subjects elicits a qualitatively improved anamnestic response, with expansion of a diversified memory B cell population able to cross-neutralize conserved and unique strain epitopes. Part A will provide rapid information about the safety and the immunogenicity of the multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine in a previously vaccinated group and in a vaccine-naïve population, and will inform Part B in terms of dosage and sample size.

Part B will be initiated after review of reactogenicity and available immunogenicity data of Part A (Cohorts 1, 4, 6) by the SRC. Part B will compare the immune response after one dose or after two doses of the multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine against the variant strains or after one dose of multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine against the reference strain vs the immune response after two doses of BNT162b2 against the reference strain observed in subjects from the Phase III BNT162-02 / C4591001 (NCT04368728) trial. Part B will also compare the immune response after one dose of the monovalent vaccine BNT162b2 (B.1.617.2) against the variant strain vs the immune response after two doses of BNT162b2 against the reference strain observed in subjects from the Phase III BNT162-02 / C4591001 trial. Part B will further include the same assessments of the B cell and T cell compartments as described in Part A in a pre-defined sample size of the cohort population.

Based on data from Part A, the dosage, sample size and trial groups planned in Part B may be adjusted via a protocol amendment.

Part C will include healthy subjects who were previously vaccinated with two or three doses of any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with a SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections). Part C will compare immune responses against the SARS-CoV-2 Omicron variant after one dose of 30 µg monovalent BNT162b2 (B.1.1.529) vaccine vs the immune response after one dose of 30 µg BNT162b2. In addition, Part C (Cohort 9) will evaluate the immune response reached after infection with the SARS-CoV-2 Omicron variant.

Part A

Part A consists of six parallel cohorts of approximately n = 20 subjects each, which will enroll subjects 18 to 55 years of age (Cohorts 1 to 6).

Cohorts 1 to 5 will enroll subjects who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose in the following five cohorts:

- **Cohort 1**: Subjects will receive one dose of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) on Day 1 (baseline in this trial), consisting of a 1:1 mixture of two BNT162b2 monovalent vaccines: 15 µg BNT162b2 (B.1.1.7), and 15 µg BNT162b2 (B.1.617.2).
- **Cohort 2**: Subjects will receive two doses of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and on Day 56 (8 weeks apart).
- **Cohort 3**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.1.7) on Day 1.
- **Cohort 4**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.617.2) on Day 1.
- **Cohort 5**: Subjects will receive one dose of 30 µg BNT162b2 on Day 1.

Cohort 6 will enroll subjects who have not received any prior prophylactic vaccine against COVID-19.

- **Cohort 6**: Subjects will receive three doses of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 21 and the third dose ~6 months after the second dose.

Part A will comprehensively describe, through the parallel Cohorts 1 to 5, the safety and the immunogenicity of one or two doses of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), in relation to the corresponding monovalent vaccine BNT162b2 (B.1.1.7) and BNT162b2 (B.1.617.2) vaccines, and the parent vaccine BNT162b2. A total dose of 30 µg is selected for the BNT162b2-based vaccines against variant strains to be tested in this trial, based on preliminary safety results of the monovalent vaccine BNT162b2 (B.1.351) vaccine against the SARS-CoV-2 B.1.351 variant strain, currently being tested as a third booster dose in the BNT162-02 / C4591001 trial. For Cohorts 1 to 4, an optional additional

lower dose level may be tested in up to 20 additional subjects per cohort, based on safety and immunogenicity data obtained with the 30 µg dosage level.

Comprehensive assessments of the humoral and cell-mediated immune responses in Cohorts 1 to 5 will evaluate if the immunological responses to each VOC is unaffected by the addition of additional antigens in the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2). Further, analyses of the B cell compartment, including memory B cells, will assess if the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) as a booster in prior vaccinated subjects elicits a qualitatively improved anamnestic response, with expansion of a diversified memory B cell population able to cross-neutralize conserved and unique strain epitopes.

Twenty (20) subjects who are COVID-19 vaccine-naïve and have not experienced COVID-19, will be enrolled in Cohort 6 to receive BNT162b2 (B.1.1.7 + B.1.617.2) given as a three-dose regimen – the first and second doses administered on Day 1 and Day 21 and the third dose ~6 months after the second dose.

Part B

Part B will be initiated after review of reactogenicity and available immunogenicity data of Part A (Cohorts 1, 4, 6) by the SRC.

Part B consists of three cohorts of n = 300 subjects each (~375 subjects will be enrolled in each cohort to ensure there are 300 evaluable subjects), which will enroll subjects 18 to 85 years old; ~60% of these subjects should be 18 to 55 years old and ~40% should be 56 to 85 years old:

- **Cohort 1** will enroll subjects from the trial BNT162-02 / C4591001 who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose. Subjects will receive on Day 1 one dose of 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2).
- **Cohort 4** will enroll subjects from the trial BNT162-02 / C4591001 who received two injections of 30 µg BNT162b2, at least 6 months after the second BNT162b2 dose. Subjects will receive on Day 1 one dose of 30 µg monovalent vaccine BNT162b2 (B.1.617.2).
- **Cohort 6** will enroll subjects who have not received any prior prophylactic vaccine against COVID-19. Subjects will receive 30 µg multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 21 and the third dose ~6 months after the second dose. Approximately 15 subjects at preselected sites in Part B will be evaluated in terms of cell-mediated immunity.

Part B will expand the safety information of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) as one booster dose in BNT162b2-experienced subjects, and as two-dose, primary vaccination regimen in subjects who are COVID-19 vaccine-naïve and have not experienced COVID-19.

Part B will also determine based on geometric mean ratios (GMR) of neutralizing titers and seroresponse rate, if the immune response of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) against the B.1.1.7 and the B.1.617.2 strains or immune response after one

dose of multivalent BNT162b2 (B.1.1.7 + B.1.617.2) vaccine against the reference strain, and the immune response of the monovalent vaccine BNT162b2 (B.1.617.2) against the B.1.617.2 strain, is immunobridged to the immune response observed against the reference strain in selected existing subjects from the Phase III trial BNT162-02 / C4591001, who received two doses of BNT162b2. The selection will ensure comparable distribution of age and sex in the control group and the BNT162b2 (B.1.1.7 + B.1.617.2) and BNT162b2 (B.1.617.2) groups. To achieve 300 evaluable subjects for each of the immunobridging comparisons, 20% non-evaluable rate is estimated, which results in the enrollment of 375 subjects in each of Part B cohorts.

In addition, Part B will compare the immune response against the reference and the variant strains after one or two doses of multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2), compared to after two doses of BNT162b2 in subjects from the Phase III BNT162-02 / C4591001 trial.

Part C

Part C consists of n = ~225 subjects who previously received two or three injections of any authorized COVID-19 RNA-based vaccine and were subsequently diagnosed with SARS-CoV-2 infection from January 2022 onwards (limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections).

Subjects in Part C will be randomized in a 2:2:1 ratio into three cohorts; ~90 subjects each in Cohorts 7 and 8 (to ensure ~80 evaluable subjects in each cohort after 11% dropout) and 45 subjects in Cohort 9. Randomization will be stratified by age group (18 to 55 years of age or 56 to 85 years of age) and by number of prior doses of COVID-19 RNA-based vaccine (two or three doses).

The sponsor may terminate the enrollment into Cohort 9 at any time in case the evolving COVID-19 epidemiology and/or the recommendations issued in the context of national vaccination campaigns no longer support enrollment of the trial population in a realistically feasible time.

Cohorts 7 to 9 will enroll subjects 18 to 85 years old; ~60% of these subjects should be 18 to 55 years old and ~40% should be 56 to 85 years old:

- **Cohort 7**: Subjects will receive one dose of 30 µg monovalent vaccine BNT162b2 (B.1.1.529) on Day 1.
- **Cohort 8**: Subjects will receive one dose of 30 µg BNT162b2 on Day 1.
- **Cohort 9**: No vaccination will be given to Cohort 9 subjects within 3 months after Visit 1. After the 3-month follow-up period, subjects in Cohort 9 will be offered a BNT162b2 vaccination, depending on the epidemiological situation, local regulatory authority recommendations, and/or variant vaccine authorization status.

Approximately 25 subjects at preselected sites in each cohort of Part C will be evaluated in terms of cell-mediated immunity.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2. For the planned assessments and visits, see the SoA in Section 1.3.

4.2 Scientific rationale for the trial design

The scientific rationale for this trial design is the following:

- The trial will comprehensively characterize the safety of the multivalent BNT162b2-based vaccine BNT162b2 (B.1.1.7 + B.1.617.2), both in subjects who are BNT162b2-experienced, and in subjects who are COVID-19 vaccine-naïve and have not experienced COVID-19.
- To enhance the generalizability of trial results, Part B will include subjects 18 to 85 years old, including younger and older adults, and Parts A and B will include subjects with pre-existing stable disease.
- The trial design allows assessment if the immune responses to each antigen (i.e., the S protein of the SARS-CoV-2 strain B.1.1.7 or B.1.617.2) is unaffected by the addition of additional antigens in the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2). It also allows assessment if the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) as one booster dose in BNT162b2-experienced subjects:
  - Elicits a qualitatively improved anamnestic response able to cross-neutralize conserved and unique strain epitopes.
  - Is quantitatively non-inferior to the immune response after two doses of the parent vaccine BNT162b2.
- In subjects who have previously received a two-dose regimen of BNT162b2 as a primary vaccination series and who will receive BNT162b2 (B.1.1.7 + B.1.617.2), it is anticipated that one dose of BNT162b2 (B.1.1.7 + B.1.617.2) will sufficiently boost the immune response against each of the B.1.1.7, B.1.617.2, and the reference strains. To investigate if a two-dose regimen of BNT162b2 (B.1.1.7 + B.1.617.2) given in a longer time interval in vaccine-experienced subjects, will result in optimized safety and immune response (Goel et al. 2021, Payne et al. 2021, Tauzin et al. 2022), subjects in Cohort 2 (Part A) will also receive a second dose of BNT162b2 (B.1.1.7 + B.1.617.2) administered after a longer time interval of 8 weeks post-Dose 1.
- The thorough clinical investigation of the multivalent vaccine BNT162b2 (B.1.1.7 + B.1.617.2) will support preparedness for the case that a multivalent BNT162b2-based vaccine against COVID-19 is needed to allow broad coverage against circulating strains at global level and to avoid the complexity of handling multiple monovalent vaccines in parallel.
- The trial design will also provide safety and immunobridging data for the monovalent vaccine BNT162b2 (B.1.617.2) as a booster dose in subjects who are BNT162b2-experienced.
- Part C of the trial will characterize the safety of BNT162b2 and BNT162b2 (B.1.1.529) in subjects who are COVID-19 RNA-based vaccine-experienced and have subsequently experienced a SARS-CoV-2 infection.

- Part C further allows assessment of the immune responses to each antigen (i.e., the S protein of the reference ancestral SARS-CoV-2 strain [Wuhan-Hu-1/ USA-WA1] or B.1.529). Part C also allows assessment of whether vaccination with the Omicron-specific vaccine BNT162b2 (B.1.1.529) in COVID-19 RNA-based vaccine-experienced individuals who experienced a SARS-CoV-2 Omicron breakthrough infection:
    - Is quantitatively superior to the immune response after one dose of the parental vaccine BNT162b2.
    - Elicits a qualitatively improved anamnestic response able to cross-neutralize conserved and unique strain epitopes.
- The thorough clinical comparison of the variant-specific vaccine BNT162b2 (B.1.529) with the parental vaccine BNT162b2 in COVID-19 RNA-based vaccine-experienced individuals that had a breakthrough infection in Part C will generate information on the comparative breadth and magnitude of immune responses in this situation, potentially supporting the choice of booster vaccine in this population.
- The subjects who will not receive a BNT162b2-based vaccine in Cohort 9 in Part C will bring valuable information about the magnitude, quality, and duration of immune responses post breakthrough infection in COVID-19 RNA-based vaccine-experienced individuals that will serve to contrast responses after an additional vaccination with the variant-specific vaccine BNT162b2 (B.1.529) or with the parental vaccine BNT162b2.

