Australian Government
Department of Health
Therapeutic Goods Administration

Delegate's Overview and Request for ACV's Advice

Active ingredient (s): BNT162b2 [mRNA]

Proprietary Product Name: COMIRNATY COVID 19 vaccine

Sponsor: Pfizer Australia Pty Ltd

Submission number: PM-2020-05461-1-2

e-Submission ID: e005671

11 January 2021

TGA Health Safety Regulation

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Delegate's Overview and Request for ACV's Advice

(The 18th ACV meeting on 15 January 2021)

Submission number **Co-ord file number** **Clinical file number**	PM-2020-05461-1-2 E20-364582 E20-364588
e-Submission Number	e005671 - (0000), e005671 - (0001), e005671 - (0002), e005671 - (0003)
Active ingredient(s)	BNT162b2 [mRNA]
Product trade name	COMIRNATY
Strengths/dose form	30 µg suspension for intramuscular injection
Sponsor	Pfizer Australia Pty Ltd
Submission description	Type A / Provisional registration of a new vaccine
Dosage and Administration	Intramuscular administration (IM) / two doses (0.3 mL each) 21 days apart.
Indication initially proposed by Sponsor	Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older
Indication proposed by the TGA delegate	COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below: Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 years of age and older. The vaccine should be used in accordance with official guidance in an officially declared pandemic. The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from the ongoing and post-market assessment.
Indication revised by Sponsor following TGA request	COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older. The use of this vaccine should be in accordance with official recommendations. The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.
Summary of data	The clinical data to support this provisional registration are largely from Study C4591001, an ongoing Phase 1/2/3,

	randomized, observer-blind, placebo-controlled study to assess immunogenicity, efficacy and safety of BNT162b2 [mRNA] vaccine. The available study results showed that BNT162b2 [mRNA] vaccine at 30μg administered as a 2-dose schedule (21 days apart) achieved a short term efficacy of 95 % against COVID-19 in individuals ≥ 16 years of age who did not have prior SARS-CoV-2 infection. The safety analysis in approximately 38,000 participates who had a median of 2 months follow up post 2nd dose revealed mild or moderate reactogenicity, low incidence of serious adverse events, and no clinically significant safety concern. Limitations of the current data include: • Safety follow up is currently limited to median two months post Dose 2 • The duration of immune response and vaccine protection is not currently known • Vaccine efficacy against asymptomatic infection and viral transmission are not yet known • The data in immunocompromised individuals are very limited • Lack of data in paediatric subjects, pregnant women, and lactating mothers Pharmacovigilance activities and post-market studies have been proposed to address these limitations (see the RMP evaluation for details).
Advice sought from the ACV	The ACV is requested to provide advice on the following specific questions: 1. Based on the evidence at this point in time, can the ACV advise whether the benefits-risks balance is positive for the use of COMIRNATY COVID-19 Vaccine in individuals 16 years and older in the Australian context to support the provisional registration? 2. Can the ACV comment on the indication proposed by the Delegate and the indication revised by the Sponsor? 3. As the safety follow up is currently limited to a median 2 months post-Dose 2, can ACV comment on the likelihood of vaccine-related AEs occurring after more than 2 months post vaccination, particularly with the new mRNA vaccine? 4. Can the ACV comment on the proposed pharmacovigilance activities? The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.
Delegate's preliminary assessment	☐ I have no reason to say, at this time, that the application for COMIRNATY should not be approved for provisional registration.

	The indication revised by the sponsor following TGA request is considered acceptable by the delegate. The Conditions for Provisional Registration is in Attachment 2. The final decision will be made following the ACV discussion.
Attachments	Attachment 1: Review of Product Information Attachment 2: Conditions for Provisional Registration Attachment 3: Appendix of Additional Tables and Figures

[redacted]

Delegate of the Secretary under regulation 39A of the Therapeutic Goods Regulations 1990

11 January 2021

Introduction

1. Background on the Condition being Prevented

COVID-19 is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2-14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhoea. Infections caused by SARS-CoV-2, and the resulting disease, COVID-19, have spread globally. On 11 March 2020, the WHO declared the COVID-19 outbreak to be a pandemic. In Australia, there are currently no licensed vaccines to prevent SARS-CoV-2 infections or COVID-19.

2. Pfizer-BioNTech COVID-19 Vaccine

Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 [mRNA], comprises a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The RNA is encapsulated in lipid nanoparticles, which enables entry into host cells, expression of the S protein, and elicitation of both antibody and cellular immune responses.

The vaccine is supplied as a white to off-white sterile frozen liquid, packaged in a multi-dose clear glass 2 mL vial with a rubber stopper, stored in -60 to -80°C. The vials are packed in cartons containing 195 multi-dose vials, and are intended for use over a short time window (calculated from its first use) due to its preservative-free composition.

3. Provisional Registration Pathway

The provisional approval pathway allows sponsors to apply for provisional registration on the ARTG. It provides access to certain promising new medicines where the public health benefit of immediate or early availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

Specific eligibility criteria for the provisional approval pathway are set out in regulations 10K and 10L of the Therapeutic Goods Regulations 1990 (the Regulations). This pathway is for certain medicines that are to treat or prevent life threatening or seriously debilitating conditions. The medicine is considered eligible if there are preliminary clinical data demonstrating that the medicine is likely to provide a major therapeutic advance and the applicant (who made the application under subsection 22C(1) of the Act) can provide sufficient evidence of a plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 year period following provisional registration.

The pprovisional determination for this vaccine was granted by TGA on 14 October 2020.

4. Australian Regulatory Status

A summary of the regulatory history of the proposed product in Australia is as follows:

- Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 [mRNA], is not registered on the ARTG.
- Pre-submission meeting was held on 18 September 2020.
- Provisional determination was granted on 14 October 2020.
- Rolling submission commenced on 23 October 2020.
- ACV meeting discussion is planned for 15 January 2021.

5. Overseas Regulatory Status

A summary of the overseas regulatory status of this vaccine is as follows:

- A similar application has been made in the USA, EU, Canada, Switzerland and New Zealand (all in October 2020).

- MHRA (UK) issued an Emergency Use Authorization (EUA) on 2 December 2020.
- Health Canada issued an interim authorization on 9 December 2020.
- FDA issued an Emergency Use Authorization (EUA) on 10 December 2020.
- The Health Sciences Authority (HSA), Singapore, issued an interim authorization on 14 December 2020.
- Swissmedic granted conditional authorisation on 19 December 2020
- EMA granted conditional authorisation on 21 December 2020.

6. Guidance Documents

Guideline on Clinical Evaluation of New Vaccines EMEA/CHMP/VMP/164653/2005

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-new-vaccines_en.pdf

Access Consortium statement on COVID-19 vaccines evidence (published on 4 December): https://www.tga.gov.au/access-consortium-statement-covid-19-vaccines-evidence

Module 3 Quality Evaluation

The Module 3 quality evaluation documents are saved as follows and these reports are attached for ACV information:

Module 3 – Quality Drug Substance: D20-3811447
Module 3 – Quality Drug Product: D20-3781630
Summary for Delegate: D21-2010290
S14 letter for labels: D21-2009386

The Module 3 delegate states that there are no significant issues identified from the Quality Evaluation of the submitted data that would indicate the product should not be provisionally registered on the basis of quality, or safety-related issues arising from the quality of the product. The manufacturing quality information submitted by the Sponsor support the provisional registration of COVID-19 Vaccine BNT162b2 [mRNA] 30 micrograms/0.3 mL concentrated suspension for injection vial. However, it should be noted that there are some issues that need to be fully resolved before it is possible to provide assurances that the product is able to meet all of the requirements of the Therapeutics Goods Act 1989 and its associated instruments. There are specific conditions and obligations to be fulfilled post approval. The proposed Module 3 conditions are detailed in the Module 3 Summary for Delegate (D21-2010290) and are also reproduced in Attachment 2 of this Overview. In terms of prior to product release to market, the batch release testing and compliance is required to be fulfilled, as well as the Sponsor's commitment not to supply any batches that have a temperature deviation during shipment. All other quality conditions are post-market conditions.

The sponsor has submitted Section 14 exemption for the use of the international label. This is considered acceptable duo to the public health emergency. Multi-dose vial presentation is also considered acceptable in the pandemic situation.

Module 4 Preclinical Evaluation

The Module 4 evaluation report is saved in TRIM ref. D21-2000512. There are no nonclinical objections to the provisional registration of the vaccine. The summary and conclusion is presented below.

- Primary pharmacology studies indicate the vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen in mice and monkeys, and conferred some protection of monkeys from infection.
- Antibodies and T cells in monkeys declined quickly over 5 weeks after the second dose of BNT162b2 (V9), raising concerns over long term immunity, which will be assessed by clinical studies according to the Sponsor.
- Repeat dose toxicity studies with the proposed vaccine and a variant, both in the LNP formulation, in rats raised no safety issues. Findings were consistent with immune stimulation and inflammation responses (injection site inflammation, increased body temperature, leucocytosis, increased large unstained cells, fibrinogen and acute phase proteins, and hypercellularity of lymphohaematopoietic tissues). Hepatocyte vacuolation (probably lipid vacuoles) was not associated with evidence of liver injury and was reversible.
- The toxicity of the LNP formulation and novel excipients ALC-0159 and ALC-0315 was assessed in one species as part of the repeat dose study with the vaccine. Neither the mRNA nor the lipid excipients of the LNP formulation are expected to have genotoxic potential. However, the potential of the LNP or the vaccine formulation for complement activation or stimulation of cytokines release was not adequately assessed in nonclinical studies. Further investigation (i.e., analysis of complement activation and cytokine stimulation) is recommended unless this particular concern is addressed by clinical data. The absence of repeat dose toxicity study in a second species and genotoxicity studies with the novel excipients was adequately justified by the Sponsor.
- Increased incidence of supernumerary lumbar ribs in rat fetuses was noted in the fertility and developmental study with the proposed vaccine. Pregnancy category B2 is considered acceptable.
- Short term protection studies, lack of pharmacokinetic data for the S antigen-encoding mRNA (BNT162b2 V9), suboptimal dosing interval in the repeat dose study, lack of repeat dose toxicity studies in a second species and genotoxicity studies with the novel excipients, and lack of studies investigating potential for autoimmune diseases were noted. However, these deficiencies are either adequately justified by the Sponsor or addressable by clinical data.
- There are no nonclinical objections to the provisional registration of the vaccine. Long term immunity, vaccine induced autoimmune diseases were not studied in the nonclinical program and should be addressed by clinical data post provisional registration. Nonclinical studies on complement activation and stimulation of cytokines release are recommended unless these issues are addressed by clinical data.

The requested changes to the Product Information is reproduced in Attachment 1.

Module 5 Clinical Evaluation

The detailed evaluation of the clinical studies is presented in the Clinical Evaluation Report (CER, see TRIM D21-2021328).

Module 5 include study reports for Study BNT162-01 and Study C4591001. The table below presents the summary of the two clinical studies.

Summary of Clinical Studies

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Study BNT162-01 is a Phase 1, First in Human (FIH) study conducted in Germany, which explored various vaccine candidates and dose levels. Please refer to Clinical Evaluation Report (CER) for details of this study. Of note, cell mediated immunity data are available from this study in a limited number of subjects aged 18-55 years. Based on the ELISpot and ICS assay results, BNT162b1 and BNT162b2 induced poly-functional and pro-inflammatory CD4+/CD8+ T cell responses in most study participants. Re-stimulation of PBMCs with peptide pools representing the encoded antigens (RBD or full-length S protein) demonstrated a helper response characterized by a robust IFNγ/IL-2 response and only minor IL-4 production. This cytokine profile indicates a favourable Th1 response and only a minimal Th2 immune response.

This study contributed to the selection of vaccine candidate and the final dose. This study is not discussed in detail in this Overview.

Study C4591001 is the focus of this Overview. Study C4591001 is a global, Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind study, conducted in healthy individuals. It began as a Phase 1/2 study in the US, and was later amended and expanded to a global Phase 2/3 study, enrolling ~44,000 participants for immunogenicity, safety, and efficacy assessment. Adolescents 12 to 17 years of age were later added. There were many protocol amendments, but the amendments are considered justified and are unlikely to affect the study conclusion. The study consists of:

- Phase 1 (to identify preferred vaccine candidate and dose level)
- Phase 2 (safety and immunogenicity in the first 360 participants who entered Phase 2/3)
- Phase 2/3 (efficacy and safety evaluation of the selected vaccine in a larger population)

The Sponsor claimed that the Clinical trials included in the application were performed in accordance with GCP.