4.3 Justification for dose

The vaccine BNT162b2 (30 µg BNT162b2 given as a course of two doses at least 21 days apart) has been authorized for emergency use or been given conditional/full marketing authorization in numerous countries worldwide. Since then, pharmacovigilance data after administration in millions of individuals worldwide has confirmed this regimen to be safe and effective for protection against COVID-19. This trial will therefore use the authorized dose regimen for BNT162b2 administration.

Although not yet proven in clinical trials, the safety and immunogenicity of the BNT162b2 vaccine variants – BNT162b2 (B.1.1.7 + B.1.617.2), BNT162b2 (B.1.1.7), BNT162b2 (B.1.617.2), and BNT162b2 (B.1.1.529) – is not expected to differ from that for the parent vaccine BNT162b2, and therefore the authorized dose regimen for BNT162b2 will be used for the vaccines against variant strains.

Where a 1:1 mixture of two vaccines against different viral strains is administered (Cohorts 1, 2, and 6), 15 µg of each vaccine will be administered, such that the total dose does not exceed 30 µg.

4.4 Trial completed and end of trial definitions

A trial subject is considered to have completed the trial if they have completed all planned visits as listed in the SoA (see Section 1.3).

The end of the trial is defined as the date of the last visit of the last subject in the trial.

4.5 Duration of all trial periods

Depending on the cohort, the planned trial duration for a subject in this trial is up to ~61 weeks (for the cohort with the longest duration: ≤1 week of screening, 8 weeks between IMP doses, and ~52 weeks-follow-up after the last IMP dose).

The estimated planned trial start (first subject first visit) and trial end (last subject last visit) are Q3-2021 and Q3-2023.

5 TRIAL POPULATION

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation.

5.1 Inclusion criteria

Volunteers are eligible for enrollment into this trial if all of the following criteria apply:

1 Have given informed consent by signing the informed consent form (ICF) before initiation of any trial-specific procedures.

2 Volunteers who at the time of consent are:

- Part A: 18 to 55 years old.
- Part B: 18 to 85 years old (~60% should be 18 to 55 years old and ~40% 56 to 85 years old).
- Part C: 18 to 85 years old (~60% should be 18 to 55 years old and ~40% 56 to 85 years old).

3 For Cohorts 1 to 5: in Part A, have received BNT162b2 vaccine (30 µg, two-dose regimen) in either a clinical trial or as part of the governmental vaccination programs at least 6 months before Visit 0. Subjects who are currently enrolled in the Phase III BNT162-02 / C4591001 trial, have already been unblinded, and have previously received two doses of BNT162b2 with Dose 2 at least 6 months earlier can be included (for Cohorts 1 and 4 in Part B, prior enrollment and dosing in the BNT162-02 / C4591001 trial is mandatory). At enrollment into Part B of this trial, their participation in the BNT162-02 / C4591001 trial will be terminated. Subjects should have not experienced COVID-19 based on medical history.

4 For Cohort 6: Are COVID-19 vaccine-naïve and have not experienced COVID-19 based on their medical history.

5 Are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other trial procedures.

6 Are overall healthy at Visit 0 in the clinical judgment of the investigator based on the medical history, clinical assessment (including physical examination, vital signs, blood and urine clinical laboratory tests, 12-lead ECG, and oral swab for NAAT-based SARS-CoV-2 testing).
Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 12 weeks before Visit 0, can be included.

Note: Volunteers who had hepatitis C (HCV) infection, but have completed curative treatment based on the medical history can be included. Volunteers who had or have hepatitis B (HBV) or HIV based on the medical history cannot be included.

7 Agree not to enroll in another trial of an IMP, starting after Visit 0 and continuously until the last planned visit in this trial.

8 Women of childbearing potential (WOCBP) must test negative in a urine beta-human chorionic gonadotropin (β-HCG) test at Visits 0 and 1. For a definition of "WOCBP", see Section 10.4.1.

9 WOCBP must agree to practice a highly effective form of contraception starting at Visit 0 and continuously until 28 days after their last IMP administration in this trial. For a definition of "highly effective form of contraception", see Section 10.4.2.

10 WOCBP must confirm that they practiced an acceptable form of contraception for the 14 days prior to Visit 0. For a definition of "acceptable form of contraception", see Section 10.4.2.

11 WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction starting after Visit 0 and continuously until 28 days after their last IMP injection in this trial.

12 Men who are sexually active with a WOCBP and have not had a vasectomy must agree to use a highly effective form of contraception with their female partner of childbearing potential starting after Visit 0 and continuously until 28 days after their last IMP injection in this trial.

13 Men must be willing to refrain from sperm donation, starting after Visit 0 and continuously until 28 days after their last vaccination.

14 For Part C, Cohorts 7, 8, and 9: have received two or three documented doses of any authorized COVID-19 RNA-based vaccine (e.g., BNT162b2 [Comirnaty] or the Moderna vaccine [Spikevax]) prior to being diagnosed with SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections).

Note: The interval between the last COVID-19 RNA-based vaccine administered and randomization should be >4 months.

The latest prior diagnosed SARS-CoV-2 infection should be at least 2 months before randomization. The latest SARS-CoV-2 infection should be documented with a result from a NAAT (as a preferable option). In case no historic NAAT result is available proving prior SARS-CoV-2 infection, the local positive result of SARS-CoV-2 N-binding antibodies done at screening will be sufficient.

5.2 Exclusion criteria

Volunteers are not eligible for enrollment if any of the following criteria apply:

1 Any existing condition which may affect vaccine injection and/or assessment of local reactions assessment, e.g., tattoos, severe scars, etc.

2 Any bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

3 Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that, in the investigator's judgment, make the subject inappropriate for the trial.

4 Any current febrile illness (body temperature ≥38.0°C/≥100.4°F) or other acute illness within 48 h prior to Day 1/IMP injection in this trial.

5 Any current or history of cardiovascular diseases, e.g., myocarditis, pericarditis, myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias, unless such disease is not considered relevant for participation in this trial in the investigator's judgment.

6 History of COVID-19 and/or clinical (based on clinically confirmed COVID-19 symptoms/signs alone if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) evidence of prior infection with SARS-CoV-2 at screening (Visit 0).

Note: not applicable for Part C.

7 History of Guillain-Barré syndrome.

8 Known or suspected immunodeficiency.

9 History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the trial IMPs.

10 History or known allergy, hypersensitivity, or intolerance to the trial IMP including any excipients of the IMPs in this trial.

11 Have received any SARS-CoV-2 vaccination other than BNT162b2 (30 µg BNT162b2 given as a course of two doses ~21 days apart).

Note: not applicable for Part C.

12 Have received a live or live attenuated vaccine within 28 days prior to Day 1/IMP injection.

13 Have received any other vaccines within 14 days before or after any IMP injection, e.g., influenza, tetanus, pneumococcal, hepatitis A or B. When possible standard or care vaccinations should be planned with the trial IMP administrations in mind.

14 Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout this trial. Inhaled/nebulized, intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

15 Receipt of blood/plasma products or immunoglobulin, from 60 days before IMP administration or planned receipt throughout this trial.

16 Participation in other trials involving IMP within 28 days or 5 half-lives (whichever is longer) prior to Visit 1 and/or during trial participation, besides participation in trials with BNT162b2.

17 Are pregnant or breastfeeding or are planning pregnancy within 28 days after last IMP treatment.

18 Are vulnerable individuals as per ICH E6 definition, i.e., are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

19 For Part C, Cohorts 7, 8, and 9: Vaccination with other non-RNA or unauthorized COVID-19 vaccines.

20 For Part C, Cohorts 7, 8, and 9: Vaccination with any COVID-19 vaccine after SARS-CoV-2 infection from January 2022 onwards (and limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections).

5.3 Lifestyle considerations

When at the trial site, trial subjects will not be allowed to smoke or to drink alcohol.

The trial subjects will be required to remain at the site for at least 30 minutes after each IMP injection.

Subjects will be asked to avoid strenuous exercise beyond their usual exercise routine for 7 days after each IMP administration.

The trial subjects will be required to practice prescribed forms of contraception and not to donate sperm or eggs (ova, oocytes) for the purposes of assisted reproduction, starting at Visit 0 and continuously until 28 days after their last IMP administration in this trial. See inclusion criteria 9 to 13. For subjects randomized to Cohort 9 these criteria only apply until randomization (Visit 1) and no further restrictions are required. In addition, the investigator or designee will instruct the trial subjects to call immediately if the selected contraception

method is discontinued or if pregnancy is known or suspected in the trial subject or partner.

Trial subjects will be required to continue following guidance from their health authorities on recommended social behaviors (e.g., mask wearing, social distancing) based on their vaccination status before trial participation.

5.4 Screen failures

Screen failures are defined as individuals who consent to participate in the trial but who are not subsequently allocated to IMP.

A minimal set of screen failure information is required to ensure transparent reporting of screening failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, date the ICF was signed, the reasons for screen failures, and any SAEs, if applicable.

If agreed with the Medical Monitor rescreening is allowed at the discretion of the investigators. Rescreened subjects will need to re-consent and will be assigned a new trial subject number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment(s), marketed product(s), intended to be administered to a trial subject according to the trial protocol.

6.1 IMPs administered

IMP name:	• BNT162b2 • BNT162b2 (B.1.1.7 + B.1.617.2) • BNT162b2 (B.1.1.7) • BNT162b2 (B.1.617.2) • BNT162b2 (B.1.1.529)
Type:	Vaccine (BNT162 RNA-LNP vaccine utilizing modRNA).
Use:	Experimental
Administration route:	Intramuscular (IM); upper arm, musculus deltoideus. The same arm may be used for both immunizations. The non-dominant arm is preferred.
Dosing regimen:	**Part A:** • Cohort 1: One dose of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2), consisting of a 1:1 mixture of 15 µg BNT162b2 (B.1.1.7) and 15 µg BNT162b2 (B.1.617.2), given on Day 1. • Cohort 2: Two doses of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2), one each on Day 1 and Day 56. • Cohort 3: One dose of 30 µg BNT162b2 (B.1.1.7) on Day 1. • Cohort 4: One dose of 30 µg BNT162b2 (B.1.617.2) on Day 1. • Cohort 5: One dose of 30 µg BNT162b2 on Day 1. • Cohort 6: Three doses (on Day 1, Day 21, and the third dose ~6 months after the second dose) of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). **Part B:** • Cohort 1: One (on Day 1) dose of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). • Cohort 4: One (on Day 1) dose of 30 µg BNT162b2 (B.1.617.2). • Cohort 6: Three doses (on Day 1, Day 21, and the third dose ~6 months after the second dose) of 30 µg BNT162b2 (B.1.1.7 + B.1.617.2). **Part C:** • Cohort 7: One dose of 30 µg BNT162b2 (B.1.1.529) on Day 1. • Cohort 8: One dose of 30 µg BNT162b2 on Day 1. • Cohort 9: No IMP injection within 3 months of Visit 1.
Sourcing:	Provided centrally by the sponsor.
Packaging and labeling:	IMP will be provided in glass vials as open-label supply. Each vial will be labeled as required per country requirements. For details, see the Pharmacy Manual.

Note: BNT162b2 (B.1.1.529) refers to the monovalent vaccine specific for SARS-CoV-2 Omicron subvariant BA.1, i.e., B.1.1.529.1.

6.2 Preparation/handling/storage/accountability

The principal investigator is responsible for IMP (and any components thereof) accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For instructions on IMP preparation, handling, and storage, see the Pharmacy Manual.

All IMPs (and any components thereof) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized trial site personnel.

The preparation of solution for injection will be performed by aseptic handling procedures by pharmaceutical personnel or other trained personnel at the trial site. Further guidance and information for the final disposition of unused IMP (and any components thereof) is provided in the Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

Laboratory personnel who will analyze the samples to generate immunogenicity data for the primary and secondary immunogenicity endpoints in Part B will be blinded to the source of samples (BNT162-17 vs BNT162-02 / C4591001) or the actual treatment.

Randomization will be applied to Part C of the trial only. At randomization, subjects will be stratified by the following factors: age group (18 to 55 years of age or 56 to 85 years of age); number of prior doses of RNA-based vaccines (two or three doses).

6.4 Trial treatment compliance

All IMP injections will be administered by a physician or by qualified medical personnel.

The date and time of each IMP injection must be recorded in the source documents and recorded in the case report form (CRF). The IMP dose and trial subject identification will be confirmed at the time of administration by a member of the trial site personnel other than the person administering the IMP.

6.5 Concomitant therapy

6.5.1 Permitted concomitant therapies

For healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 12 weeks before Visit 0, the continued use of the ongoing stable therapy is allowed.

The use of antipyretics and other pain medication to treat symptoms after IMP administration or for ongoing conditions is permitted, but not for prophylaxis. See the guidance on antipyretics and other pain medication in Section 6.5.2.

Inhaled, topical, or localized injections of corticosteroids (e.g., intraarticular or intrabursal administration) are permitted.

Administration of nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., paracetamol/acetaminophen at doses of up to 4 g/day, is permitted to treat symptoms after IMP administration or for ongoing conditions (but not for prophylaxis). Other concomitant medication may be considered on a case by case basis by the investigator, if required after consultation with the sponsor’s Medical Monitor.

6.5.2 Prohibited concomitant therapies

Trial subjects should not receive any live or live attenuated vaccination within 28 days before or after any IMP injection, e.g., measles, mumps, and rubella (MMR); oral polio vaccine (OPV); varicella; yellow fever unless medically indicated. See exclusion criteria 11.

Trial subjects should not receive any other vaccines within 14 days before or after any IMP injection, e.g., influenza, tetanus, pneumococcal, hepatitis A or B. When possible, standard or care vaccinations should be planned with the trial IMP administrations in mind. See exclusion criteria 12.

Trial subjects should not receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout this trial. Inhaled/nebulized, intraarticular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. See exclusion criteria 13.

Receipt of blood/plasma products or immunoglobulins from Visit 0 or planned receipt throughout this trial. See exclusion criteria 14.

Trial subjects should not receive any non-trial SARS-CoV-2 vaccine during the BNT162-17 trial.

Trial subjects should not receive prophylactic antipyretics and other pain medication to prevent symptoms associated with IMP administration. However, if a trial subject is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to IMP administration in this trial.

Trial subjects should not receive prophylactic medications intended to prevent symptoms associated with COVID-19. However, if a trial subject is taking a medication for another condition, even if it may have such properties, this does not exclude the volunteer from enrollment into this trial.

6.5.3 Recording of concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the trial subject receives from Visit 0 until Visit 1, and for 1 month after each IMP dose (at the times listed in the SoA, Section 1.3), and any medications due to medical history started before Visit 0 (i.e., prior medication) must be recorded in the CRF along with the:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited medications should be recorded in the CRF for the whole duration of trial subject participation in the trial.

6.6 Dose modifications

In Part A, for Cohorts 1 to 4, an optional additional lower dose level may be tested in up to 20 additional subjects per cohort.

6.7 Access to trial treatment after the end of the trial

Not applicable.

7 DISCONTINUATION OF TRIAL TREATMENT AND TRIAL SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

7.1.1 Criteria to permanently discontinue IMP administration

Note that discontinuation from IMP does not represent withdrawal/discontinuation from the trial. Trial subjects permanently discontinued from IMP administration should still complete all assessments planned in the SoA (Section 1.3).

Reasons for definitive discontinuation from IMP include the following:

- SAEs warranting discontinuation;
- other trial-related safety concerns;
- subject or investigator request;
- pregnancy;
- deterioration in trial subject health at the time of IMP injection (at the discretion of the investigator).

In the event of trial subject permanent discontinuation from IMP, it must be documented on the appropriate CRF/in the medical records if the trial subject is discontinuing further receipt of trial treatment, or also from trial procedures, post-treatment follow-up, future collection of additional information and/or consent.

7.1.2 Criteria for temporarily delaying enrollment or administration of IMP

The are no criteria defined which trigger temporarily delaying trial subject enrollment.

There are medical conditions or situations which may delay administration of IMP as follows:

- Current febrile illness (body temperature ≥38.0°C/≥100.4°F) or other acute illness within 48 h before any IMP administration. This includes current symptoms that could represent a potential COVID-19 illness.
- The second IMP injection may also be delayed for medical reasons (e.g., influenza vaccination) and such delays should be as short as possible, e.g., ≤3 weeks for non-live or attenuated vaccines, ≤5 weeks for live attenuated vaccines, ≤12 weeks if SARS-CoV-2 infection is confirmed, etc.

The circumstances leading to any delayed administration of IMP and the resulting delay should be discussed with the sponsor's Medical Monitor.

7.2 Trial subject discontinuation or withdrawal from the trial

A trial subject may withdraw from the trial at any time at his/her own request or may be discontinued from the trial at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Withdrawals are expected to be uncommon.

Reasons for discontinuation from the trial include the following:

- Refused further trial procedures
- Lost to follow-up
- Death
- Trial terminated by sponsor
- Trial subject request
- Investigator request
- Important protocol deviation per the investigator after consultation with the Medical Monitor
- Receipt of non-trial SARS-CoV-2 vaccination during the trial

If the trial subject withdraws consent for data processing, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

For trial subjects who withdraw consent, the investigator must clarify whether consent for research sample storage/processing (if given) is also withdrawn. If yes, then they must be informed that any research samples collected will be destroyed. The investigator must document research sample destruction in the Investigator's Site File (ISF) and inform the sponsor about the withdrawal of consent immediately.

If possible, permanently discontinued trial subjects will complete all assessments planned for the Early Termination Visit.

7.3 Lost to follow-up

A trial subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a trial subject fails to return to the trial site for a required trial visit:

- The trial site must attempt to contact the trial subject and reschedule the missed visit as soon as possible and counsel the trial subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the trial subject wishes to continue in the trial.

- Before a trial subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the trial subject (where possible, three telephone calls and, if necessary, a certified letter to the trial subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the trial subject's medical record.
- If the trial subject continues to be unreachable, they will be considered to have withdrawn from the trial.

7.4 Replacement of permanently discontinued trial subjects

Permanently discontinued trial subjects will not be replaced.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial subjects must have given informed consent (i.e., have signed the ICF) before initiation of any trial-specific procedures are performed.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the trial subject should continue or discontinue IMP administration.

Adherence to the trial protocol requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential trial subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all trial subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

See the SoA (Section 1.3) for all planned time points for assessments.

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Clinical assessment

8.2.1.1 Physical examinations including body weight

Body weight (in kg or pounds) will be measured and recorded at screening.

Subject height (in cm or inches) will be measured and recorded.

Complete and symptom-orientated physical examinations will be performed at the time points listed in the SoA in Section 1.3.

- A (complete) physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A symptom-orientated physical examination includes an overall health judgment.

8.2.1.2 Vital signs

Vital signs comprising oral body temperature, heart rate, and blood pressure (systolic and diastolic) will be assessed at the times given in the SoA (Section 1.3).

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vitals signs measurements should be preceded by at least 5 minutes of rest for the trial subject in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will be measured with trial subjects in seated position.

8.2.1.3 Clinical laboratory tests

See Section 10.2 for the list of clinical laboratory tests to be performed at baseline and the limited times given in the SoA (Section 1.3).

All protocol-required clinical laboratory tests (see Section 10.2) must be conducted in accordance with the local laboratory standard. The investigator must review the laboratory report, document this review with signature and date.

If laboratory values from non-protocol-specified laboratory assessments performed at the laboratory require a change in trial subject management or are considered clinically significant by the investigator (e.g., SAE, AE), then the results must be recorded in the CRF.

8.2.1.4 Electrocardiograms

Standard 12-lead ECGs will be recorded at the times given in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc; according to Bazett) intervals.

All ECGs will be judged by the investigator as clinically significant (yes/no); only the investigator assessment, description of abnormalities, and heart rate will be recorded in the CRF.

For reporting and surveillance purposes, all ECGs may be forwarded to a central vendor for assessment.

8.2.2 Oral body temperature (in °C or °F)

Oral body temperature (in °C or °F) will be assessed at the times given in the SoA (Section 1.3). Body temperature will be measured and recorded to one decimal place. Body temperature will be converted to °C for reporting.

8.2.3 Subject e-diaries for assessment of reactogenicity (local and systemic reactions)

Subject e-diaries will be issued, trained, and collected by trial site personnel at the visits given in the SoA (Section 1.3).

The trial site personnel will remind the subject to record the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP injection and then every day in the evening for a total of seven consecutive days.

The trial site personnel will remind the subject to measure their oral body temperature using the provided thermometer or device and record their oral body temperature in the e-diary every day including the day of IMP injection.

The reporting on the CRF of local and systemic reactions will be based on the subject's assessments only.

The trial site personnel should review daily the e-diary entries of their trial subjects.

All reported Grade 4 local and/or systemic reactions must be confirmed by an investigator or a medically qualified person.

The grading of reported solicited local and systemic reactions will be performed using the grading scale tables given in Sections 8.2.3.1 and 8.2.3.2, which are based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

8.2.3.1 Assessments of intensity for local reactions

Redness and swelling/induration will be measured and recorded in centimeters or inches and then categorized during analysis as absent, mild, moderate, severe or potentially life-threatening, based on the grading scale in Table 9. Likewise, pain (perceived) and tenderness (elicited) at the injection site will be assessed by the trial subject as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 9.

Table 9: Local reaction grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially life-threatening (Grade 4)**
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ redness [a]	2.5 cm to 5.0 cm (0.98 in to 1.96 in)	>5.0 cm to 10.0 cm (>1.96 in to 3.94 in)	>10 cm (>3.94 in)	Necrosis or exfoliative dermatitis
Induration/ swelling [b]	2.5 cm to 5.0 cm (0.98 in to 1.96 in)	>5.0 cm to 10.0 cm (>1.96 in to 3.94 in)	>10 cm (>3.94 in)	Necrosis

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
b. Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

8.2.3.2 Assessments of intensity for systemic reactions

Symptoms of systemic reactions

Symptoms of systemic reactions will be assessed by the trial subject as absent, mild, moderate, severe, or potentially life-threatening, according to the grading scale in Table 10.