Study C4591001

Immunogenicity Analysis

Phase 1 Immunogenicity

The Phase 1 part evaluated the safety, tolerability, and immunogenicity of 2 vaccine candidates. Participants were randomised 4:1 to receive active vaccine or placebo. The following two vaccine candidates were administered IM in a two-dose regimen:

- BNT162b1 (dose levels: 10, 20, 30, 100 μg) – containing modRNA encoding SARS-CoV-2 receptor-binding domain
- BNT162b2 (dose levels: 10, 20, 30 μg) – containing modRNA encoding SARS-CoV-2 spike glycoprotein (S) (i.e., the candidate subsequently chosen as the proposed product)

For each of the 2 candidates evaluated, younger participants (18-55 years old) received escalating dose levels (N = 15 per dose level, 4:1 ratio between vaccine and placebo) with progression to subsequent dose levels, and the older age group (65-85 years old, N = 15 per dose level, 4:1 randomization ratio between vaccine and placebo) when safety data for the preceding groups were deemed acceptable by the IRC.

A total of 90 subjects were involved in the Phase 1 assessment of BNT162b2 [mRNA].

SARS-CoV-2 neutralizing titres and IgG antigen-binding levels (S1-binding IgG and RBD binding IgG) were measured on days 7 and 21 after dose 1 (pre-dose 2); days 7 and 14, and 1 month after Dose 2. The results of Phase I immunogenicity showed that:

In the younger age group (18 – 55 years):

- At 7 days after Dose 2, SARS-CoV-2 50 % neutralizing GMTs in the 20-μg and 30 μg dose groups were higher for BNT162b2 recipients than for BNT162b1 recipients. The GMTs were similar in the 10-μg dose group for both recipients. At 1 month after Dose 2 (Day 52), GMTs remained substantially higher than those at the earlier time points after dose 1 for both BNT162b1 and BNT162b2 recipients.
- From before vaccination to 7 days post Dose 2, GMFRs of SARS-CoV-2 50 % neutralizing titres were substantially high (compared to earlier time points after Dose 1) for BNT162b1 and BNT162b2 recipients at the 30μg dose.
- From before vaccination to 7 days after Dose 2, all participants at the 30-μg dose level who received BNT162b1 or BNT162b2 achieved a ≥ 4-fold rise in SARS-CoV-2 50 % neutralizing titres.

In the older age group (65 – 85 years):

- At 7 days after Dose 2, SARS-CoV-2 50 % neutralizing GMTs in the 30-μg dose group were higher for BNT162b2 recipients than for BNT162b1 recipients. At 1 month after Dose 2 (Day 52), the SARS-CoV-2 50 % neutralizing GMTs in the 30-μg dose group were similar for both BNT162b1 and BNT162b2 recipients.
- From before vaccination to 7 days after Dose 2, the GMFR of SARS-CoV-2 50 % neutralizing titres were substantially high (compared to earlier time points after Dose 1) for BNT162b1 and BNT162b2 recipients at the 30-μg dose level.
- From before vaccination to 7 days after Dose 2, most participants who received BNT162b1 or BNT162b2 at the 30-μg dose level achieved a ≥ 4-fold rise in SARS-CoV-2 50 % neutralizing titres.

The immunogenicity results from the Phase 1 part demonstrated that BNT162b2 elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody levels in both younger and older adults. Immune responses were generally stronger in the younger group than in the older group. The neutralizing titre GMTs were higher than those observed in a Healthy Convalescent Serum panel from people recovered from COVID-19. Responses were evident after the first dose and substantially boosted after the second dose. The results support the need for a 2-dose regimen. Safety and tolerability data of the Phase 1 part is described in the Vaccine Safety Analysis section of this Overview. The safety data demonstrated that the reactogenicity profile of BNT162b2 is more favourable than BNT162b1 in both younger and older adults. BNT162b2 at the 30μg dose level was therefore selected for the Phase 2/3 part of the study.

Phase 2 Immunogenicity

The Phase 2 part of Study C4591001 commenced with selected candidate BNT162b2 at the 30μg dose level administered to participants who were randomized 1:1 to receive vaccine or

placebo. The Phase 2 portion evaluated immunogenicity and reactogenicity for 360 participants enrolled into the study when the Phase 2/3 part commenced. Immunogenicity results from 360 participants demonstrated that BNT162b2 at 30 µg elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody responses at 1 month after Dose 2, similar to those observed in Phase 1 part of the study. The neutralizing titres and S1-binding GMCs were higher in the younger age cohort compared with the older age cohort.

Vaccine Efficacy Analysis

Phase 2/3 of Study C4591001 was designed to evaluate the safety and efficacy of BNT162b2 at the 30µg dose level, given in 2 doses 21 days apart in a larger population. The study objective and the two primary endpoints are described below:

Phase 2/3 study objectives and primary efficacy endpoints

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

The secondary efficacy endpoints, which were based on different approaches to COVID-19 case evaluation criteria, are described below:

- **COVID-19 confirmed at least 14 days after Dose 2**: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
- **Severe COVID-19**: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
- **CDC-defined COVID-19**: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

Participant Selection: initial selection was for adults 18 years and older. The protocol was later amended to include subjects 16 years and older, and then 12 years and older (Participants older than 18 years of age began enrollment from July 27,2020, 16 to 17 years of age began from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020). The Sponsor does not seek indication for 12-15 years old, as the number of subjects is limited at the time of submission. Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, could be included. Participants with known stable infection with HIV, hepatitis C virus or hepatitis B virus could be included. It is noted that people with the following conditions were excluded:

- Other medical or psychiatric conditions, including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of participation or, in the investigator's judgment, made the participant inappropriate for the study.
- Immunocompromised individuals and individuals who received treatment with immunosuppressive therapy.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Participants who had previous clinical or microbiological diagnosis of COVID-19 disease.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention
- Women who are pregnant or breastfeeding

The Phase 2/3 part is designed as an adaptive, event-driven trial. The 95.0% credible interval for vaccine efficacy (VE) and the probability of VE greater than 30 % were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6 % for probability of vaccine efficacy greater than 30 %, to compensate for the interim analysis and to control the overall type 1 error rate at 2.5 %.

Confirmed COVID-19 cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and required at least 1 symptom consistent with COVID-19 disease. The symptoms included: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting. Approximately 44,000 participants were enrolled and randomised 1:1 to receive 2 doses of the Vaccine or placebo, separated by 21 days. Randomization was stratified by age: 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum (see **Table 1** Attachment 3). Note that subjects 12 through 15 years of age were not included in the efficacy analysis.

Disposition and Demographic Characteristics of the Study Population

The proportions of all randomised participants (n=43,651) included in the efficacy analysis were similar in the BNT162b2 and placebo groups (**Table 1** and **Table 2** Attachment 3). Most participants who were excluded from the evaluable efficacy population had not received all vaccinations as randomized or did not receive Dose 2 within the predefined window (i.e., 19 to 42 days after Dose 1). The efficacy population include 82.8 % White, 8.9 % Black or African American, 4.5 % Asian, and 26.8 % Hispanic/Latino participants. The median age was 52 years and participants were balanced for gender. The younger (16 -55 years of age) and older (≥56 years of age) groups comprised 57.2 % and 42.6 % of participants respectively. Obese participants made up around 35% of the population. Approximately 20% of participants had baseline comorbidities.

Result of the First Primary Endpoint: Vaccine Efficacy (VE) Without Prior Evidence of SARS-CoV-2 Infection – 7 Days After Dose 2 – Final Analysis

The interim analysis (4 November 2020) based on 94 COVID-19 cases successfully demonstrated high vaccine efficacy. This was followed by the second (and final) analysis, which was based on 170 accumulated COVID-19 cases. The final analysis was performed on 14 November 2020, by which time 43,651 participants had been randomised. The focus of this Overview will be the final efficacy analysis:

Among the 36,523 efficacy evaluable participants who had no evidence of existing or prior SARS-CoV-2 infection (18,198 in the vaccine group and 18,325 in the placebo groups), 8 cases of COVID-19 with onset at least 7 days after the 2nd dose were observed among vaccine recipients and 162 among placebo recipients. The Vaccine Efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0 %. The 95 % CI was 90.3 % to 97.6 %, indicating that the true VE is at least 90.3 % with a 97.5 % probability given the observed data.

Vaccine Efficacy - First COVID-19 Occurrence from 7 days after dose 2 - Subjects <u>without</u> evidence of infection prior to 7 days after dose 2 - Efficacy Evaluation (7 days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

<u>Result of the Second Primary Efficacy Endpoint</u>

Vaccine Efficacy - First COVID-19 Occurrence from 7 days after dose 2 - Subjects <u>with or without</u> evidence of infection prior to 7 days after dose 2-Efficacy Evaluation (7 days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

<u>Vaccine Efficacy by Subgroups</u>

For the primary endpoints, VE was evaluated for subgroups by age, gender; race, ethnicity, and country (see **Table 3** and **Table 4**, Attachment 3). Table 3 presents the VE in subjects without evidence of prior infection and Table 4 presents the VE in subjects with or without evidence of prior infection. Among participants without prior evidence of SARS-CoV-2 infection, VE was >93 % in all subgroups, with the exception of "all others" race group (89.3 %) and Brazil (87.7 %). The VE was 94.7 % (95 % CI: 66.7 %, 99.9 %) in participants older than 65 years of age (1 case in BNT162b2 group vs 19 cases in placebo group). An additional analysis of age subgroups showed observed VE in those older than 75 years of age was 100 % (0 cases in BNT162b2 group vs 5 cases in placebo group (95 % CI: -13.1 %, 100.0 %) (**Table 5** Attachment 3).

Among participants with or without prior evidence of SARS-CoV-2 infection (Table 4), VE was >93 % in all subgroups, with the exception of "all others" race group (78.2 %), Brazil (75.4 %), and positive prior SARS-CoV-2 infection at baseline (-7.1 %, 1 case in each group).

<u>Post Hoc Subgroup Analyses by Risk Status</u>

Post hoc analyses of efficacy based on risk status were performed (**Table 6**, attachment 3). Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for at-risk participants was 95.3 %, as compared with 94.7 % for those not at-risk. VE for participants ≥ 65 years of age and at-risk was 91.7 %, as compared with 100 % for those ≥ 65 years of age and not at-risk. VE was similar in obese (95.4 %) and non-obese (94.8 %) participants.

<u>Results for the Secondary Efficacy Endpoints</u>

The observed VE against confirmed COVID-19 occurring at least 14 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, was 94.2 %, with 8 and 139 cases in the BNT162b2 and placebo groups respectively. The

posterior probability of >99.99 % for the true VE > 30 % met the pre-specified success criterion of >98.6 % for this endpoint. The 95 % CI for the vaccine efficacy was 88.7 % to 97.2 %.

Among participants with or without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after Dose 2 was 94.4 %, with 8 and 144 cases in the BNT162b2 and placebo groups, respectively. The posterior probability of >99.99 % for the true VE > 30 % met the pre-specified success criterion of >98.6 % for this endpoint. The 95 % CI for the vaccine efficacy was 89.1 % to 97.3 %.

Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the observed VE of 66.3 % against severe COVID-19 occurring at least 7 days after Dose 2 did not meet the pre-specified success criterion of the posterior probability >98.6 %, due to the small number of severe cases (1 in the BNT162b2 group, 3 in the placebo group) observed after Dose 2 in the study. Additional analysis conducted in all cases after the first dose (1 vs 9 cases, respectively) showed the evidence of an effect on severe cases (VE = 88.9 % with a 95 % CI of 20.1 to 99.7 %).

The efficacy analyses using CDC-defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

<u>All Confirmed Cases of COVID-19 After Dose 1 (post-hoc analysis)</u>

All reports of COVID-19 with onset at any time after Dose 1 are presented in the table below:

Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

This provides a summary of cases for all participants in the Dose 1 all-available efficacy population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group. The estimated VE against confirmed COVID-19 occurring after Dose 1 was 82 % (95 % CI: 75.6 %, 86.9 %), with an estimated VE of 52.4 % (95 % CI: 29.5 %, 68.4 %) against confirmed COVID-19 occurring after Dose 1 but before Dose 2.