If a fever of ≥39.0°C/≥102.1°F is recorded by a subject during the 7-day post-injection e-diary period, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a trial subject's fever as >40.0°C/>104.0°F for recording in the trial database. If a trial subject experiences a confirmed fever >40.0°C/>104.0°F, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of IMP, further IMP injections will be discontinued in that trial subject.

Table 10: Systemic reaction grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially life-threatening (Grade 4)**
Fever (oral temperature of ≥38.0°C/≥100.4°F)	≥38.0°C/≥100.4°F to 38.4°C/101.1°F	≥38.5°C/≥101.2°F to 38.9°C/102.0°F	≥39.0°C/≥102.1°F to 40.0°C/104.0°F	>40.0°C/>104.0°F
Vomiting	1 to 2 times in 24 h	>2 times in 24 h	Requires intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Nausea	No interference with activity or 1 to 2 episodes/24 h	No interference with activity or >2 episodes/24 h	Prevents daily activity, requires outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsening joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

8.2.4 Oral swabs for NAAT-based SARS-CoV-2 testing for screening and surveillance

Oral swabs for (NAAT-based) SARS-CoV-2 testing will be collected by trial site personnel at the time points provided in the SoA (Section 1.3).

The NAAT-based analysis of oral swabs for SARS-CoV-2 will be performed by a local laboratory. The most commonly used devices eventually come with pre-defined test panels that test for a range of pathogens and not just for SARS-CoV-2. Thus, inevitably and automatically, incidental data for the pathogens other than SARS-CoV-2 will be generated when using such devices. Since this incidental data is not required by this trial, only the results for SARS-CoV-2 will be recorded in the CRF, analyzed, and reported as described in this protocol. If a test result for SARS-CoV-2 or another pathogen must be reported to relevant authorities, this notification will be done by the trial site.

Additionally, any potentially SARS-CoV-2 – infected and/or symptomatic trial subjects will be asked to return *ad hoc* to the site for SARS-CoV-2 diagnostics as soon as possible. Oral swabs for SARS-CoV-2 genomic sequencing will also be collected and analyzed at a later time point at a central laboratory.

Instructions on the sample handling and shipping to the analysis site will be provided in a Laboratory Manual. The methodology used includes NAAT-based analysis and SARS-CoV-2 digital drop polymerase chain reaction (ddPCR).

The below definition of “confirmed COVID-19” cases for the purpose of surveillance during the trial is based on the US FDA guidance for Industry “Development and Licensure of Vaccines to Prevent COVID-19”.

Confirmed COVID-19: presence of one or more of the below symptoms and SARS-CoV-2 NAAT positive test either at the central laboratory or at a local testing facility (using a certified test):

- Fever or chills
- New or increased cough
- New or increased shortness of breath or difficulty breathing
- Fatigue
- Headache
- New or increased muscle or body aches (pain)
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

8.2.5 Serological testing for SARS-CoV-2 N-binding antibodies

Blood will be drawn by trial site personnel for serological testing for SARS-CoV-2 N-binding antibodies by serum SARS-CoV-2 nucleocapsid protein enzyme-linked immunosorbent assay (ELISA) testing at the time points provided in the SoA (Section 1.3).

SARS-CoV-2 nucleocapsid protein ELISA testing will be performed at a central laboratory (not applicable for Part C screening).

8.2.6 SARS-CoV-2 sequencing

Swabs for SARS-CoV-2 genomic sequencing storage will be collected by trial site personnel at the time points provided in SoA (Section 1.3).

The swabs will be inserted into collection tubes pre-filled with stabilizer solution. The swabs must be stored in the central laboratory at a minimum -70°C/-94°F until the end of the trial.

SARS-CoV-2 genomic sequencing including SARS-CoV-2-ddPCR will be performed, even if no COVID-19 symptoms are shown.

Instructions on the sample handling and shipping to the analysis site will be provided in a Laboratory Manual.

The outcome of SARS-CoV-2 genomic sequencing would be SARS-CoV-2 S antigen sequences and/or whole genome sequences and assigned (where possible) to known viral variants.

8.3 Adverse events and SAEs

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE or AESI and are responsible for following up all AEs and SAEs.

Solicited events that are derived from the subject e-diaries should not be additionally reported as AEs unless the event meets criteria for an SAE or starts after Day 7 or starts on Days 1 to 7 and continues past Day 7.

In addition, all solicited Grade 4 events need to be medically confirmed.

8.3.1 Time period and frequency for collection of AE, AESI, and SAE information

All AEs, AESI, and SAEs (including a death) will be recorded at the time points listed in the SoA in Section 1.3.

For subjects who receive a non-trial SARS-CoV-2 vaccination, AEs/SAEs will be collected as specified above until the date when the subject was vaccinated with the non-trial SARS-CoV-2 vaccine. The AEs/SAEs expected to be captured after non-trial SARS-CoV-2 vaccination are within the frame of post-marketing safety data reporting.

Cohort 9 subjects will be offered a booster vaccination with the locally marketed Pfizer-BioNTech RNA-based COVID-19 vaccine after the EOT has been completed. If subjects choose to receive this vaccination, the recording and follow-up of any safety events will

follow post-marketing rules and such events will not be recorded within the trial documentation.

Investigators are not obligated to actively seek AEs or SAEs at any time after a trial subject has been discharged from the trial, however, if the investigator learns of any SAE (including a death), that they consider to be reasonably related to the IMP administration or trial participation, the investigator must promptly notify the sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the trial subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each trial subject at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the trial subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.1.7.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator must submit any updated SAE data to the sponsor within 24 h of receipt of the information as indicated in Section 10.3.1.10.

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the trial subject is lost to follow-up or the trial subject withdraws consent. If no final status is reached by the time the trial subject is discharged from the trial, the investigator must confirm the unavailability of a final status.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE/AESI via the provided SAE/AESI form by the investigator to the sponsor within 24 h of the site's awareness is essential so that legal obligations and ethical responsibilities for the safety of trial subjects, and the safety of a trial treatment under clinical investigation and regulatory reporting obligations are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies involved in the conduct of trials with the same IMP about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authorities, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and

investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial Safety Management Plan.

All serious adverse reactions, the nature, severity or outcome of which is not consistent with the reference safety information are “unexpected serious adverse reactions”. The expectedness assessment for all related SAEs is based on the reference safety information included in Section 7.8.2 of the current BNT162 IB.

Safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

For the IMP, it is the sponsor’s or delegate’s responsibility to perform SUSAR reporting to the applicable regulatory authorities, IECs/IRBs, within the timelines stipulated in the respective country regulations. Reporting to the investigators will follow country-specific regulatory requirements and applicable guidelines.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor should review it and then file it together with the IB. If required by local requirements, the investigator will notify the relevant IECs/IRBs.

8.3.5 Pregnancy testing and handling of pregnancies

For WOCBP, pregnancy tests will be performed using commercial kits at the times given in the SoA (see Section 1.3).

Pregnancy information (information on trials subjects who become pregnant or information for female partners of male trial subjects who become pregnant) will be collected for pregnancies that occurred after the date of the first injection of IMP until the subject terminates or completes the trial.

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female subject (or if a male subject’s partner becomes pregnant, written informed consent from both).

As described in Section 7.1.1, subject pregnancy will trigger permanent discontinuation of IMP administration.

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Death events

Any death that occurs within the observation period will be reported as an SAE.

In case of a fatal event, the event term should not be “death” but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only for the AE leading to death the outcome “fatal” should be selected. If the cause of death is

unknown and cannot be ascertained at the time of reporting, “unexplained death” should be documented as event term.

8.3.7 Disease-related events/outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse events of special interest

The following will be reported as AESIs:

- Myocarditis (all Levels of Certainty including “Possible cases” (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible Case), Myocarditis_Version_1.0_15 July 2021_FINAL_for Posting)
- Pericarditis (all Levels of Certainty including “Possible cases” (1 to 3) as per Brighton Collaboration Case Definition) 1 to 3 (Possible case), Pericarditis_Version_1.0_15 July 2021_FINAL_for Posting)
- Anaphylaxis
- Thromboembolic events (e.g., deep vein thrombosis, stroke, myocardial infarction)
- Immune thrombocytopenia
- Immune based neurologic events (e.g., optic neuropathy, Guillain-Barré syndrome)

If an AESI is reported, the investigator should inform the sponsor as outlined in Section 10.3.1.10. For the treatment of myocarditis and pericarditis, see Section 8.5.

8.4 Treatment of overdose

Any dose of trial treatment above the planned doses specified in this protocol will be considered an overdose. In the event of overdose:

- Closely monitor the trial subject for any AE/SAE and laboratory abnormalities (at least for 7 days).
- (At the discretion of the investigator) Give symptomatic treatment.
- Inform the sponsor’s Medical Monitor as soon as possible; the sponsor’s Medical Monitor should agree with the investigator regarding any action triggered, e.g., trial subject withdrawal from the trial or (if applicable) trial treatment.
- Document the quantity of the excess dose overdose in the CRF.

8.5 Treatment for specific adverse reactions

The adverse reactions determined for BNT162b2 from the available unblinded clinical trial data (from BNT162-02 / C4591001) are mostly reflective of mild to moderate local and systemic reactogenicity events. The most frequent adverse reactions in trial subjects 16 years of age and older were injection site pain, fatigue, headache, myalgia and chills, arthralgia, pyrexia and injection site swelling, and were usually mild or moderate in intensity and resolved within a few days after vaccination. Additional adverse reactions

determined from the clinical trial data are lymphadenopathy, nausea and malaise. Since authorization of BNT162b2, anaphylaxis has been reported and determined to be an adverse reaction. For details see the current BNT162 IB.

Treatment of these adverse reactions is at the discretion of the investigators; however, the following suggestions are provided:

- After the first occurrence of flu-like symptomatology including fever, subjects can be treated with standard therapeutic dose of acetaminophen (preferable), or a nonsteroidal anti-inflammatory drug if acetaminophen is contraindicated.
- Ensure adequate hydration of trial subjects on the day of immunization, e.g., by asking trial subjects to drink water (0.5 to 1.0 L) before each site visit and during the ~2 h after each immunization per trial site standard.

If subjects experience enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 3 days, symptom kinetics that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered, and the Medical Monitor should be informed.

If any trial subjects report symptoms that could represent myocarditis or pericarditis, please follow the CDC Clinical Considerations for myocarditis and pericarditis following COVID-19 vaccination published on 28 MAY 2021 (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html):

- For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis is unlikely.
- Consider consultation with:
- Cardiology for assistance with cardiac evaluation and management.
- Infectious disease and/or rheumatology to assist in this evaluation.

Where available, evaluate for potential etiologies of myocarditis and pericarditis, particularly acute COVID-19 infection (e.g., polymerase chain reaction [PCR] testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid-binding antibodies), and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing.

8.6 Safety stopping criteria

The SRC will review and evaluate the collected safety data for Part A, Part B, and Part C independently. The SRC will review and evaluate all reported SAEs and AESIs from the trial approximately every 4 weeks during the trial until all subjects have completed 28 days follow-up and as described in the SRC charter.

A decision to stop treatment for an individual subject or to terminate the trial may be taken by the sponsor and investigator if safety concerns are identified by the SRC.

All SAEs and SUSARs will be reviewed by the SRC as soon as possible. Any trial SAE or SUSAR in Part A may trigger a temporary stop of IMP administration to new subjects in Part A until the SRC has reviewed and discussed the relevant data and agree on a recommendation to allow or permanently stop further IMP administration for Part A.

8.7 Pharmacokinetics

Not applicable.

8.8 Pharmacodynamics

Not applicable.

8.9 Genetics

Blood and/or isolated peripheral blood mononuclear cells (PBMCs) of subjects in the biomarker/PBMC subgroup may be used for human leukocyte antigen (HLA) typing to allow additional analysis, e.g., characterization of T-cell receptor or B-cell receptor repertoire and/or phenotypic characterization of antigen-specific T cells. Data generated with these additional analyses may provide information about the HLA dependency of immune response (e.g., if distinct HLA types have stronger/better immune response towards SARS-CoV-2).

Blood samples will only be used for genetic analysis if the trial subjects have provided separate informed consent for this genetic analysis.

8.10 Immune responses

Immune responses will be assessed at the times listed in the SoA (Section 1.3).

Instructions on the sample collection, handling, and shipping will be provided in a Laboratory Manual.

If recommended by the SRC, e.g., for subjects who present AEs which are potentially immune mediated, stored samples may be tested retrospectively for relevant clinical parameters (e.g., troponin, cytokine).

Leftover biosamples (blood, the derived PBMCs, or serum), after completion of the serology assessments will be used for the analyses as described in Section 8.10.3 (i.e., for explorative biomarker/immunogenicity research purposes).

Trial subjects will be asked if leftover biosamples may also be used for explorative research purposes, e.g., to develop methods, assays, etc., related to BNT162 vaccine candidates. The use of leftover samples for these purposes will require a separate informed consent (see Section 10.1.3).

8.10.1 Humoral immunogenicity assessments

Humoral immunogenicity assessments comprise:

- Humoral immunogenicity assessments: A functional antibody titer, e.g., virus neutralization test (VNT) or an equivalent assay (e.g., pseudo-virus neutralization test [pVNT]), or serum immunoglobulin (Ig) ELISA.
- Seronegative is defined as titers below the starting dilution (i.e., below the limit of detection for the assay).
- SR after immunization is defined as follows:
- for seronegative pre-immunization sera: a titer which is 4-fold the limit of detection.
- for seropositive pre-immunization sera: a titer which is 4-fold the measured pre-immunization titer.

8.10.2 T and B cell-mediated immune responses

For a subset of subjects in Parts A, B, or C, samples will be collected for assessment of T cell- and B cell-mediated immune responses to VOCs and reference strains:

- T-cell responses include responses mediated by immune cells such as CD4 and CD8 T cells and their functional phenotypic subset by, e.g., enzyme-linked immunospot (ELISpot), intracellular cytokine staining (ICS), multimer analyses, cytokine secretion assays, flow cytometry, and other tests.
- These analyses may further include CD4 and CD8 T cells, Th1-specific cytokines (e.g., IFN-gamma, TNF-alpha, IL-2, or IL-12) and Th2-specific cytokines (e.g., IL-4, IL-5, IL-10, IL-13) to analyze the induction of either balanced Th1/Th2 responses, or of unbalanced Th1-dominant or Th2-dominant immune responses, respectively.
- B cell analyses will include characterization of SARS-CoV-2 S protein-specific B cells to identify B cells recognizing conserved and strain-specific epitopes, further single cell variability diversity joining analysis and somatic hyper-mutation analysis may also be performed.
- Some of the sample may be used for sequencing of trial subjects' antibody and/or B cell receptor heavy- and light-chain genes, T-cell receptor genes, and/or mRNAs, for further understanding the B cell, T cell, and antibody repertoires.

8.10.3 Explorative research

For consenting subjects in all cohorts, after completion of the planned investigations of the immune response, any residual biosamples may be used for explorative biomarker/immunogenicity research. In addition, in Cohorts 1 to 5 (inclusive), additional blood will be drawn for explorative biomarker/immunogenicity research at the times given in the SoA (Section 1.3).

This research may include investigation of vaccine-induced immune responses, including against SARS-CoV-2 variants by use of, but not limited to, phenotypic or functional characterization of antigen-specific B cells and T cells (e.g., by flow cytometry-based phenotyping including multimer staining), analysis of B cell receptor /T cell receptor

repertoire (e.g., by next generation sequencing, in subjects that consent to genetic testing [see Section 10.1.3]) and multiplex-cytokine analysis. This explorative research may also be used to develop methods, assays, etc.

In addition, residual biosamples may be stored and analysis may be performed on exploratory biomarkers thought to play a role in the mechanism of action of BNT162 and other BioNTech vaccine candidates to evaluate their association with observed clinical responses to BNT162 or other vaccine candidates.

Biosamples for explorative research purposes will be retained for use for up to 5 years after the end of the trial. Subjects will be informed about biosample storage and consent will be obtained. The tube with the biosample will be labeled with a number (optionally also with a bar code) to keep the subject's identity confidential; the tube label will not include information that could be used to identify the subject. Results of the analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and biosamples. Research biosamples and all data generated using the biosamples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for biosample shipment outside Germany, and a potential withdrawal of consent. The results of the sample analysis for explorative research will not be shared with the subject.

8.11 Baseline data

8.11.1 Demographic data

At screening, the following demographic data will be recorded for all trial subjects:

- Age (in years/months)
- Sex (male/female)
- Ethnic group

8.11.2 Medical history

Medical history information will be recorded at the times given in the SoA (Section 1.3).

8.12 Blood collection

The total blood volume drawn over any 46-day period in any cohort is always less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs or *ad hoc* COVID-19 visits. Assuming there are no COVID-19 visits, the total volume of blood drawn for subjects in each cohort is summarized below.

Cohort	Maximum total blood drawn	Blood sampling period
Part A: Cohorts 1, 3, 4, and 5	760 mL	Approximately 53 weeks
Part A: Cohort 2	1,110 mL	Approximately 61 weeks
Part A: Cohort 6	1,085 mL	Approximately 56 weeks
Part B: Cohort 1 and 4	115 mL	Approximately 53 weeks
Part B: Cohort 6	1,085 mL	Approximately 56 weeks
Part C: Cohorts 7 and 8	1,015 mL	Approximately 53 weeks
Part C: Cohort 9	685 mL	Approximately 12 weeks

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Statistical hypotheses will only be tested in Part B, separately for each cohort. Immunobridging success in each Part B cohort requires demonstration of non-inferior antibody levels in both geometric mean titers (GMTs) and SR rates against both VOCs (B.1.1.7 and B.1.617.2) in Cohorts 1 and 6 and against B.1.617.2 in Cohort 4 after the booster dose vs antibody levels against reference strain after two doses of BNT162b2. Where, booster dose is defined as the 1st dose of BNT162b2 (B.1.1.7 + B.1.617.2) for Cohort 1, 1st dose of BNT162b2 (B.1.617.2) for Cohort 4 and 2nd dose BNT162b2 (B.1.1.7 + B.1.617.2) for Cohort 6. In addition, non-inferiority of immune response against reference strain 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) in Cohort 6 subjects with evidence of prior infection vs immune response against reference strain 1 month after two doses of BNT162b2 in subjects without evidence of infection will also be assessed using the same success criteria.

9.1.1 GMT non-inferiority

The primary statistical hypothesis for GMT non-inferiority of each variant and reference strain is:

H_0: $\mu_{ratio} \leq 0.67$ vs H_1: $\mu_{ratio} > 0.67$

where 0.67 corresponds to a 1.5-fold margin for non-inferiority, and μ_{ratio} is the ratio of GMT of VOC specific NT at 1 month after booster dose or 1 month after the second dose of BNT162b2 (B.1.1.7 + B.1.617.2) to the reference NT at 1 month after second dose of BNT162b2 or ratio of GMT of reference strain NT at 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to 1 month after the second dose of BNT162b2.

GMT VOC non-inferiority success for Cohorts 1 and 6 will be declared if the lower bound of the 2-sided 95% confidence intervals (CIs) for (1) $GMR_{B.1.1.7/ref}$ (GMT of B.1.1.7 ÷ GMT of reference) and (2) $GMR_{B.1.617.2/ref}$ (GMT of B.1.617.2 ÷ GMT of reference) are both greater than 0.67. GMT reference strain non-inferiority success for Cohort 6 will be declared if the lower bound of the 2-sided 95% CI for $GMR_{ref/ref}$ (GMT of reference ÷ GMT of reference) is greater than 0.67. GMT VOC non-inferiority success for Cohort 4 will be declared if the lower bound of the 2-sided 95% confidence interval $GMR_{B.1.617.2/ref}$ (GMT of B.1.617.2 ÷ GMT of reference) is greater than 0.67.

9.1.2 SR non-inferiority

The primary statistical hypothesis for SR non-inferiority for each variant and reference strain is:

H_0: $\pi_{variant} - \pi_{reference} \leq -10\%$ vs H_1: $\pi_{variant} - \pi_{reference} > -10\%$

where $\pi_{variant}$ is the SR against the VOC at 1 month after booster dose or 1 month after the second dose of BNT162b2 (B.1.1.7 + B.1.617.2) or SR against the reference strain at 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) and $\pi_{reference}$ is the SR against the reference strain at 1 month after second dose of BNT162b2.

The SR VOC non-inferiority success for Cohorts 1 and 6 will be declared if the lower bounds of the 2-sided 95% CIs for the difference of (1) SR of B.1.1.7 – SR of reference and (2) SR of B.1.617.2 – SR of reference are both greater than -10%. The SR reference strain non-inferiority success for Cohort 6 will be declared if the lower bounds of the 2-sided 95% CIs for the difference in SRs of reference is greater than -10%. The SR VOC non-inferiority success for Cohort 4 will be declared if the lower bound of the 2-sided 95% CI for the difference of SR of B.1.617.2 – SR of reference is greater than -10%.

SR is defined as a ≥4-fold rise in neutralizing titer from baseline. For subjects with a baseline titer less than the lower limit of quantitation (<LLOQ), seroresponse is defined as a post-vaccination titer of ≥4× LLOQ.

9.1.3 Multiplicity considerations

Multiplicity considerations are only relevant for Part B. The fixed sequential testing procedure will be used for multiplicity control for each cohort separately, all at 1-sided 2.5% level of significance.

For Cohort 1 and Cohort 4, the hypotheses will be tested in the following sequence:

- Non-inferiority in terms of GMTs
- Non-inferiority in terms of SRs

For Cohort 6, the hypotheses will be tested in the following sequence:

- Non-inferiority of immune response against reference strain in terms of GMT
- Non-inferiority of immune response against reference strain in terms of SR
- Non-inferiority of immune response against VOCs vs reference strain in terms of GMTs
- Non-inferiority of immune response against VOCs vs reference strain in terms of SRs

9.2 Sample size determination

Planned enrollment is ~1,470 subjects; ~120 in Part A (~20 in each of the six cohorts), ~1,125 in Part B (~375 in each of the three cohorts), and ~225 in Part C (~80 in each of Cohort 7 and Cohort 8 and ~45 in Cohort 9).

9.2.1 Part A

The sample size for Part A of the trial is not based on any statistical hypothesis testing. Part A comprises 20 subjects per cohort, corresponding to a total of 120 subjects.

9.2.2 Part B

GMR: assuming an observed GMR of 0.8 and standard deviation of 0.7 (log scale), 300 evaluable subjects will provide 87% power at alpha = 0.025 (1-sided) to demonstrate non-inferiority of VOC vs reference strain response. Table 11 demonstrates the power for testing GMT for each variant strain vs reference strain at alpha = 0.025 (1-sided).