The early onset of protection can be viewed in **Figure 5** Attachment 3, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group.

Vaccine Safety Analysis

Safety was evaluated in Study BNT162-01 (FIH) and in three Phases of Study C4591001. This Overview focuses on the safety analysis of Study C4591001. The safety analyses are descriptive with no formal statistical hypothesis testing. The cut-off date for safety data is 14 November 2020.

Study C4591001 Phase 1

The 10 µg, 20 µg, and 30 µg doses tested for BNT162b1 and BNT162b2 were well tolerated. The BNT162b1 candidate at 100 µg was discontinued after the first dose due to the reactogenicity profile. Reactogenicity was generally higher after Dose 2 than Dose 1. The frequency of local and systemic reactogenicity was generally lower for BNT162b2 compared to BNT162b1, especially after the 2nd dose. Reactogenicity events after each dose for both candidates in older adults were milder and less frequent than those observed in younger adults. The majority of events were mild or moderate. There were no SAEs or discontinuations because of AEs. Overall, fewer AEs were experienced by participants who received BNT162b2 compared with those who received BNT162b1, with the least number of participants experiencing AEs in the BNT162b2 older age group. Clinical laboratory evaluations showed a transient decrease in lymphocytes that was observed in all age and dose groups after Dose 1, which resolved within a few days, and was not associated with any other clinical sequelae.

The report received by TGA on 10 December 2020 included additional follow-up from 1 month after dose 2 (29 August 2020) to 4 months after Dose 2 (the data cut-off 14 November 2020): 1 severe SAE (neuritis; due to an antecubital fossa blood draw) was reported in the younger age group. No additional AEs were reported in the younger or older age group between 29 August 2020 to data cut-off date of 14 November 2020.

Study C4591001 Phase 2/3

The safety analysis have been done on all enrolled participants (n= 43252), the reactogenicity subset (n= 8,183), participates with a follow up more than 2 months after dose 2 (n=19037), and participants with a median follow up of 2 months after dose 2. This Overview focuses on the safety analysis of

(1) Local and systemic reactogenicity in the reactogenicity subset of 8,183 subjects, and

(2) AE analysis in around 38,000 participants with a median of 2 months follow up post Dose 2.

The primary safety endpoints were solicited, specific local or systemic AEs and use of antipyretic or pain medication within 7 days after each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (reactogenicity subset), and unsolicited AEs (without prompts from the electronic diary) through 1 month after the 2nd dose, and through 6 months after the 2nd dose.

Demographic characteristics of the approximately 38,000 participants with a median of 2 months of follow-up after Dose 2 were similar between BNT162b2 and placebo groups (**Table 7** Attachment 3). There were no clinically meaningful differences by age, gender, race, ethnicity, or baseline SARS-CoV-2 status in the vaccine and placebo group. Across the two groups, about 20.5 % had any comorbidity (**Table 8** Attachment 3). The most frequently reported comorbidities were diabetes (8.4 %) and pulmonary disease (7.8 %), which were reported at similar frequencies in each group.

The reactogenicity subset: as of 14 November 2020, the reactogenicity subset was comprised of 8,183 participants (which included the 360 participants in Phase 2). **Table 9** and **Table 10** (Attachment 3) present a summary of the local and systemic reactogenicity analysis.

Local reactions:

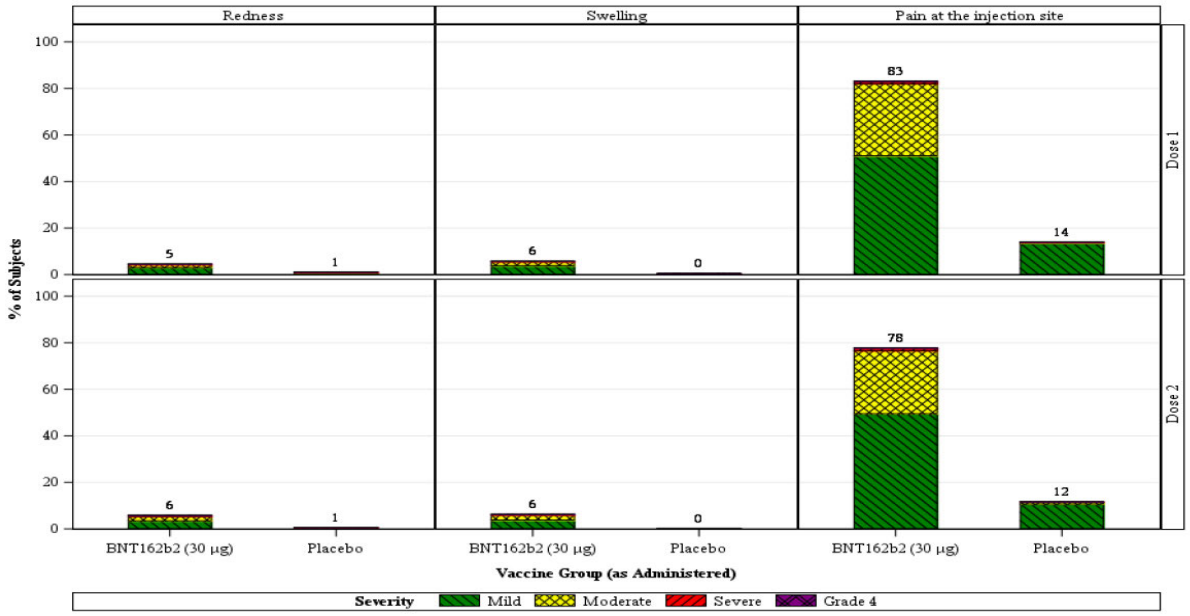
In the BNT162b2 group, pain at the injection site was reported more frequently in the younger group than in the older group (see **Figure 2**) with similar frequency after Dose 1 and Dose 2 of BNT162b2 in the younger group (83.1 % vs 77.8 %) and older group (71.1 % vs 66.1 %).

In the BNT162b2 group, frequencies of redness and swelling were similar in the younger and older age group after Doses 1 and 2. Frequencies of redness were similar after Dose 1 and Dose 2 of BNT162b2 in the younger age group (4.5 % vs 5.9 %) and in the older age group (4.7 % vs 7.2 %). Frequencies of swelling were similar after Dose 1 and Dose 2 of BNT162b2 in the younger age group (5.8 % vs 6.3 %) and in the older age group (6.5 % vs 7.5 %). In the placebo

group, redness and swelling were reported infrequently in the younger (≤ 1.1 %) and older (≤ 1.2 %) groups after Doses 1 and 2.

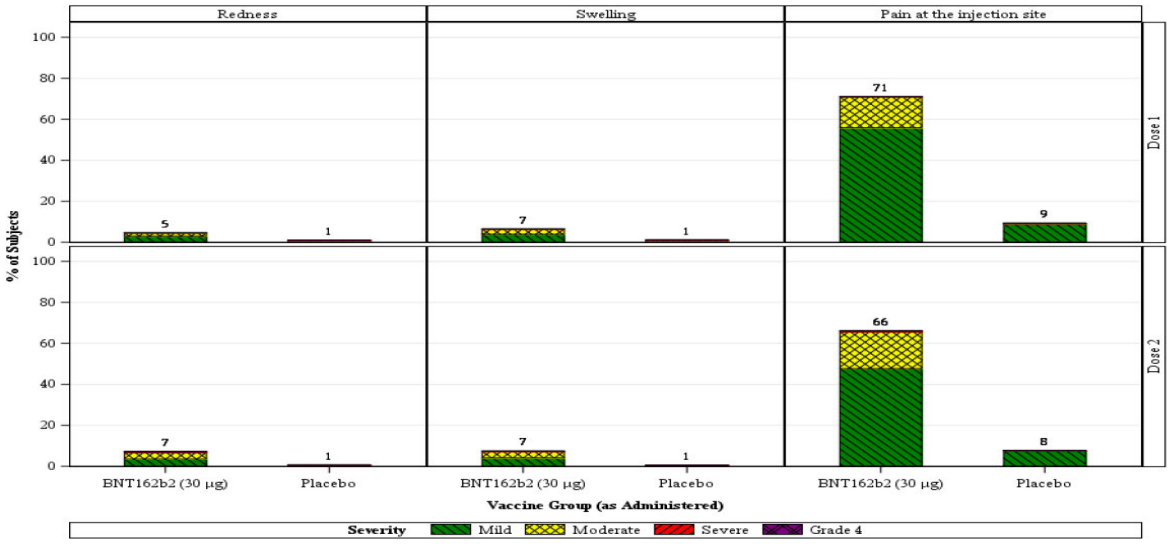
Across age groups, pain at the injection site did not increase after Dose 2, and redness and swelling were generally similar in frequency after Dose 1 and Dose 2. Most local reactions were mild or moderate. Few severe local reactions were reported after either dose. The frequency of any severe local reactions after Dose 1 and after Dose 2 was ≤ 0.7 %. No grade 4 reactions were reported. The local reactions for the BNT162b2 group after either dose had a median onset between Day 1 and Day 3, and ranges were similar in the younger and older age groups. The local reactions after either dose resolved with median durations between 1 to 2 days, which were similar in the younger and older age groups.

Figure 1 - Participants reporting local reactions, by maximum severity, within 7 days after each dose, by age group – Reactogenicity subset for Phase 2/3 Analysis – Safety Population age group: 16-55 years



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_lr_max_age_p3

Figure 2 - Participants reporting local reactions, by maximum severity, within 7 days after each dose, by age group - Reactogenicity subset for Phase 2/3 Analysis – Safety population age group: > 55 years

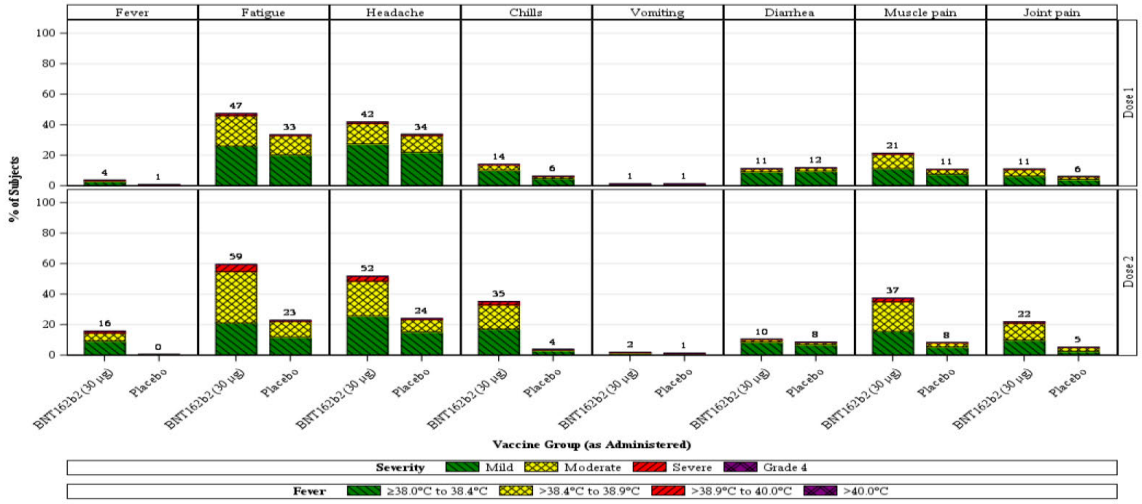


Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_lr_max_age_p3

Systemic reactions:

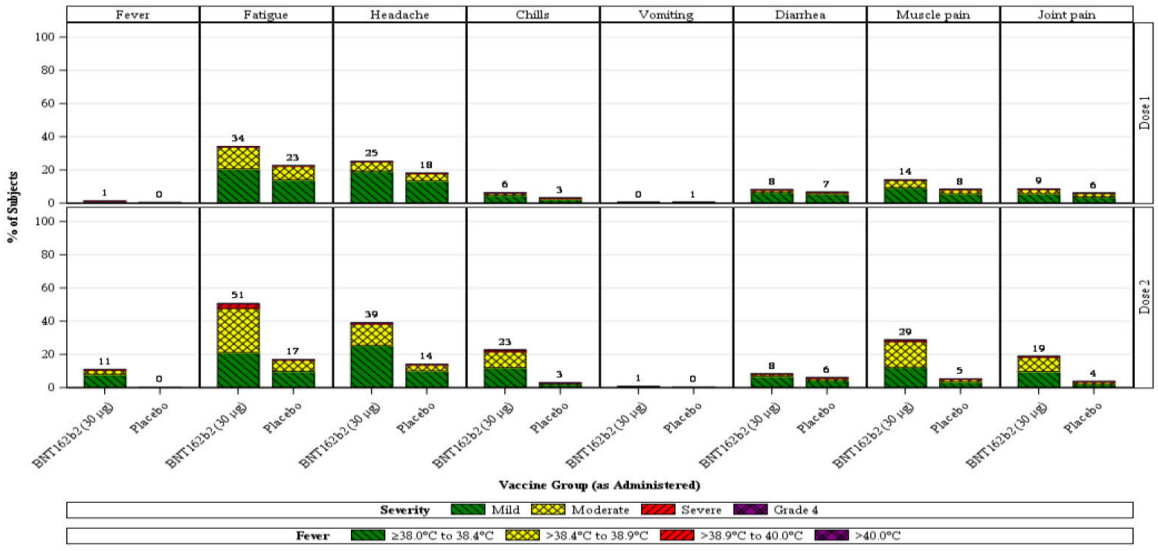
Systemic events were generally increased in frequency and severity in the younger age group (**Figure 3**) compared with the older age group (**Figure 4**), with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events were reported less frequently in the placebo group than in the BNT162b2 group, for both age groups and doses, with some exceptions. In the younger age group, vomiting and diarrhoea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 3). In the older age group, fever and joint pain (after Dose 1) and vomiting and diarrhoea (after Dose 1 and Dose 2) were reported at similar frequencies in the placebo group and the BNT162b2 group (Figure 4).

Figure 3 – Participants reporting systemic events, by maximum severity, within 7 days after each dose, by age group – Reactogenicity subset for Phase 2/3 Analysis – Safety population age group: 16-55 years.



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_se_max_age_p3

Figure 4 – Participants reporting systemic events, by maximum severity, within 7 days after each dose, by age group – Reactogenicity subset for Phase 2/3 Analysis – Safety population age group: > 55 years.



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_IA_P3_2MPD2/adce_f001_se_max_age_p3

In the BNT162b2 group, systemic events after Dose 1 were generally lower in frequency than after Dose 2 across age groups: fever (2.7 % vs 13.6 %), fatigue (41.5 % vs 55.5 %), headache (34.5 % vs 46.1 %), chills (10.6 % vs 29.6 %), muscle pain (18.0 % vs 33.5 %), and joint pain (9.9 % vs 20.5 %). Diarrhoea and vomiting frequencies were generally similar. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was Day 2 to Day 3, and ranges were similar in the younger and older age groups. All systemic events resolved with median duration of 1 day, which was similar in the younger and older age groups. The median duration of either fever or chills from first to last day after Dose 1 and Dose 2 was 1 day, for both younger and older age groups. Other than fatigue and headache, most systemic events were infrequent in the placebo group.

Analysis of Adverse Events:

A total of 37,707 participants who were randomized on or before 9 October 2020 were vaccinated with Dose 1. One of these participants did not sign an informed consent and is therefore not included in any analysis population. The remaining 37,706 participants had a median follow-up time of 2 months after Dose 2. Of these, 19,067 (50.6 %) had at least 2 months of follow-up after Dose 2. HIV-positive participants (n = 120) were included for counting purposes in demographic and disposition summaries; however, these participants were not included in the summary of safety or efficacy endpoint results. Therefore, 37,586 participants were included in the AE analyses presented here.

The summary of AEs in these 37,586 participants (from Dose 1 to 1 month after Dose 2) is presented in **Table 11** and **Table 12** of Attachment 3. Among these 37,586 participants, the most frequent AEs reported up to 1 month after Dose 2 were reactogenicity events, in the System Organ Classes (SOCs) of:

- general disorders and administration site conditions (18.6 % vaccine vs. 3.9 % placebo)
- musculoskeletal and connective tissue disorders (7.3 % BNT162b2 vs. 2.0 % placebo)
- nervous system disorders (6.1 % BNT162b2 vs. 2.4 % placebo)
- infections and infestations (1.5 % BNT162b2 vs. 1.5 % placebo)
- gastrointestinal disorders (2.9 % BNT162b2 vs. 1.9 % placebo).

Comparing the younger versus older BNT162b2 age groups, AE incidences in these SOCs were:

- general disorders and administration site conditions (21.1 % vs 15.2 %)
- musculoskeletal and connective tissue disorders (8.3 % vs 5.9 %)
- nervous system disorders (6.9 % vs 4.9 %)
- infections and infestations (1.5 % vs 1.6 %)
- gastrointestinal disorders (3.0 % vs 2.8 %).

The numbers of overall participants who reported at least 1 AE (27.0 % vs 12.5 %) were higher in the BNT162b2 group as compared with the placebo group and at least 1 related AE (20.8 % vs 5.1 %). The most frequent AEs in the BNT162b2 group were injection site pain (2,108 [11.2 %]), pyrexia (1,144 [6.1 %]), chills (998 [5.3 %]), fatigue (1,026 [5.5 %]), headache (966 [5.1 %]), and myalgia (904 [4.8 %]). During this time period from Dose 1 to 1 month after Dose 2, most of these AEs were reported during the e-diary 7-day reporting period. The majority of these AEs were reported in the younger age group: injection site pain (1,358 [12.5 %]), pyrexia (819 [7.6 %]), chills (693 [6.4 %]), fatigue (690 [6.4 %]), headache (649 [6.0 %]), and myalgia (628 [5.8 %]).

This trend continued to be seen through the data cut-off date for all enrolled participants (n= 43,252 participants). The higher frequency of reported unsolicited non-serious adverse events among BNT162b2 recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset.

Adverse Events by Subgroups: no clinically meaningful differences in AE frequencies were observed by age, sex, race, ethnicity, or baseline SARS-CoV-2 status subgroups.

Adverse Events of Clinical Interest: the CDC's list of AESIs for COVID-19, including the terms potentially indicative of severe COVID-19 or serious autoimmune and neuroinflammatory disorders, was considered in the review of reported AEs.

> **Lymphadenopathy:** in the BNT162b2 group, 64 participants (0.3 %) reported an AE of lymphadenopathy (54 in the younger age group and 10 in the older age group), and 6 in the placebo group. In cases where location was specified, lymphadenopathy occurred in the arm and neck region. Most lymphadenopathy events were reported within 2 to 4 days after vaccination. The mean duration was 10 days and 12 events were ongoing at the time of the data cut-off date. A total of 47 out of these 64 lymphadenopathy events were judged by the investigator as related to study intervention.
>
> **Hypersensitivity**: in the younger age group, an AE of **angioedema** 13 days after Dose 1 (both eyes) and **hypersensitivity** (allergy attack; no additional information available at the time of this report) was reported in 1 participant each (BNT162b2 group), and an AE of drug hypersensitivity (oral penicillin reaction) was reported in 1 participant who received placebo; all were assessed by the investigator as unrelated to study intervention. There were 6 participants reported "Drug hypersensitivity" in the vaccine group compared to 1 in placebo group (see Table 42, page 175 of Clinical Overview). Post-market monitoring for hypersensitivity events should be conducted.
>
> **Facial paralysis**: there were 4 reports of facial paralysis (Bell's palsy) in the vaccine group with none in the placebo group (see Table 42, page 187 of Clinical Overview).

SAEs: among the 37,586 participants with a median of 2 months of follow-up after Dose 2, from Dose 1 to 1 month after Dose 2 the proportions of participants who reported at least 1 SAE was similar in the BNT162b2 group (0.5 %) and in the placebo group (0.4 %). Three of the SAEs in the BNT162b2 group and none in the placebo group were assessed as related to study intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy.

A total of 12 participants had SAEs of appendicitis; 8 in the BNT162b2 group and 4 in the placebo group. None were assessed as related to study intervention. An observation of 12 appendicitis events across both treatment groups is not greater than expected based on background rates (estimated in a US Electronic Health Records database).

Up to cut-off date of 14 November 2020, the number of participants who reported SAEs was similar in the two groups (0.7 % for BNT162b2 vs 0.5 % for the placebo group). With the additional follow-up time, another SAE assessed by the investigator as related to study intervention in the BNT162b2 younger age group was reported: 1 event of lower back pain and bilateral lower extremity pain with radicular paraesthesia (onset Day 47 after Dose 2).

Severe AEs, SAEs, and AEs leading to withdrawal were few, and were reported by ≤ 1.2 %, ≤ 0.5 %, and ≤ 0.2 % respectively, in both groups. Discontinuations due to related AEs were reported in 14 participants in the BNT162b2 group and 7 participants in the placebo group.

Deaths: there were 6 participants, all in Phase 3, who died before the data cut-off date of 14 November 2020. There were 2 deaths in the BNT162b2 group (arteriosclerosis and cardiac arrest) and 4 deaths in the placebo group that were assessed as not related to study intervention.

Severe COVID-19 Illness: the protocol had pre-specified stopping rules that included monitoring of severe COVID-19 cases, and these stopping criteria were not met. The confinement of the majority of severe cases to the placebo groups suggests no evidence for vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD).

The safety profile of all enrolled participants (n = 43,252 participants) who had variable follow up from Dose 1 to the data cut-off date (14 November 2020) is consistent with the safety profile in the participants who had at least 2 months of follow-up after Dose 2.

The safety evaluation is still ongoing. Participants continue to be monitored for unsolicited adverse events, including SAEs up to six months after the last vaccine dose.

Safety in Special Population

Pregnant women: at the time of the data cut-off (14 November 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancies. These participants continue to be followed for pregnancy outcomes. The data to support safety in pregnancy are inadequate at this stage. This vaccine is therefore not recommended for use during pregnancy.

Paediatric population: There were only 100 participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo) recruited in the Phase 2/3 study under protocol amendment 7. The safety and efficacy of BNT162b2 in participants <16 years of age have not been established. The Sponsor is not seeking indication for < 16 years old in the current submission, and will undertake further study in paediatric subjects to assess the vaccine response in the paediatric population.

Immunocompromised individuals: immunocompromised individuals and individuals who received treatment with immunosuppressive therapy were excluded from the clinical trial. There were data for limited number of participants with stable HIV infection. The AEs reported in this group are consistent with the all enrolled population.

Post-marketing AE reports

There were a number of reports of anaphylaxis reactions to Pfizer BioNTech's COVID-19 vaccine in the United Kingdom (UK) and in the United States following the vaccine rollout. The two cases in the UK occurred on December 8, 2020. Both individuals in the U.K. had a history of severe allergic reactions and carried adrenaline auto injectors. They both were treated and have recovered.

Anaphylactic reaction is now included as an identified risk for this vaccine. The updated Australian PI has included statement of "Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty" and "Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine". Hypersensitivity to the active substance or to any of the vaccine excipients have been included as Contraindication. The FDA document for Health Care Professionals include the statement of "Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine".

RMP Evaluation

The final RMP evaluation report is saved in TRIM D21-2006172

The EU RMP 1.0 was provided to the TGA on the 29 December 2020. The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies as described in the EU RMP are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Anaphylaxis	✓†	✓*	✓	–
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	✓†	✓*	–	–
Missing information	Use in pregnancy and while breast feeding	✓	✓*	✓	–
	Use in immunocompromised patients	✓	✓*	✓	–
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	✓	✓*	✓	–
	Use in patients with autoimmune or inflammatory disorders	✓	✓*	–	–
	Interaction with other vaccines	✓	✓*	✓	–
	Long term safety data	✓	✓*	–	–

†Data capture Aid
*Clinical trials

The summary of the safety concerns above are considered acceptable.

The sponsor has been asked to implement specific targeted follow-up forms to monitor AESI in Australia and to provide vaccine traceability plan prior to the vaccine supply.

With regards to additional pharmacovigilance activities, the sponsor has proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 Interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study for vaccine interactions) and 5 Non-Interventional studies (4 safety and 1 effectiveness).