SR: assuming an SR difference of -3% (variant SR – reference SR) and 97% reference SR, 300 evaluable subjects will provide 96% power at alpha = 0.025 (1-sided). Table 12 demonstrates the power for testing SR for each variant strain vs reference strain at alpha = 0.025 (1-sided) to demonstrate non-inferiority of VOC vs reference strain response.

To account for a 20% non-evaluable rate, 375 subjects will be enrolled for each cohort.

In Cohort 6, assuming 80% subjects with evidence of prior infection, 240 evaluable subjects will contribute to the hypotheses for non-inferiority of immune response against reference strain. Table 11 and Table 12 show the power to demonstrate non-inferiority of immune response against reference strain under various assumptions in terms of GMT and SR, respectively.

Table 11: Power analysis for immunogenicity GMT hypotheses

Test	Margin	Assumed GMR	Number of evaluable subjects	SD log scale	Power
VOC vs reference strain GMT non-inferiority	0.67	0.8	300	0.65	92%
				0.70	87%
				0.75	82%
Reference strain vs reference strain GMT non-inferiority	0.67	0.8	240	1.05	46%
		0.9	240	1.05	87%
		1.0	240	1.05	99%

GMT = geometric mean titer; GMR = geometric mean ratio; SD = standard deviation; VOC = variant of concern.

Table 12: Power analysis for immunogenicity SR hypotheses

Test	Margin	SR difference	Number of evaluable subjects	Reference SR	Power
VOC vs reference strain SR non-inferiority	-10%	-3%	300	98%	98%
				97%	96%
				95%	90%
Reference strain vs reference strain SR non-inferiority	-10%	-3%	240	98%	95%
				97%	91%
				95%	83%
	-10%	-5%	240	98%	65%
				97%	59%
				95%	50%

Margin is the lower bound of 95% CI.
CI = confidence interval; SR = seroresponse; VOC = variant of concern.

9.2.3 Part C

No confirmatory hypothesis testing is planned for Part C. However, exploratory analysis may be performed on selected endpoints. To describe the immune profile 80 evaluable subjects per cohort in Cohorts 7 and 8 and 40 evaluable subjects in Cohort 9 are considered adequate based on experience in previous trials conducted by BioNTech in the BNT162 program.

Table 13 below demonstrates the power for testing GMT for variant strain post BNT162b2 vs post BNT162b2 (B.1.1.529) at alpha = 0.025 (1-sided) to demonstrate superiority.

To account for ~11% non-evaluable rate, Part C will randomize 225 subjects in a 2:2:1 ratio (90 each for Cohorts 7 and 8 and 45 in Cohort 9).

Table 13: Power analysis for immunogenicity GMT comparison

Test	Margin	Assumed GMR (GMT variant ÷ GMT ref)	Number of evaluable subjects	Standard deviation (log value)	Power
GMT superiority	1.0	1.75	80	1.0	94%

Margin is the lower bound of 95% CI for GMR.
GMT = geometric mean titer; GMR = geometric mean ratio.

9.3 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All subjects who signed informed consent.
Safety Set	All subjects who received at least one dose of IMP.
Immunogenicity Analysis Set	All eligible randomized/assigned subjects who receive the trial intervention to which they are randomized or assigned, have a valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations that can confound immunogenicity data.
Reactogenicity Set	All subjects included in the Safety Set with any e-diary data reported after IMP injection.

9.4 Statistical analyses

This section gives a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The statistical analysis plan (SAP), with all details of statistical analyses, will be finalized prior to database snapshot for the primary analysis.

Unless otherwise specified, all statistical analysis will be performed by cohort and separately for Part A, Part B, and Part C. Safety analyses will be performed on the Safety Set. Antibody analyses will be performed on the Immunogenicity Analysis Set.

9.4.1 General considerations

Categorical variables will be summarized presenting absolute and relative frequencies (n and %) of subjects in each category.

Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum, and maximum.

Analysis of antibody titers will be performed on natural log scale and the results will be exponentiated back to original scale.

9.4.2 Safety endpoints

The safety endpoints are defined in Section 3.

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system to get a system organ class and preferred term (PT) for each AE.

Reactogenicity

Solicited local and systemic reactions (from the subject e-diary) will be summarized using the Safety Set. In general, solicited reactions will be analyzed for each immunization, i.e.:

- Up to 7 d after each IMP injection

For each injection, the number and percentage of subjects reporting at least one local reaction or systemic reaction (i.e., solicited data collected using subject e-diaries) will be summarized for each of the following types using the Safety Set:

- Any local reactions or systemic reactions
- Grade ≥3 local reactions or systemic reactions

Moreover, the number and percentage of subjects reporting at least one local reaction will be summarized by worst grade using the Safety Set.

Unsolicited TEAEs

The number and percentage of subjects reporting at least one treatment-emergent adverse event (TEAE; defined in Section 10.3.1) will be summarized by PT nested within system organ class for each of the following AE types using the Safety Set:

- Any AE
- Related AE
- Grade of AE
- Related Grade ≥3 AE
- AESI
- Any solicited AE that starts on Days 1 to 7 and continues longer than 7 d post-vaccination or starts after Day 7 or is an SAE
- Any SAE
- Related SAE

Moreover, the number and percentage of subjects with any AE will be summarized by worst grade by PT nested within system organ class.

Additional AE analyses may be described in the SAP.

9.4.3 Immunogenicity endpoints

The immunogenicity endpoints are defined in Section 3. The scheduled time points for assessment are given in the SoA (see Section 1.3).

9.4.3.1 Geometric mean ratios

The GMT non-inferiority for each Part B cohort will be tested using GMR for the Immunogenicity Analysis Set, estimated by the ratio of GMT of VOC specific NT 1 month after the final trial dose to the GMT of reference specific NT 1 month after the second dose of BNT162b2 or ratio of GMT of reference strain NT at 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to 1 month after the second dose of BNT162b2. A linear regression model with age, sex and group (each Part B cohort vs reference) as explanatory variables and natural log transformed antibody titers as dependent variable will be used to calculate the adjusted GMR and 2-sided 95% CI.

The GMR of Part C Cohorts 7 over Cohort 8 will be reported for the Immunogenicity Analysis Set, estimated by the ratio of GMT of VOC specific NT 1 month after one dose of IMP in Cohort 8 to that of Cohort 7.

As exploratory analysis, unadjusted GMR for the Immunogenicity Analysis Set, 95% CIs will also be reported for the above comparisons.

The detailed statistical methodology will be specified in the SAP.

9.4.3.2 Seroresponse

The SR non-inferiority for Part B will be tested using difference (SR variant – SR reference) for the Immunogenicity Analysis Set, estimated by the difference of VOC specific SR 1 month after the final trial dose to reference specific SR 1 month after Dose 2 of BNT162b2 or difference of reference strain SR at 3 weeks after one dose of BNT162b2 (B.1.1.7 + B.1.617.2) to reference strain SR at 1 month after the second dose of BNT162b2. The difference will be estimated using minimum risk weights and stratified by sex and age group (18 to 55 years, 56 to 85 years). The associated 95% CI will be calculated using stratified Newcombe confidence interval weighted with minimum risk to combine the stratum components and continuity correction.

The SR difference of Part C Cohort 7 vs Cohort 8 will be reported for the Immunogenicity Analysis Set, estimated by the difference of VOC specific SR 1 month after one dose of IMP in Cohort 8 to that of Cohort 7. The difference will be estimated using minimum risk weights and stratified by randomization stratification factors; associated 95% CI will be calculated using stratified Newcombe confidence interval weighted with minimum risk to combine the stratum components and continuity correction.

As exploratory analysis, unadjusted difference of SR for the Immunogenicity Analysis Set will be calculated as the difference in SRs between VOC and reference. The 95% CI will be obtained using Newcombe Score Confidence Limits.

9.4.3.3 Geometric means

The geometric means on NT for each cohort will be calculated separately for Part A, Part B, and Part C as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

9.4.4 Exploratory endpoints

The exploratory endpoints are defined in Section 3. Exploratory analyses will be described in the SAP.

9.4.5 Other safety analyses

All other safety analyses will be based on the Safety Set and will be summarized descriptively by group unless otherwise stated.

Details of the other safety analyses will be described in the SAP.

9.4.6 Other analyses

Other analyses will be described in the SAP.

9.5 Interim analyses

No formal interim statistical analysis is planned. Primary immunogenicity analysis for all Part B cohorts and for Part C Cohorts 7 and 8 will be performed after completion of 1-month post-dose visit.

9.6 Data monitoring committee

No Data Monitoring Committee is planned. An SRC is planned, for details see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

10.1.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to the relevant IEC/IRB for review and (if required) approval by the IEC/IRB before the trial is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

The coordinating investigator or delegate will be responsible for the following:

- Providing written summaries of the status of the trial to the relevant IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IECs/IRBs.
- Notifying the IECs/IRBs of SAEs or other significant safety findings as required by IEC/IRB procedures.

- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IECs/IRBs, EU 536/2014 (if applicable), and all other applicable local regulations.

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

10.1.2 Financial disclosure

All investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed consent process

Informed consent must be obtained before any trial-specific screening procedure is performed.

Trial subjects must be informed that their participation is voluntary.

The investigator or his/her representative will explain the nature of the trial to the trial subject and answer all questions regarding the trial.

Trial subjects will be required to sign a statement of informed consent that meets the requirements of local regulations (e.g., 21 CFR 50), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IECs/IRBs or trial site.

The medical record must include a statement that written informed consent was obtained before the trial subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Trial subjects must be informed in a timely manner if new information becomes available that may impact their willingness to participate in the trial. If required, trial subjects will be re-consented to updated written information and consent forms.

Trial subjects who are rescreened must re-consent.

A copy of the ICF(s) must be provided to the trial subject.

Trial subjects must be re-consented to the most current version of the ICF during their participation in the trial.

Separate informed consent will be obtained for the use of leftover blood for genetics (see Section 8.9) and for research purposes (see Section 8.10.3).

10.1.4 Data protection

Trial subjects will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. Any trial subject records or datasets that are transferred to the sponsor will contain the identifier only; trial subject names or any information which would make the trial subject identifiable will not be transferred.

Trial subjects must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the trial subject who will be required to give consent for their data to be used as described in the informed consent.

Trial subjects who withdraw consent must be informed that the data collected up until consent was withdrawn will still be used by the sponsor as described in the ICF.

Trial subjects must be informed that their medical records may be examined by sponsor quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

10.1.5 Committees - SRC

Safety reviews of the unblinded data will be conducted by the SRC approximately every 4 weeks and on an *ad hoc* basis. The SRC will review all safety data, including AESIs, and SAEs, as well as laboratory data and other relevant safety data.

After all subjects enrolled into Part A, Part B, and Part C have completed their 1-month follow-up visit, the SRC members will continue to receive safety data (related AEs, AESIs, SAEs) on a monthly basis, but further SRC meetings will occur approximately every 6 months unless triggered earlier by SRC member requests or if SUSARs/AESIs are reported.

The SRC will be constituted and act according to written procedures described in a charter. The SRC will prepare written minutes of its meetings.

The SRC will at least comprise a sponsor medical representative, the Medical Monitor, a statistician, coordinating investigator, a sponsor-independent investigator, and on an *ad hoc* basis, a representative for the respective trial site depending on the trial subject in question. The SRC will include an independent cardiologist as an *ad hoc* member to advise on specific issues or questions in case of suspected myocarditis or pericarditis.

10.1.6 Dissemination of clinical trial data

A final ICH E3 conform clinical trial report integrating the results for all defined and secondary outcome measures and the results for select exploratory endpoints available at the time of the final report drafting will be prepared by the sponsor. The results of the explorative research will be reported separately.

In all cases, trial results will be reported in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the trial or the country in which the trial was conducted.

Clinical trial data and documentation will be disseminated as required per applicable laws and regulations, e.g., the EU Regulation No 536/2014, EU Regulation 1049/2001, and the US Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801). Clinical documents under such laws include protocols and protocol amendments, SAPs, ICH E3 clinical study reports.

This clinical trial will be registered, and trial results publicly posted, on publicly accessible trial registries (e.g., ClinicalTrials.gov, the EU Clinical Trials Register, etc.) in accordance with the applicable regulations.

If this clinical trial is used to support marketing authorization packages/submissions, the sponsor will comply with the EU Policy 0070, the proactive publication of clinical data on the European Medicines Agency (EMA) website. Clinical data, under Phase I of this policy, includes clinical overviews, clinical summaries, ICH E3 clinical study reports, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Under Phase II of this policy, “clinical data” includes the publishing of individual patient data.

Even if not required by applicable laws and regulations, this trial will be registered, and trial results be publicly posted on ClinicalTrials.gov. In addition, expert summaries of the outcomes for all primary and secondary outcome measures (irrespective of outcome) and lay summaries, will be posted on a publicly accessible website.

The results for all primary and secondary outcome measures, irrespective of outcome, may be submitted for publication in academic journals (for further details, see Section 10.1.10).

10.1.7 Data quality assurance

All trial subject data relating to the trial will be recorded in a CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit trial-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other parties (e.g., contract research organization [CRO]).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from

source documents; that the safety and rights of trial subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source documents

Source documents including subject e-diaries provide evidence for the existence of the trial subject and substantiate the integrity of the data collected. Source documents are filed in the ISF.

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject e-diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

10.1.9 Trial and site start and closure

The trial start date is the date on which the trial will be open for enrollment of trial subjects at any site.

The site start date is the date on which the site will be open for enrollment of trial subjects.

The sponsor reserves the right to close the trial site or terminate the trial or a group within the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of trial subjects by the investigator.
- Discontinuation of further trial treatment development.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the trial subject and should assure appropriate follow-up.

10.1.10 Publication policy

The results for all primary and secondary outcome measures, irrespective of outcome, will be submitted by the sponsor for publication in academic journals. The results of this trial may also be presented by the sponsor at scientific meetings.

The results of this trial may be published or presented at scientific meetings by the investigator. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This will allow the sponsor to protect proprietary information and to provide comments.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any trial treatment-related information necessary for the appropriate scientific presentation or understanding of the trial results.

Unless agreed in advance otherwise, site- or subpopulation-specific analyses may only be published after the outcomes of the primary endpoint analyses have been published.

The sponsor will comply with the requirements for the publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-site trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

10.1.11 Protocol preparation and approval

This protocol has been prepared, reviewed and approved, including wet ink sign-off by the sponsor's responsible person, in accordance with the sponsor's standard operating procedures. Documentation of this process is filed in the TMF.

10.2 Clinical laboratory tests

Blood and urine will be collected for clinical laboratory tests at the times given in the SoA (Section 1.3). The below list is the required minimum, but local sites may include additional parameters.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

Clinical chemistry

Alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium.

Follicle stimulating hormone: Only in women who are not considered WOCBP.

Urinalysis

Dipstick: glucose, bilirubin, ketone, specific gravity (1 mL ≙ 1 g), blood, pH, protein, urobilinogen, nitrite, and leukocytes.

Microscopic urinalysis: If warranted by dipstick results, urine sediment will be microscopically examined for presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

10.3 Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE, TEAE, and AESIs

- An AE is any untoward medical occurrence in a trial subject, temporally associated with the use of trial treatment, whether or not considered related to the IMP.
  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is clinically significant), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.
- A TEAE is defined as any AE with an onset after the first IMP injection or worsened after the first IMP injection (if the AE was present before the first administration of IMP).
- For a definition of AESIs, see Section 8.3.8.

10.3.1.1 Events meeting the AE definition

- Any abnormal laboratory test results or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, and which are considered clinically significant in the medical and scientific judgment of the investigator, may be considered as AEs.
- New conditions or (at the discretion of the investigator) any worsening of a pre-existing condition detected or diagnosed after Visit 0.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE.

10.3.1.2 Events <u>not meeting</u> the AE definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.1.3 Suspected adverse reaction

All untoward and unintended responses to an IMP-related to any dose administered.

- The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship and an alternative etiology is not apparent.

10.3.1.4 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.
- The term “life-threatening” in the definition of “serious” refers to an event in which the trial subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires trial subject hospitalization or prolongation of existing hospitalization.
- In general, hospitalization signifies that the trial subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out trial subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
- Results in persistent disability/incapacity.

  This definition is not intended to include cases of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or is a birth defect.
- Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the trial subject or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.1.5 Suspected unexpected serious adverse reactions

All suspected adverse reactions related to an IMP that occur in this trial and that are both unexpected and serious are SUSARs. SUSARs are subject to expedited reporting.

10.3.1.6 Use of the terms “severe” and “serious”

Severity (intensity or grade) and seriousness need to be assessed independently for each AE and be recorded in the CRF. For a definition of the terms “severe” and “serious” for AEs, see:

- Section 10.3.1.7 for AEs.
- Section 10.3.1.4 for SAEs (see Section 10.3.1.10 for SAE reporting instructions).

10.3.1.7 Recording and follow-up of AE and/or SAE

AE and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation as defined in Section 8.3.1.

Data pertaining to AEs will be collected during each trial visit and the clinical significance of any sign or symptom needs to be evaluated by the investigator.

- Clinically significant findings need to be documented as AEs in the source data and CRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation), should not be documented as AE.
- AEs that are related to one clinical event should be subsumed under that event when recorded on the CRF. For example, elevated creatinine, nausea, vomiting, hypercalcemia should be subsumed under renal failure if that explains the etiology for the subsumed signs and symptoms.
- The investigator will then record AE information in the CRF and perform an assessment on:
- Intensity, see the section “Assessment of AE and/or SAE intensity” for guidance on the assessment of intensity,
- Seriousness,
- Outcome,
- Causal relationship of the AE to the trial treatment,

- Any trial treatment action and/or any other action taken.
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the CRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all trial subject identifiers, with the exception of the trial subject number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of AE and/or SAE intensity

The assessment of AE and/or SAE intensity should be done consistently for all subjects treated with the same treatment and dose. In case of doubt, the Medical Monitor should be consulted.

The intensity of AEs or SAEs will be graded by the investigator. For further guidance refer to the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Where specific guidance for an adverse event term is not provided, the following general approach should be followed:

- Grade 1 - Mild; does not interfere with the subject's usual function.
- Grade 2 - Moderate; interferes to some extent with the subject's usual function.
- Grade 3 - Severe; interferes significantly with the subject's usual function.
- Grade 4 - Potentially life-threatening; life-threatening consequences, urgent intervention required.

Actions taken by the investigator

Actions taken by the investigator as a result of an AE must be documented.

Action(s) taken with trial treatment (IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Drug withdrawn
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

Other action(s) that may be taken by the investigator include:

- None

- Remedial drug therapy
- Other specific treatment(s) of AE (to be specified)

Outcome

The investigator has to assess the outcome of an AE (and not the trial subject's outcome) at the time of documentation based on the following criteria:

- Recovered/resolved * (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the trial subject deceases due to another cause)
- Recovered/resolved with sequelae * (= trial subject recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal ** (= death due to the AE)
- Unknown (e.g., in case the trial subject is lost to follow-up)

* Generally, an AE is defined as recovered/resolved if all symptoms have ceased, no medication for treatment of the event is taken anymore and no other measures (e.g., hospitalization) are ongoing.

If the trial subject has developed permanent or chronic symptoms or if the event requires long term medication(s), the AE is defined as recovered/resolved with sequelae as soon as no changes of symptoms and/or medication(s) are expected anymore.

An AE that is documented as a worsening of a medical condition already known at baseline, is defined as recovered as soon as the medical condition has returned to baseline status.

** In case of a fatal event, the event term should not be "death" but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only the AE leading to death will be attributed with the outcome "fatal". All other AEs ongoing at the time of death will be attributed with the outcome "not recovered/not resolved". A copy of an autopsy report should be submitted if available.

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment/trial procedure and each occurrence of each AE/SAE.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

It is sufficient to document the causality in the source data and CRF as:

- Related (= there is a reasonable possibility of a causal relationship) or
- Not related (= there is no reasonable possibility of a causal relationship)

Relationship to trial treatment

- The relationship or association of an AE or SAE to a trial treatment will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.
- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected.

Relationship to trial procedures including trial treatments

- In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure-related AEs can occur on the site of injection of the trial treatment e.g., redness, swelling, hematoma, or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.1.8 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC, and ENTR/CT-3 (see Section 10.3.1.4).

In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

- AEs and SAEs occurring after trial subject discharge from the trial must only be reported by the investigator to the sponsor if a relationship to trial treatment or trial procedure is suspected.
- Planned hospitalizations required by the protocol will not be considered as reportable SAEs.

10.3.1.9 Documentation of particular situations

AEs that are secondary to other events:

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be documented as an independent AE in source data and CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.
- If vomiting results in severe dehydration, both events should be documented as AEs separately.

Abnormal clinical laboratory results and vital signs values:

Not every laboratory or vital signs abnormality needs to be documented as AE. For clinically significant laboratory/vital signs abnormalities the following definitions and documentation rules apply:

- If a laboratory/vital signs abnormality is a sign of a disease or syndrome, the laboratory/vital signs abnormality is clinically significant and only the diagnosis of the causing disease or syndrome needs to be documented as AE.
- If a clinical laboratory/vital signs abnormality results in specific symptoms but no diagnosis of a disease or syndrome can be made, the laboratory/vital signs abnormality is clinically significant and only the symptoms need to be documented as AEs.
- If a clinical laboratory/vital signs abnormality is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.
- If a clinical laboratory/vital signs abnormality is not considered clinically significant by the investigator, then an AE does not need to be documented.

AEs associated with an overdose or error in drug administration:

- An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE. For a definition of an overdose, see Section 8.4.
- All AEs associated with an overdose or incorrect administration should be documented as AE in source data and CRF and reported as SAE if applicable.

10.3.1.10 Reporting of SAEs and AESIs

All SAEs and AESIs (even if non-serious) which occur in a trial subject during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following knowledge of the event.

All SAEs occurring after the end of the observation period only have to be reported to the sponsor if the investigator suspects a relationship to trial medication or the trial procedure.

SAE and AESI reporting to sponsor

For the period of observation, see Section 8.3.1.

For every SAE and AESI (even in the AESI is non-serious), the investigator needs to complete the applicable paper report form which must be sent to the sponsor via one of the following reporting methods:

- Safety Report Fax No.: [redacted]
- Safety Report E-mail Address: [redacted]

Information for final description and evaluation of a case report may not be available within the required time frames for reporting. Nevertheless, for regulatory purposes, initial reports should be submitted if the following minimal information is available:

- An identifiable trial subject (trial subject number)
- A suspected medicinal product
- An identifiable reporting source (investigator/trial site identification)
- An event or outcome that can be identified as serious

All SAE/AESI follow-up information should be sent to the sponsor (indicating that this is a "follow-up" report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending. In addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the SAE term and trial subject number.

A copy of the submitted SAE/AESI report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the IECs/IRBs or authority and retain documentation of these submissions in the ISF.