Study Number	Country	Interventional/ Non-Interventional	Purpose
C4591001	Global	Interventional	Safety
C4591015	Not available at this time	Interventional	Safety
C4591010	EU	Non-Interventional	Safety
C4591011	US	Non-Interventional	Safety
C4591012	US	Non-Interventional	Safety
ACCESS/VAC4EU	EU	Non-Interventional	Safety
C4591014	EU, US	Non-Interventional	Effectiveness [a]
BNT162-01 Cohort 13	EU	Interventional	Safety
C4591018	US	Interventional	Safety
Safety and immunogenicity in high risk adults [b]	EU, US	Interventional	Safety
Co-administration study with seasonal influenza vaccine	Not available at this time	Interventional	Safety

a. Vaccine effectiveness is not a safety concern;
b. On review of preliminary information from BNT162-01 cohort 13, C4591001 HIV-infected and high-risk populations and C4591018, a further safety and immunogenicity study is anticipated in up to 150 adult subjects with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments or in conditions.

Table 13 Attachment 3 presents more details of the planned and ongoing studies. The results from these studies will help to address the missing information identified in the summary of safety concerns.

No Australian specific studies have been planned. The data from the studies planned to be conducted overseas are considered applicable to the Australian population.

Please see Attachment 2 for RMP Conditions of Registration.

Delegate's Discussion

Unmet public health need

With respect to the incidence rate of COVID-19, Australia is currently in a better situation in comparison to some other countries. However, the situation is far from the normal life we led pre-COVID-19. The COVID-19 outbreaks have been occurring frequently, and the consequential travel restriction and border closure have been having a negative impact on our daily life. A safe and effective vaccine is one of the important tools in our fight against the COVID-19 pandemic. No COVID-19 vaccine is currently registered in Australia. There is an unmet need for safety and effective COVID-19 vaccines during the current public health emergency.

Short term efficacy and safety data for provisional registration

Pfizer has submitted the short-term result from the pivotal study to support the provisional registration of BNT162b2[mRNA] COVID-19 vaccine. The submitted pivotal study has an overall good study design, including representative study population and acceptable statistical considerations. The result from this study have demonstrated that BNT162b2 [mRNA] at 30 µg administered as a 2-dose schedule (21 days apart) achieved a short term vaccine efficacy of 95 % against PCR-confirmed COVID-19 in subjects ≥ 16 years of age without prior evidence of SARS-CoV-2 infection. This was demonstrated in a larger randomised placebo-controlled Phase III trial, with many subjects being followed for a median of 2 months post Dose 2. The vaccine efficacy was consistent across age, gender, race and ethnicity demographics. Vaccine efficacy was also demonstrated in those with one or more comorbidities. The analysis of tolerability and safety of the vaccine detected short-lived, mild to moderate local and systemic reactogenicity, low incidence of severe or serious events, and no clinically significant safety concerns among participants who were followed for a median 2 months after the 2nd dose of the vaccine.

The submitted safety data is only short term at this stage, but the data have fulfilled the requirement as set out in the "Access Consortium statement on COVID-19 vaccines evidence"

(published on TGA website on 4 December 2020). The statement specified the minimum requirement that trial participants must be followed for a median of at least 2 months after receiving their final vaccine dose. It is acknowledge that most adverse reactions to vaccines occur within 4-6 weeks from vaccination. The EMA has stated that conditional marketing authorisation for a COVID-19 vaccine could be based on review of at least 6 weeks post-vaccination safety data. (https://www.ema.europa.eu/en/documents/other/ema-considerations-covid-19-vaccine-approval_en.pdf).

From the perspective of vaccine efficacy, a 2-month median follow-up is considered as the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The duration of protection is not yet known and is to be assessed in the ongoing trial.

Data limitations

In addition to the unknown longer-term safety and unknown duration of vaccine protection, there are other limitations with the submitted data. The following questions have not yet been addressed:

- Vaccine efficacy against asymptomatic infection and viral transmission
- The concomitant use of this vaccine with other vaccines
- Vaccine data in pregnant women and lactating mothers
- Vaccine efficacy and safety in immunocompromised individuals
- Vaccine efficacy and safety in paediatric subjects (< 16 years old)
- A correlate of protection has yet to be established. The vaccine immunogenicity cannot be considered and used as the surrogate for vaccine protective efficacy at this stage.

Although the vaccine efficacies against certain outcomes have been demonstrated in the pivotal study, the real-world vaccine effectiveness when this vaccine is rolled out to a larger and more diverse population is not known. The vaccine efficacy in the Aboriginal and Torres Strait Islander population is not studies. Pfizer has planned to conduct at least one post-authorisation effectiveness study, a non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (Study C4591014).

The proposed post-market studies (see Table 13 Attachment 3) will help to address the limitation of the current information. Although no Australian specific studies have been planned, the data from the studies planned to be conducted overseas are considered applicable to the Australian population.

Pharmacovigilance and risk management plan

Detailed RMP evaluation is included for ACV information. The sponsor has included the followings as missing information in the updated EU-RMP (version 1.0):

- Use in pregnancy and while breast feeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in patients with autoimmune or inflammatory disorders
- Interaction with other vaccines
- Long term safety data

The Sponsor has also include relevant statements in the PI to specify the populations where the vaccine efficacy and safety data is to be further assessed.

Anaphylactic reaction is now included as an identified risk for this vaccine. The updated PI has included statement of "Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced

anaphylaxis to the first dose of Comirnaty" and "Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine". Hypersensitivity to the active substance or to any of the vaccine excipients have been included as Contraindication.

The Sponsor has proposed the additional pharmacovigilance activities and post-market studies to assess the vaccine in immunocompromised subjects, in paediatric subjects, and in pregnant women. The delegate is of the view that the proposed pharmacovigilance activities and study plan is adequate to identify and characterise the risks of the vaccine.
A national coordinated traceability plan that covers the release by the manufacturer, the entire distribution chain, prescription, dispensing and patient administration is to be further discussed between the Sponsor and the Australian COVID-19 vaccine taskforce. The sponsor should provide this traceability plan to the TGA for review before the supply of the product.

Delegate's action

Taking into consideration of the unmet public health need and the very high short term efficacy with acceptable safety demonstrated in the submitted studies, the delegate is of the view that provisional registration of BNT162b2[mRNA]) COVID-19 Vaccine is appropriate for the use of this vaccine to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 years of age and older. The pivotal study is ongoing for a total of 24 months. The longer-term efficacy and safety data are to be submitted to the TGA for evaluation before a full registration can be considered.

Since the use of BNT162b2[mRNA] COVID-19 Vaccine is evaluated through the provisional pathway, a clear statement should be included in the PI with regards to the nature of the registration. It should also be emphasized that the decision of provisional approval is made on the basis of short term efficacy and safety data, and the continued approval depends on the evidence of longer term efficacy and safety from the ongoing and post-market assessment.

The delegate proposes the provisional approval of this vaccine for a revised indication, and the sponsor has been requested to revise the indication to the following:

> *COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below:*
>
> *Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 years of age and older.*
>
> *The vaccine should be used in accordance with official guidance in an officially declared pandemic.*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from the ongoing and post-market assessment.*

Following the delegate's request, the Sponsor submitted the update PI on the 5th January 2021, with the indications revised to below:

> *COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below:*
> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

The ACV's advice is requested for a number of questions (see the cover page of this Overview), including the advice and comments on the indication wording.

The proposed conditions of the provisional registration are specified in Attachment 2.

This Overview is submitted for ACV advice. The final decision will be made following the ACV discussion.

Attachments

Attachment 1: Review of the Product Information (PI)

1. The updated PI was provided to the TGA on the 5th January 2021 following TGA request . The indication is now revised to the following:

   *COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below:*
   Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

   The use of this vaccine should be in accordance with official recommendations.

   The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

   The indication wording will be discussed at the ACV meeting.

2. Following the email request by the delegate, Pfizer agrees to include this in the next PI update.

   Traceability
   In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

3. Please revise the black triage statement to the following as recommended by both clinical and RMP evaluators:

   ▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

4. Please revise the PI statement according to the recommendations made by the Module 4 evaluator below:

   4.6 Fertility, pregnancy and lactation

   Effects on fertility

   The statement proposed in Section 5.3 *Preclinical safety data – Reproductive toxicity* should be moved here with minor modification.

   "In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 µg each, spanning between pre-mating day 21 and gestation day 20). SARS CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate. ~~Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3 Preclinical safety data).~~"

   Use in pregnancy

As discussed in the assessment, Pregnancy Category B2 is considered appropriate for this product. Following changes are recommended.

"Pregnancy Category B2

There is limited experience with use of COMIRNATY in pregnant women. ~~Animal studies do~~ A combined fertility and developmental toxicity study in rats showed increased occurrence of supernumerary lumbar ribs in fetuses from COMIRNATY-treated female rats ~~did not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, r post-natal development~~ (see Effects on fertility ~~Section 5.3 Preclinical safety data~~). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus."

Use in lactation

It is recommended that findings of the rat study be stated.

"It is unknown whether BNT162b2 [mRNA] is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Effects on fertility)."

5.1 Pharmacodynamic properties

Mechanism of action

Statements on the mechanism of action are supported by nonclinical data. Minor editorial changes are suggested.

"The nucleoside-modified messenger RNA in COMIRNATY is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. COMIRNATY elicits both neutralising antibody and cellular immune responses to the ~~spike (~~S~~)~~ antigen, which may contribute to protection against COVID-19."

5.3 Preclinical safety data

Statements regarding general and reproductive toxicity should be removed from this section. The statement on genotoxicity and carcinogenicity is acceptable.

"~~Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity.~~

~~General toxicity~~

~~Rats intramuscularly administered COMIRNATY (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory~~

~~response, as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.~~

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of COMIRNATY (lipids and mRNA) are not expected to have genotoxic potential.

~~Reproductive toxicity~~

~~Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No COMIRNATY data are available on vaccine placental transfer or excretion in milk.~~"

Attachment 2: Conditions for Provisional Registration

Terms and conditions were imposed upon the authorization with respect to quality, clinical, labelling, and Risk Management Plan requirements:

Clinical conditions:

The following study reports of the two ongoing studies will have to be submitted before a definitive authorization can be considered:

- Submit safety analysis at 6 months post Dose 2 from Study C4591001 (Phase 2/3) when the analysis is available
- Submit the final completed study report for Study C4591001 with 24 months follow up duration when it became available.
- Submit final study reports for study BNT162-01 once completed, including data on healthy subjects

When available, further data relating to vaccine efficacy against asymptomatic disease, vaccine efficacy in immunocompromised subjects, paediatric subjects, pregnant women, lactating mother, and the information relating to post-market safety and effectiveness studies should be provided to the TGA to update the Product information.

RMP conditions:

The Comirnaty EU-Risk Management Plan (RMP) (version 1.0, dated 21 December 2020; DLP 17 December 2020), with Australian Specific Annex (version 0.1, dated 5 January 2021), included with submission PM-2020-05461-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than six calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than six monthly until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, Comirnaty safety summary reports (including safety data for patients in Australia) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

A national coordinated traceability plan that covers the release by the manufacturer, the entire distribution chain, prescription, dispensing and patient administration must be in place at launch of Comirnaty. The sponsor should provide this traceability plan to the TGA for review before the supply of the product.

Comirnaty (BNT162b2 [mRNA]) COVID-19 VACCINE) is to be included in the Black Triangle Scheme due to provisional approval. The PI and CMI for Comirnaty must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

Quality conditions:

The Sponsor has submitted the list of manufacturing sites along with the responsibilities in the production of the BNT162b2 DS and DP and specified functions. Some GMP clearances are currently under review by the TGA. The review of the GMP clearances will be completed for all the manufacturing sites prior to the TGA delegate's decision (Section 3.2.S.2.1 and 3.2.P.3.1 Manufacturers/Section 3.2.A.1).

Prior to the vaccine release to the market, the batch release testing and compliance is required to be fulfilled, as well as the Sponsor's commitment not to supply any batches that have a temperature deviation during shipment.