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via: E-mail: [redacted]

For medical questions, the sponsor's Medical Monitor for this trial should be contacted.

10.4 Contraceptive guidance and collection of pregnancy information

The following guidance is based on the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials issued in 2020 (CTFG 2020).

10.4.1 Definitions

Women of childbearing potential

For the purpose of this document, a woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with one of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For trial subjects with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel review of the trial subject's medical records, medical examination, or medical history interview.

Post-menopausal female

For the purpose of this document, a post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one follicle stimulating hormone measurement is required.

Females on hormonal replacement therapy and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their hormonal replacement therapy during the trial. Otherwise, they must discontinue hormonal replacement therapy to allow confirmation of post-menopausal status before trial enrollment.

Male trial subjects

Male trial subjects with previous successful bilateral vasectomy or orchidectomy, or those who are truly abstinent or exclusively homosexual are deemed as being "not of reproductive potential".

10.4.2 Contraception guidance

Trial subjects must meet the “Reproductive status” inclusion criteria, including contraception requirements, as listed in Section 5.1.

The investigator or delegate should advise the subject how to achieve highly effective contraception. The following birth control methods may be considered as highly effective:

- Combined estrogen and progestogen-based contraception hormonal contraception associated with inhibition of ovulation [a], i.e., established use of:
- oral,
- intravaginal, or
- transdermal hormonal methods of contraception.
- Progesterone-only based contraception associated with inhibition of ovulation [a], i.e., established use of:
- oral,
- injected, or
- implanted hormonal methods of contraception. [b]
- Intrauterine device. [b]
- Intrauterine hormone-releasing system. [b]
- Bilateral tubal occlusion. [b]
- Vasectomy (for a male subject or male partner of a female subject). [b, c]
- Sexual abstinence. [d]

a Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
b Contraception methods that in the context of this guidance are considered to have low user dependency.
c Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial subjects and that the vasectomized partner has received medical assessment of the surgical success.
d In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Unless practicing true sexual abstinence, the following birth control methods may be considered as acceptable but potentially not highly effective methods:

- Male or female condom with a spermicidal agent; both female and male condom should not be used together. [e]
- Cap diaphragm or sponge with a spermicidal agent. [e]

e A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

10.4.3 Collection of pregnancy information

Pregnancy information will be recorded at the times listed in the SoA (Section 1.3).

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female subject (or if a male subject's partner becomes pregnant, written informed consent from the pregnant partner).

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a trial subject's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or E-mail given in Section 10.3.1.10. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the ISF.

The investigator will collect follow-up information on the trial subject/trial subject's partner and the neonate and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the IMP. Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

10.4.4 Sperm donation

Trial subjects must comply with the inclusion criteria prohibiting sperm donation listed in Section 5.1.

10.5 Genetics

Not applicable.

10.6 Liver safety: Suggested actions and follow-up assessments

Not applicable.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with trial subject care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

10.7.2 Trial site personnel assigned trial-related duties

The principal investigator or deputy may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator or deputy must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

10.7.3 Contract research organizations

Documentation of all involved CROs must be maintained by the sponsor according to GCP and applicable regulatory requirements. This includes documentation of any delegation of responsibilities to CROs.

10.7.4 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

10.8 Country-specific requirements

Not applicable.

10.9 Protocol amendments and updates

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF for all protocol amendments and updates.

Also, changes made to the protocol during the protocol amendments or updates are described in the document Protocol Amendment History which is available upon request. This Protocol Amendment History is filed together with the respective protocol in the TMF.

10.9.1 Amendment 1.0 (update from protocol version 1.0 to 2.0)

The amendment implements updates in response to Center for Biologics Evaluation and Research (CBER) comments (dated 07 AUG 2021) on protocol version 1.0.

10.9.2 Amendment 2.0 (update from protocol version 2.0 to 3.0)

The amendment implements updates for clarification, updates reflecting the decision to perform SAR-CoV-2 viral genome sequencing for all subjects (and not just if triggered), and adaptions to the statistical analysis reflecting discussion of booster data analysis with the FDA which requires the exclusion of certain protocol deviations from the primary analysis and thereby makes the Per Protocol Set redundant.

10.9.3 Amendment 3.0 (update from protocol version 3.0 to 4.0)

This amendment implements three additional cohorts (Cohorts 7, 8, and 9) within Part C, comprising an additional ~410 subjects who:

- have received two or three doses of any authorized COVID-19 RNA-based vaccine, e.g., 30 µg BNT162b2 (Comirnaty) or the Moderna vaccine (Spikevax), and
- had a breakthrough SARS-CoV-2 infection from January 2022 on (limited to a period when there was a high prevalence of SARS-CoV-2 Omicron infections).

Subjects in Part C will receive either 30 µg of the monovalent BNT162b2 (B.1.1.529) as a third or fourth dose, 30 µg BNT162b2 as a third or fourth dose, or no vaccination within 3 months of Visit 1.

In addition, a third dose of the multivariant vaccine has been added for Cohort 6, Parts A and B comprising BNT162b2-naïve subjects, with planned visits at pre-Dose 3, 1-week post-Dose 3, and 1-month post-Dose 3.

For subjects who receive non-trial SARS-CoV-2 vaccinations, blood samples for humoral immunogenicity and T-cell and B-cell response assessments will not be collected, and they will be discontinued from the BNT162-17 trial.

The amendment also includes updates for clarification and an updated Table 8, which following the request of the IEC in Germany now includes information on the SARS-CoV-2 Omicron variant.

10.9.4 Amendment 4.0 (update from protocol version 4.0 to 5.0)

This update implements a change in eligibility criteria for Part C. Eligibility criteria were updated to correspond to the existing regulatory guidance, clarifying the required time

frame between the last dose of the COVID-19 RNA-based vaccine and first IMP dose. The two-month window between the documented SARS-CoV-2 infection and trial IMP administration was implemented to reduce heterogeneity in baseline VNT levels which may affect immune responses after trial vaccine administration. The mandatory NAAT test as a confirmation of prior SARS-CoV-2 infection was adjusted according to suggested updated algorithms for SARS-CoV-2 infection diagnostics.

In addition, based on the recent immunogenicity data from the BNT162b2 Omicron variant vaccine in the BNT162-16 trial, the sample size and expected GMR have been adjusted accordingly.

10.9.5 Amendment 5.0 (update from protocol version 5.0 to 6.0)

This update implements a correction, specifically the insertion of Table 5.

10.9.6 Amendment 6.0 (update from protocol version 6.0 to 7.0)

This amendment implements updates in response to FDA comments (dated 08 JUN 2023) and the decision to include additional immunogenicity analyses in the primary objectives and secondary objectives for COVID-19 vaccine-naïve subjects (Cohort 6) in Part B.

See the table below for a summary of the reasons for major changes compared to the previous version. Minor editorial changes, such as the correction of typing errors or formatting, are not specifically listed here. A redline draft showing all content updates is available upon request.

Section	Reason for change
All sections	The date and version number were updated.
All applicable sections	Updates to clarify that the original Omicron strain B.1.1.529 has since been renamed B.1.1.529.1 (known as Omicron BA.1), with the Omicron lineage having expanded into multiple sublineages. Notes were added in applicable sections.
Title page	The sponsors medical representative was updated. The document history was updated to reflect this update.
1 and 2.2	1 (Trial rationale) and 2.2 (Trial rationale) updated to reflect the current BNt162b2 authorization status. Updates to clarify that the original Omicron strain B.1.1.529 has since been renamed B.1.1.529.1 (known as Omicron BA.1), with the Omicron lineage having expanded into multiple sublineages. Updates to explain how the data from Part B of the trial will be used.
1 and 3	1 (Objectives and endpoints) and 3 (Objectives and endpoints) Updates for clarification, to reflect the additional immunogenicity analyses, and correction. This included the addition of two Primary objectives (Immunogenicity) and two secondary objectives for Part B.
1 and 4.1	1 (Trial design) and 4.1 (Overall design) Update to reflect addition of new analyses.
1.3	1.3 (Schedule of activities) Update of applicable table headers to reflect a change from “BNT162-naïve subjects” to “COVID-19 vaccine-naïve subjects”
ABBREVIATIONS/ TERMS	Updates to reflect updates elsewhere and addition of missing entries.
2.1.1	2.1.1 (Overview of the disease)

Section	Reason for change
	Updates to reflect the current disease status.
2.3.1	2.3.1 (Risk assessment) Updates to add data cutoff dates.
6.3	6.3 (Measures to minimize bias: randomization and blinding) Text updated for clarification.
8.3.4	8.3.4 Regulatory reporting requirements for SAEs) Text updated for clarify where to find reference safety information in the current BNT162 IB.
9.1	9.1 (Statistical hypotheses) Updates to reflect the additional immunogenicity analyses.
9.1.1	9.1.1 (GMT non-inferiority) Insertions to reflect the additional immunogenicity analyses.
9.1.2	9.1.2 (SR non-inferiority) Insertions to reflect the additional immunogenicity analyses.
9.1.3	9.1.3 (Multiplicity considerations) Insertions to reflect the additional immunogenicity analyses.
9.2.2	9.2.2 (Part B) Insertions to reflect the additional immunogenicity analyses.
9.4.3.1	9.4.3.1 (Geometric mean ratios) Insertions to reflect the additional immunogenicity analyses.
9.4.3.2	9.4.3.2 (Seroresponse) Insertions to reflect the additional immunogenicity analyses.
10.3.1.10	10.3.1.10 (Reporting of SAEs and AESIs) Updates for clarifications on the new e-mail addresses and fax number for safety reporting.
10.9.6	10.9.6 [Amendment 6.0 (update from protocol version 6.0 to 7.0)] Section added to summarize this update.

10.10 Data collection and management

The trial documentation must be adequate for the reconstruction of the trial.

10.10.1 Case report forms

CRFs will be completed through use of an electronic data capture (EDC) system. Trial site personnel will receive training and have access to a manual for appropriate CRF completion. The CRFs will be submitted electronically to the sponsor via the system and should be handled in accordance with instructions from the sponsor.

All CRFs should be completed by designated, trained trial site personnel. CRFs should be reviewed, verified, and then electronically signed and dated by the investigator or a designee.

At the end of the trial, the investigator will receive trial subject data for his/her trial site in a readable format that must be kept with the trial records. Acknowledgment of receipt of the trial subject data will be required.

10.10.2 Trial subject reported outcomes

Not applicable.

10.10.3 Data management

The CRO (see the title page) will be responsible for data management of this trial, including quality checking of the data.

Data entered manually will be submitted to the sponsor through use of an EDC system, data extracts, and reports. Trial sites will be responsible for data entry into the EDC system. In the event of discrepant data, the data management service provider will request data clarification from the trial sites, which the trial sites will resolve electronically in the EDC system.

The data management service provider will produce a Trial Data Validation Specification document that describes the quality checking to be performed on the data. CRFs and correction documentation will be maintained in the EDC system's audit trail.

Central laboratory data will be sent directly to the data management service provider.

System backups for data stored by the sponsor and records retention for the trial data will be in accordance with regulatory requirements.

10.10.4 Investigator's Site File and the TMF

The principal investigator or deputy is responsible for the filing of all essential documents in an ISF. The sponsor or a delegated CRO is responsible for the timely filing of all essential documents in the TMF. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator or deputy must ensure that all source data and documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. The principal investigator or deputy must take measures to prevent accidental or premature destruction of these documents.

The principal investigator or deputy must keep the ISF, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

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