Batch Release Testing and Compliance
It is a condition of registration that all independent batches of BNT162b2 [mRNA] COVID-19 vaccine imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

For each independent batch of the product imported into Australia, the Sponsor must supply the following:

- A completed Request for Release Form, available from vaccines@health.gov.au.
- Complete summary protocols for manufacture and QC, including all steps in production in the agreed format.
- At least 20 (twenty) vials (Samples) of each manufacturing batch of BNT162b2 [mRNA] COVID-19 vaccine with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted) representative of all batches of product seeking distribution in Australia.
- At least 5 (five) vials (Samples) of any further consignments of a manufacturing batch of BNT162b2 [mRNA] COVID-19 vaccine with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted). Further consignments cover batches previously supplied to TGA for the purposes of batch release testing but are seeking to be supplied again.
- If the manufacturing batch has been released in Europe or United Kingdom a copy of the EU Official Control Authority Batch Release (OCABR) certificate (or equivalent from the UK) must be provided.
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Sponsors must provide all requested Samples and data in sufficient time (at least 5 business days) prior to any distribution date to allow the TGA to perform testing and

review. Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

Samples and data should be forwarded to the Biotherapeutics Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing. The address for courier delivery is:

ATTN: Batch Release Coordinator,
Batch Release Unit,
TGA Laboratories Branch,
136 Narrabundah Lane,
Symonston, ACT 2609.

The shipments (including reagents) to TGA are the responsibility of the Australian Sponsor/Agent who will be required to facilitate the import and customs clearance process.

Certified Product Details

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines]. The CPD should be sent as a **single bookmarked PDF** document to Vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

Post approval commitments

Section 3.2.S.5 Reference standards or materials: There are no current issues with the methodologies and tools used in testing of the reference material. However, there is a lack of data submitted, with only one batch of the clinical reference material (CRM) tested, while primary reference material (PRM) and working reference materials (WRM) are still under development. As post-approval commitments the Sponsor should:

- Supply the data for the PRM and WRM once generated and the Certificates of Analysis of reference standards made available upon request.
- Submit additional stability data (for a duration of 1-6 months and 12-60 months) for reference standards and materials as soon as it becomes available.
- Provide a protocol for the establishment of replacement reference standards (WRMs) including acceptance criteria and verification data.
- TGA should be notified of any change to the source of the lipid reference materials.

Section 3.2.S.7.2 Post-approval stability protocol and stability commitment: The Sponsor has provided a post-approval commitment that upon completion of the ICH stability protocols, a minimum of 1 batch of BNT162b2 DS manufactured will be

enrolled in the commercial stability program at the long term storage conditions of -20±5°C for each year that DS is manufactured. Additionally, a post-approval commitment for the DP that a minimum of 1 batch be placed in the commercial stability program at the long term storage condition of -90 to -60 °C each year of DP manufacture. As post-approval stability commitments:

- Additional stability data (long term, accelerated and thermal stress study data for a duration of ≥6 months for a minimum of 2-3 clinical or commercial batches) should be submitted as it becomes available. Once additional data have been submitted to the TGA for evaluation, an extended shelf life and/or change in storage conditions for the DS and/or DP may be considered.
- Amend the Modules 3.2.S.7.2 and 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment in the dossier to be in accordance with ICH[1] guidelines and TGA[2] requirements to include a minimum of 3 PPQ batches of DS and DP to be placed in the commercial stability program at the long term storage conditions.
- Data and updated protocols for the currently ongoing thermal cycling studies should be submitted once available.
- Any out of specification stability results for DS and/or DP should be submitted to the TGA as soon as they are generated.
- Should a temperature excursion occur, the TGA should be informed before the batch is released as detailed in the guideline T*emperature excursions of biological medicines*[3] under deviations from approved storage conditions. **A commitment is required not to supply any batches that have a temperature deviation during shipment.**

Section 3.2.S.4.3 and 3.2.P.5.4 Batch analysis: Post-approval commitments by the Sponsor include:

- Provide a quality risk assessment or investigation report to explain the reason for the deviation in trend (~10 fold increase) observed for the final 3 batches of commercial scale material manufactured at Pfizer, Andover (20Y513C501 20Y513C601 20Y513C701). Additionally, any remediation work that may have been implemented should be outlined.
- Provide clarification of the role of Polymum Scientific in the commercial manufacturing process and confirm if batch analysis for DP batches manufactured at Pfizer, Puurs are representative of the final proposed commercial manufacturing process.

Commercial scale batches: Post-approval commitments by the Sponsor include:

- Perform testing of future process-validation batches of the commercial scale finished product according to the comparability testing protocol/plan and results provided for assessment by the TGA when available.
- Provide the process validation data from the commercial scale batches/lots in order to confirm the consistency of the finished product manufacturing process. Results provided for assessment by the TGA when available.

[1] 3AB5a; ICH Q5C Quality of Biotechnological Products: Stability testing of Biotechnological/Biological Products (https://www.ema.europa.eu/en/documents/scientific-guideline/quality-biotechnological-products-stability-testing-biotechnological/biological-products_en.pdf)
[2] Stability testing for prescription medicines (Biological medicines: Specific requirements) https://www.tga.gov.au/book/144-specific-requirements-stability-biological-medicines
[3] https://www.tga.gov au/temperature-excursions-biological-medicines

Attachment 3: Additional Tables and Figures

Table 1: Efficacy Population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 17NOV2020 (18:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adsl_eff_pop

Table 2: Demongraphic Characteristics - subjects without evidence of infection prior to 7 days after dose 2-Evaluable efficacy (7 days) population

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18242) n[b] (%)	Placebo (N[a]=18379) n[b] (%)	Total (N[a]=36621) n[b] (%)
Sex			
Male	9318 (51.1)	9225 (50.2)	18543 (50.6)
Female	8924 (48.9)	9154 (49.8)	18078 (49.4)
Race			
White	15110 (82.8)	15301 (83.3)	30411 (83.0)
Black or African American	1617 (8.9)	1617 (8.8)	3234 (8.8)
American Indian or Alaska native	118 (0.6)	106 (0.6)	224 (0.6)
Asian	815 (4.5)	810 (4.4)	1625 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)	77 (0.2)
Multiracial	448 (2.5)	402 (2.2)	850 (2.3)
Not reported	86 (0.5)	114 (0.6)	200 (0.5)
Ethnicity			
Hispanic/Latino	4886 (26.8)	4857 (26.4)	9743 (26.6)
Non-Hispanic/non-Latino	13253 (72.7)	13412 (73.0)	26665 (72.8)
Not reported	103 (0.6)	110 (0.6)	213 (0.6)
Country			
Argentina	2561 (14.0)	2539 (13.8)	5100 (13.9)
Brazil	1232 (6.8)	1223 (6.7)	2455 (6.7)
Germany	121 (0.7)	126 (0.7)	247 (0.7)
South Africa	287 (1.6)	279 (1.5)	566 (1.5)
USA	14041 (77.0)	14212 (77.3)	28253 (77.1)
Age group			
12-15 Years	46 (0.3)	42 (0.2)	88 (0.2)
16-55 Years	10428 (57.2)	10507 (57.2)	20935 (57.2)
>55 Years	7768 (42.6)	7830 (42.6)	15598 (42.6)
≥65 Years	3980 (21.8)	4038 (22.0)	8018 (21.9)
Age at vaccination (years)			
Mean (SD)	50.6 (15.70)	50.4 (15.81)	50.5 (15.76)
Median	52.0	52.0	52.0
Min, max	(12, 89)	(12, 91)	(12, 91)

Table 3: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Table 4 Vaccine Efficacy – First COVID-19 occurrence from 7 days after Dose 2, by subgroup – subjects with or without evidence of infection prior to 7 days after Dose 2 – Evaluable efficacy (7 days) population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.
i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adc19ef Table Generation: 18NOV2020 (15:55)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_sg_eval

Table 5 Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by requested subgroup – subjects without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Table 6: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Table 7 Demographic characteristics - ~38,000 subjects for Phase 2/3 analysis – Safety population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Sex			
Male	9639 (51.1)	9436 (50.1)	19075 (50.6)
Female	9221 (48.9)	9410 (49.9)	18631 (49.4)
Race			
White	15636 (82.9)	15630 (82.9)	31266 (82.9)
Black or African American	1729 (9.2)	1763 (9.4)	3492 (9.3)
American Indian or Alaska native	102 (0.5)	99 (0.5)	201 (0.5)
Asian	801 (4.2)	807 (4.3)	1608 (4.3)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Ethnicity			
Hispanic/Latino	5266 (27.9)	5277 (28.0)	10543 (28.0)
Non-Hispanic/non-Latino	13482 (71.5)	13459 (71.4)	26941 (71.5)
Not reported	112 (0.6)	110 (0.6)	222 (0.6)
Country			
Argentina	2883 (15.3)	2881 (15.3)	5764 (15.3)
Brazil	1145 (6.1)	1139 (6.0)	2284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
USA	14460 (76.7)	14454 (76.7)	28914 (76.7)
Age group			
16-55 Years	10889 (57.7)	10896 (57.8)	21785 (57.8)
>55 Years	7971 (42.3)	7950 (42.2)	15921 (42.2)
Age at vaccination (years)			
Mean (SD)	50.5 (15.65)	50.3 (15.72)	50.4 (15.68)
Median	52.0	52.0	52.0
Min, max	(16, 89)	(16, 91)	(16, 91)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	201 (1.1)	235 (1.2)	436 (1.2)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	5517 (29.3)	5460 (29.0)	10977 (29.1)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	6578 (34.9)	6481 (34.4)	13059 (34.6)
Obese (≥30.0 kg/m^2)	6556 (34.8)	6662 (35.3)	13218 (35.1)
Missing	8 (0.0)	8 (0.0)	16 (0.0)

Table 8 Baseline Charlson comorbidities - ~38,000 subjects for Phase 2/3 analysis – Safety population

Charlson Comorbidity Index Category	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any Malignancy	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascular Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congestive Heart Failure	88 (0.5)	83 (0.4)	171 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	99 (0.5)	113 (0.6)	212 (0.6)
Diabetes Without Chronic Complication	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hemiplegia or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Leukemia	12 (0.1)	10 (0.1)	22 (0.1)
Lymphoma	22 (0.1)	32 (0.2)	54 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulcer Disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal Disease	123 (0.7)	133 (0.7)	256 (0.7)
Rheumatic Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:21)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_p3_saf

Table 9 Local reactions, by maximum severity, within 7 days after each dose – Reactogenicity subset for Phase 2/3 analysis – Safety population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Redness[d]						
	Any	4093	189 (4.6)	(4.0, 5.3)	4090	45 (1.1)	(0.8, 1.5)
	Mild	4093	125 (3.1)	(2.5, 3.6)	4090	28 (0.7)	(0.5, 1.0)
	Moderate	4093	55 (1.3)	(1.0, 1.7)	4090	11 (0.3)	(0.1, 0.5)
	Severe	4093	9 (0.2)	(0.1, 0.4)	4090	6 (0.1)	(0.1, 0.3)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Swelling[d]						
	Any	4093	250 (6.1)	(5.4, 6.9)	4090	32 (0.8)	(0.5, 1.1)
	Mild	4093	159 (3.9)	(3.3, 4.5)	4090	13 (0.3)	(0.2, 0.5)
	Moderate	4093	84 (2.1)	(1.6, 2.5)	4090	16 (0.4)	(0.2, 0.6)
	Severe	4093	7 (0.2)	(0.1, 0.4)	4090	3 (0.1)	(0.0, 0.2)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Pain at the injection site[e]						
	Any	4093	3186 (77.8)	(76.5, 79.1)	4090	488 (11.9)	(11.0, 13.0)
	Mild	4093	2178 (53.2)	(51.7, 54.8)	4090	468 (11.4)	(10.5, 12.5)
	Moderate	4093	980 (23.9)	(22.6, 25.3)	4090	18 (0.4)	(0.3, 0.7)
	Severe	4093	28 (0.7)	(0.5, 1.0)	4090	2 (0.0)	(0.0, 0.2)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Any local reaction[f]	4093	3216 (78.6)	(77.3, 79.8)	4090	525 (12.8)	(11.8, 13.9)
2	Redness[d]						
	Any	3758	243 (6.5)	(5.7, 7.3)	3749	26 (0.7)	(0.5, 1.0)
	Mild	3758	132 (3.5)	(2.9, 4.2)	3749	16 (0.4)	(0.2, 0.7)
	Moderate	3758	93 (2.5)	(2.0, 3.0)	3749	9 (0.2)	(0.1, 0.5)
	Severe	3758	18 (0.5)	(0.3, 0.8)	3749	1 (0.0)	(0.0, 0.1)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Swelling[d]						
	Any	3758	256 (6.8)	(6.0, 7.7)	3749	16 (0.4)	(0.2, 0.7)
	Mild	3758	148 (3.9)	(3.3, 4.6)	3749	8 (0.2)	(0.1, 0.4)
	Moderate	3758	98 (2.6)	(2.1, 3.2)	3749	7 (0.2)	(0.1, 0.4)
	Severe	3758	10 (0.3)	(0.1, 0.5)	3749	1 (0.0)	(0.0, 0.1)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Pain at the injection site[e]						
	Any	3758	2730 (72.6)	(71.2, 74.1)	3749	372 (9.9)	(9.0, 10.9)
	Mild	3758	1831 (48.7)	(47.1, 50.3)	3749	350 (9.3)	(8.4, 10.3)
	Moderate	3758	866 (23.0)	(21.7, 24.4)	3749	22 (0.6)	(0.4, 0.9)

Table 9 continued:

14.364. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Severe	3758	33 (0.9)	(0.6, 1.2)	3749	0	(0.0, 0.1)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Any local reaction[f]	3758	2748 (73.1)	(71.7, 74.5)	3749	396 (10.6)	(9.6, 11.6)
Any dose	Redness[d]						
	Any	4108	389 (9.5)	(8.6, 10.4)	4106	64 (1.6)	(1.2, 2.0)
	Mild	4108	233 (5.7)	(5.0, 6.4)	4106	38 (0.9)	(0.7, 1.3)
	Moderate	4108	129 (3.1)	(2.6, 3.7)	4106	20 (0.5)	(0.3, 0.8)
	Severe	4108	27 (0.7)	(0.4, 1.0)	4106	6 (0.1)	(0.1, 0.3)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Swelling[d]						
	Any	4108	430 (10.5)	(9.5, 11.4)	4106	42 (1.0)	(0.7, 1.4)
	Mild	4108	257 (6.3)	(5.5, 7.0)	4106	17 (0.4)	(0.2, 0.7)
	Moderate	4108	156 (3.8)	(3.2, 4.4)	4106	21 (0.5)	(0.3, 0.8)
	Severe	4108	17 (0.4)	(0.2, 0.7)	4106	4 (0.1)	(0.0, 0.2)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Pain at the injection site[e]						
	Any	4108	3455 (84.1)	(82.9, 85.2)	4106	700 (17.0)	(15.9, 18.2)
	Mild	4108	2041 (49.7)	(48.1, 51.2)	4106	660 (16.1)	(15.0, 17.2)
	Moderate	4108	1355 (33.0)	(31.5, 34.4)	4106	38 (0.9)	(0.7, 1.3)
	Severe	4108	59 (1.4)	(1.1, 1.8)	4106	2 (0.0)	(0.0, 0.2)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Any local reaction[f]	4108	3481 (84.7)	(83.6, 85.8)	4106	748 (18.2)	(17.0, 19.4)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = number of subjects reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Mild: >2.0 to 5.0 cm; moderate: >5.0 to 10.0 cm; severe: >10.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.
f. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:54) Source Data: adfacevd Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adce s010 lr p3 saf

Table 10 Systemic events, by maximum severity, within 7 days after each dose – reactogenicity subset for Phase 2/3 analysis – Safety population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Fever						
	≥38.0°C	4093	111 (2.7)	(2.2, 3.3)	4090	27 (0.7)	(0.4, 1.0)
	≥38.0°C to 38.4°C	4093	87 (2.1)	(1.7, 2.6)	4090	12 (0.3)	(0.2, 0.5)
	>38.4°C to 38.9°C	4093	16 (0.4)	(0.2, 0.6)	4090	8 (0.2)	(0.1, 0.4)
	>38.9°C to 40.0°C	4093	7 (0.2)	(0.1, 0.4)	4090	5 (0.1)	(0.0, 0.3)
	>40.0°C	4093	1 (0.0)	(0.0, 0.1)	4090	2 (0.0)	(0.0, 0.2)
	Fatigue[d]						
	Any	4093	1700 (41.5)	(40.0, 43.1)	4090	1172 (28.7)	(27.3, 30.1)
	Mild	4093	970 (23.7)	(22.4, 25.0)	4090	719 (17.6)	(16.4, 18.8)
	Moderate	4093	695 (17.0)	(15.8, 18.2)	4090	439 (10.7)	(9.8, 11.7)
	Severe	4093	35 (0.9)	(0.6, 1.2)	4090	14 (0.3)	(0.2, 0.6)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Headache[d]						
	Any	4093	1413 (34.5)	(33.1, 36.0)	4090	1100 (26.9)	(25.5, 28.3)
	Mild	4093	976 (23.8)	(22.5, 25.2)	4090	747 (18.3)	(17.1, 19.5)
	Moderate	4093	412 (10.1)	(9.2, 11.0)	4090	331 (8.1)	(7.3, 9.0)
	Severe	4093	25 (0.6)	(0.4, 0.9)	4090	22 (0.5)	(0.3, 0.8)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Chills[d]						
	Any	4093	434 (10.6)	(9.7, 11.6)	4090	203 (5.0)	(4.3, 5.7)
	Mild	4093	317 (7.7)	(6.9, 8.6)	4090	151 (3.7)	(3.1, 4.3)
	Moderate	4093	108 (2.6)	(2.2, 3.2)	4090	49 (1.2)	(0.9, 1.6)
	Severe	4093	9 (0.2)	(0.1, 0.4)	4090	3 (0.1)	(0.0, 0.2)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Vomiting[e]						
	Any	4093	37 (0.9)	(0.6, 1.2)	4090	37 (0.9)	(0.6, 1.2)
	Mild	4093	32 (0.8)	(0.5, 1.1)	4090	31 (0.8)	(0.5, 1.1)
	Moderate	4093	5 (0.1)	(0.0, 0.3)	4090	5 (0.1)	(0.0, 0.3)
	Severe	4093	0	(0.0, 0.1)	4090	1 (0.0)	(0.0, 0.1)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Diarrhea[f]						
	Any	4093	402 (9.8)	(8.9, 10.8)	4090	388 (9.5)	(8.6, 10.4)
	Mild	4093	324 (7.9)	(7.1, 8.8)	4090	317 (7.8)	(6.9, 8.6)
	Moderate	4093	72 (1.8)	(1.4, 2.2)	4090	69 (1.7)	(1.3, 2.1)
	Severe	4093	6 (0.1)	(0.1, 0.3)	4090	2 (0.0)	(0.0, 0.2)

Table 10 continued:

14.372. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	New or worsened muscle pain[d]						
	Any	4093	738 (18.0)	(16.9, 19.2)	4090	398 (9.7)	(8.8, 10.7)
	Mild	4093	424 (10.4)	(9.4, 11.3)	4090	275 (6.7)	(6.0, 7.5)
	Moderate	4093	300 (7.3)	(6.5, 8.2)	4090	118 (2.9)	(2.4, 3.4)
	Severe	4093	14 (0.3)	(0.2, 0.6)	4090	5 (0.1)	(0.0, 0.3)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	New or worsened joint pain[d]						
	Any	4093	406 (9.9)	(9.0, 10.9)	4090	247 (6.0)	(5.3, 6.8)
	Mild	4093	248 (6.1)	(5.3, 6.8)	4090	163 (4.0)	(3.4, 4.6)
	Moderate	4093	151 (3.7)	(3.1, 4.3)	4090	83 (2.0)	(1.6, 2.5)
	Severe	4093	7 (0.2)	(0.1, 0.4)	4090	1 (0.0)	(0.0, 0.1)
	Grade 4	4093	0	(0.0, 0.1)	4090	0	(0.0, 0.1)
	Any systemic event[g]	4093	2421 (59.1)	(57.6, 60.7)	4090	1922 (47.0)	(45.5, 48.5)
	Use of antipyretic or pain medication[h]	4093	996 (24.3)	(23.0, 25.7)	4090	545 (13.3)	(12.3, 14.4)
2	Fever						
	≥38.0°C	3758	512 (13.6)	(12.5, 14.8)	3749	14 (0.4)	(0.2, 0.6)
	≥38.0°C to 38.4°C	3758	325 (8.6)	(7.8, 9.6)	3749	7 (0.2)	(0.1, 0.4)
	>38.4°C to 38.9°C	3758	155 (4.1)	(3.5, 4.8)	3749	4 (0.1)	(0.0, 0.3)
	>38.9°C to 40.0°C	3758	31 (0.8)	(0.6, 1.2)	3749	3 (0.1)	(0.0, 0.2)
	>40.0°C	3758	1 (0.0)	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Fatigue[d]						
	Any	3758	2086 (55.5)	(53.9, 57.1)	3749	756 (20.2)	(18.9, 21.5)
	Mild	3758	793 (21.1)	(19.8, 22.4)	3749	409 (10.9)	(9.9, 12.0)
	Moderate	3758	1150 (30.6)	(29.1, 32.1)	3749	331 (8.8)	(7.9, 9.8)
	Severe	3758	143 (3.8)	(3.2, 4.5)	3749	16 (0.4)	(0.2, 0.7)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Headache[d]						
	Any	3758	1732 (46.1)	(44.5, 47.7)	3749	735 (19.6)	(18.3, 20.9)
	Mild	3758	960 (25.5)	(24.2, 27.0)	3749	486 (13.0)	(11.9, 14.1)
	Moderate	3758	696 (18.5)	(17.3, 19.8)	3749	230 (6.1)	(5.4, 7.0)
	Severe	3758	76 (2.0)	(1.6, 2.5)	3749	19 (0.5)	(0.3, 0.8)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Chills[d]						
	Any	3758	1114 (29.6)	(28.2, 31.1)	3749	125 (3.3)	(2.8, 4.0)
	Mild	3758	558 (14.8)	(13.7, 16.0)	3749	100 (2.7)	(2.2, 3.2)
	Moderate	3758	494 (13.1)	(12.1, 14.3)	3749	25 (0.7)	(0.4, 1.0)

Table 10 continued:

14.372. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Severe	3758	62 (1.6)	(1.3, 2.1)	3749	0	(0.0, 0.1)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Vomiting[e]						
	Any	3758	51 (1.4)	(1.0, 1.8)	3749	30 (0.8)	(0.5, 1.1)
	Mild	3758	37 (1.0)	(0.7, 1.4)	3749	21 (0.6)	(0.3, 0.9)
	Moderate	3758	9 (0.2)	(0.1, 0.5)	3749	9 (0.2)	(0.1, 0.5)
	Severe	3758	5 (0.1)	(0.0, 0.3)	3749	0	(0.0, 0.1)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Diarrhea[f]						
	Any	3758	356 (9.5)	(8.6, 10.5)	3749	276 (7.4)	(6.5, 8.2)
	Mild	3758	293 (7.8)	(7.0, 8.7)	3749	217 (5.8)	(5.1, 6.6)
	Moderate	3758	57 (1.5)	(1.2, 2.0)	3749	54 (1.4)	(1.1, 1.9)
	Severe	3758	6 (0.2)	(0.1, 0.3)	3749	5 (0.1)	(0.0, 0.3)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	New or worsened muscle pain[d]						
	Any	3758	1260 (33.5)	(32.0, 35.1)	3749	260 (6.9)	(6.1, 7.8)
	Mild	3758	528 (14.1)	(13.0, 15.2)	3749	168 (4.5)	(3.8, 5.2)
	Moderate	3758	669 (17.8)	(16.6, 19.1)	3749	88 (2.3)	(1.9, 2.9)
	Severe	3758	63 (1.7)	(1.3, 2.1)	3749	4 (0.1)	(0.0, 0.3)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	New or worsened joint pain[d]						
	Any	3758	772 (20.5)	(19.3, 21.9)	3749	170 (4.5)	(3.9, 5.3)
	Mild	3758	366 (9.7)	(8.8, 10.7)	3749	89 (2.4)	(1.9, 2.9)
	Moderate	3758	379 (10.1)	(9.1, 11.1)	3749	76 (2.0)	(1.6, 2.5)
	Severe	3758	27 (0.7)	(0.5, 1.0)	3749	5 (0.1)	(0.0, 0.3)
	Grade 4	3758	0	(0.0, 0.1)	3749	0	(0.0, 0.1)
	Any systemic event[g]	3758	2627 (69.9)	(68.4, 71.4)	3749	1267 (33.8)	(32.3, 35.3)
	Use of antipyretic or pain medication[h]	3758	1570 (41.8)	(40.2, 43.4)	3749	427 (11.4)	(10.4, 12.5)
Any dose	Fever						
	≥38.0°C	4108	582 (14.2)	(13.1, 15.3)	4106	38 (0.9)	(0.7, 1.3)
	≥38.0°C to 38.4°C	4108	378 (9.2)	(8.3, 10.1)	4106	18 (0.4)	(0.3, 0.7)
	>38.4°C to 38.9°C	4108	167 (4.1)	(3.5, 4.7)	4106	11 (0.3)	(0.1, 0.5)
	>38.9°C to 40.0°C	4108	35 (0.9)	(0.6, 1.2)	4106	7 (0.2)	(0.1, 0.4)
	>40.0°C	4108	2 (0.0)	(0.0, 0.2)	4106	2 (0.0)	(0.0, 0.2)
	Fatigue[d]						
	Any	4108	2585 (62.9)	(61.4, 64.4)	4106	1461 (35.6)	(34.1, 37.1)

Table 10 continued:

14.372. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population

		Vaccine Group (as Administered)					
		BNT162b2 (30 µg)			Placebo		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Mild	4108	984 (24.0)	(22.7, 25.3)	4106	800 (19.5)	(18.3, 20.7)
	Moderate	4108	1429 (34.8)	(33.3, 36.3)	4106	635 (15.5)	(14.4, 16.6)
	Severe	4108	172 (4.2)	(3.6, 4.8)	4106	26 (0.6)	(0.4, 0.9)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Headache[d]						
	Any	4108	2265 (55.1)	(53.6, 56.7)	4106	1402 (34.1)	(32.7, 35.6)
	Mild	4108	1237 (30.1)	(28.7, 31.5)	4106	887 (21.6)	(20.4, 22.9)
	Moderate	4108	930 (22.6)	(21.4, 23.9)	4106	475 (11.6)	(10.6, 12.6)
	Severe	4108	98 (2.4)	(1.9, 2.9)	4106	40 (1.0)	(0.7, 1.3)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Chills[d]						
	Any	4108	1312 (31.9)	(30.5, 33.4)	4106	289 (7.0)	(6.3, 7.9)
	Mild	4108	688 (16.7)	(15.6, 17.9)	4106	219 (5.3)	(4.7, 6.1)
	Moderate	4108	553 (13.5)	(12.4, 14.5)	4106	67 (1.6)	(1.3, 2.1)
	Severe	4108	71 (1.7)	(1.4, 2.2)	4106	3 (0.1)	(0.0, 0.2)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Vomiting[e]						
	Any	4108	84 (2.0)	(1.6, 2.5)	4106	62 (1.5)	(1.2, 1.9)
	Mild	4108	66 (1.6)	(1.2, 2.0)	4106	47 (1.1)	(0.8, 1.5)
	Moderate	4108	13 (0.3)	(0.2, 0.5)	4106	14 (0.3)	(0.2, 0.6)
	Severe	4108	5 (0.1)	(0.0, 0.3)	4106	1 (0.0)	(0.0, 0.1)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Diarrhea[f]						
	Any	4108	644 (15.7)	(14.6, 16.8)	4106	576 (14.0)	(13.0, 15.1)
	Mild	4108	511 (12.4)	(11.4, 13.5)	4106	453 (11.0)	(10.1, 12.0)
	Moderate	4108	121 (2.9)	(2.4, 3.5)	4106	116 (2.8)	(2.3, 3.4)
	Severe	4108	12 (0.3)	(0.2, 0.5)	4106	7 (0.2)	(0.1, 0.4)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	New or worsened muscle pain[d]						
	Any	4108	1573 (38.3)	(36.8, 39.8)	4106	549 (13.4)	(12.3, 14.4)
	Mild	4108	659 (16.0)	(14.9, 17.2)	4106	350 (8.5)	(7.7, 9.4)
	Moderate	4108	840 (20.4)	(19.2, 21.7)	4106	190 (4.6)	(4.0, 5.3)
	Severe	4108	74 (1.8)	(1.4, 2.3)	4106	9 (0.2)	(0.1, 0.4)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	New or worsened joint pain[d]						
	Any	4108	968 (23.6)	(22.3, 24.9)	4106	360 (8.8)	(7.9, 9.7)
	Mild	4108	458 (11.1)	(10.2, 12.2)	4106	206 (5.0)	(4.4, 5.7)
	Moderate	4108	476 (11.6)	(10.6, 12.6)	4106	148 (3.6)	(3.1, 4.2)
	Severe	4108	34 (0.8)	(0.6, 1.2)	4106	6 (0.1)	(0.1, 0.3)
	Grade 4	4108	0	(0.0, 0.1)	4106	0	(0.0, 0.1)
	Any systemic event[g]	4108	3181 (77.4)	(76.1, 78.7)	4106	2255 (54.9)	(53.4, 56.4)
	Use of antipyretic or pain medication[h]	4108	1909 (46.5)	(44.9, 48.0)	4106	810 (19.7)	(18.5, 21.0)

Table 11 Number (%) of subjects reporting at least 1 Adverse event from Dose 1 to 1 month after Dose 2 - ~38,000 subjects for Phase 2/3 analysis – Safety population

	Vaccine Group (as Administered)	
Adverse Event	**BNT162b2 (30 µg) (N^a=18801) n^b (%)**	**Placebo (N^a=18785) n^b (%)**
Any event	5071 (27.0)	2356 (12.5)
Related[c]	3915 (20.8)	953 (5.1)
Severe	220 (1.2)	109 (0.6)
Life-threatening	18 (0.1)	20 (0.1)
Any serious adverse event	103 (0.5)	81 (0.4)
Related[c]	3 (0.0)	0
Severe	57 (0.3)	48 (0.3)
Life-threatening	18 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	34 (0.2)	25 (0.1)
Related[c]	14 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	2 (0.0)	4 (0.0)
Death	1 (0.0)	2 (0.0)

Table 12: Number (%) subjects reporting at least 1 AE from dose 1 to cut-off date 14 Nov 2020- Subjects with at least 2 months follow up time after dose 2 for Phase 2/3 analysis –safety population

	Vaccine Group (as Administered)		
Adverse Event	**BNT162b2 (30 µg) (N[a]=9531) n[b] (%)**	**Placebo (N[a]=9536) n[b] (%)**	**Total (N[a]=19067) n[b] (%)**
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related[c]	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related[c]	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

Table 13: planned and ongoing studies

Study Title *Study Type* Category	Summary of Objectives	Safety concerns addressed	Protocol Link Milestone	
A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals Interventional Category 2	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	C4591001	
			CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Safety surveillance of the Pfizer COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization Non-interventional Category 3	Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in a cohort of people within the Department of Defense Healthcare System	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	C4591011	
			Interim reports submission:	30-Jun-2021
				31-Dec-2021
				30-Jun-2022
				31-Dec-2022
			Final CSR submission:	31-Dec-2023

Table 13: Planned and ongoing studies

Study Title *Study Type* Category	Summary of Objectives	Safety concerns addressed	Protocol Link Milestone	
Post-Emergency Use Authorization active surveillance of adverse events of special interest among individuals in the Veteran's Affairs Health System receiving Pfizer BioNTech Coronavirus Disease 2019 (COVID 19) vaccine Non-interventional Category 3	Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	C4591012	
			Interim reports submission:	30-Jun-2021
				31-Dec-2021
				30-Jun-2022
				31-Dec-2022
			Final CSR submission:	31-Dec-2023
A Post-Approval active surveillance safety study to monitor real-world safety of the Pfizer-BioNTech COVID-19 vaccine in the EU Non-interventional Category 3	Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	C4591010	
			Final draft protocol submission for EMA review:	31-Jan-2021
			Final CSR submission:	31-Mar-2024
A Phase 2/3, Placebo-Controlled, randomized, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older Interventional Category 3	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	C4591015	
			Protocol draft submission:	28-Feb-2021
			Final CSR submission:	30-Apr-2023

Table 13: Planned and ongoing studies

Study Title *Study Type* Category	Summary of Objectives	Safety concerns addressed	Protocol Link Milestone	
A test-negative design to evaluate the effectiveness of BNT162b2 against acute respiratory illness due to SARS-CoV-2 infection among adults ≥18 years of age Non-interventional Category 3	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	Vaccine effectiveness [a]	C4591014	
			Protocol draft submission:	31-Mar-2021
			Final CSR submission:	30-Jun-2023
Immunogenicity of COVID-19 mRNA vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses Interventional Category 3	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	BNT162-01 Cohort 13	
			IA submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022
Phase II study of BNT162b2 in adults receiving immunomodulators for rheumatoid arthritis Interventional Category 3	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	C4591018	
			Protocol submission:	28-Feb-2021
			IA submission:	31-Dec-2021
Safety and immunogenicity in high risk adults Interventional Category 3	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Not available	
			Protocol submission:	30-Jun-2021
			Final CSR submission:	31-Dec-2022

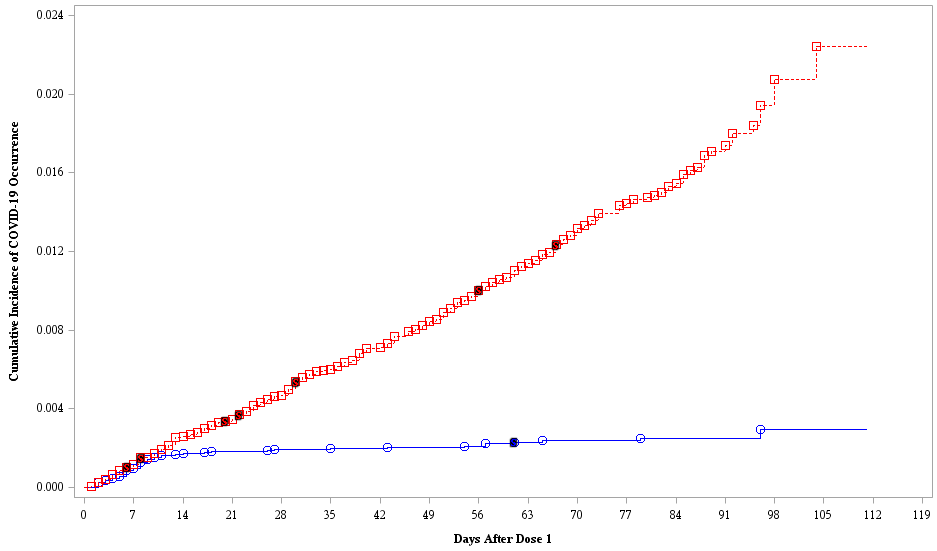
Table 13: Planned and ongoing studies

Study Title ***Study Type*** **Category**	**Summary of Objectives**	**Safety concerns addressed**	**Protocol Link** **Milestone**	
A Post-Approval Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the Pfizer BioNTech COVID 19 vaccine in the EU Non-interventional Category 3	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	ACCESS/VAC4EU	
			Protocol submission:	28-Feb-2021
			Final CSR submission:	31-Jan-2024
Co-administration study with seasonal influenza vaccine Interventional Category 3	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Not available	
			Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

a. Vaccine effectiveness is not a safety concern; however, Effectiveness study is included in this table per EMA clarification received on 16 December 2020.

Figure 5

Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



No. with events/No. at risk

A:	0/21314	21/21230	37/21054	39/20481	41/19314	42/18377	42/17702	43/17186	44/15464	47/14038	48/12169	48/9591	49/6403	49/3374	50/1463	50/398	50/0	
B:	0/21258	25/21170	55/20970	73/20366	97/19209	123/18218	143/17578	166/17025	192/15290	212/13876	235/11994	249/9471	257/6294	267/3301	274/1449	275/398	275/0	

A: BNT162b2 (30 µg) B: Placebo

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_d1_aai