Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Authorisation for Temporary Supply

COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA)

concentrate for solution for injection

The Public Assessment Report summarises the initial assessment at the time of approval in December 2020. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics on this page and the Summary of Coronavirus Yellow Card reporting.

Department of Health and Social Care (DHSC) Pfizer Limited & BioNTech Manufacturing GmbH

LAY SUMMARY

COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection (BNT162b2 RNA)

This is a summary of the Public Assessment Report (PAR) for COVID-19 mRNA Vaccine BNT162b2. It explains how this product was assessed and authorised under Regulation 174 of the Human Medicine Regulations, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

The product will be referred to as BNT162b2 in this lay summary for ease of reading.

For practical information about using BNT162b2 patients should read the Information for UK recipients or contact their doctor or healthcare practitioner.

What is BNT162b2 and what is it used for?
BNT162b2 is a vaccine indicated for active immunisation to prevent COVID-19 caused by the SARS-CoV-2 virus, in individuals 12 years of age and older.

How does BNT162b2 work?
When a person is given BNT162b2, it triggers the body to naturally produce antibodies and stimulates immune cells to protect against COVID-19.

How is BNT162b2 used?
The pharmaceutical form of this medicine is an injection. Following dilution with saline, BNT162b2 is given to you by an authorised practitioner as an intramuscular injection into the muscle at the top of the upper arm (deltoid muscle). You should receive two doses (each 0.3mL) given 21 days apart.

For further information on how BNT162b2 is used, refer to the Information for UK Healthcare Professionals and the Information for UK recipients available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This vaccine can only be obtained with a prescription.

If a person has any questions concerning the vaccine, they should ask the administering healthcare practitioner.

What benefits of BNT162b2 have been shown in studies?
BNT162b2 has been studied in approximately 43,000 individuals 16 years of age and older who were equally allocated to the vaccine or a placebo. Those who received vaccination with BNT162b2 had a reduction in the rate of COVID-19 illness compared to those who received placebo (8 cases of COVID-19 illness in the vaccinated group compared to 162 cases in the placebo group). These results were observed 7 days following the second dose in study participants with no evidence of prior SARS-CoV-2 infection.

A similar benefit of the vaccine was observed in subjects with one or more other medical conditions that increase the risk of severe COVID-19 disease, such as obesity, hypertension, diabetes, or asthma.

What are the possible side effects of BNT162b2?
The most common side effects with BNT162b2 (which may affect more than 1 in 10 people) were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain and fever. Adverse events were usually mild or moderate in intensity and resolved within a few days after vaccination.

Why was BNT162b2 approved?
It was concluded that BNT162b2 has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects observed with use of this vaccine are considered to be similar to those seen with other vaccines. Therefore, the MHRA concluded that the benefits are greater than the risks and recommended that this medicine can be authorised for temporary supply during the COVID-19 pandemic.

What measures are being taken to ensure the safe and effective use of BNT162b2?
All new medicines approved require a Risk Management Plan (RMP) to ensure they are used as safely as possible. An RMP has been agreed for the use of BNT162b2 in the UK. Based on this plan, safety information has been included in the Information for UK Healthcare Professionals and the Information for UK recipients, including the appropriate precautions to be followed by healthcare professionals and patients.

All side effects reported by patients/healthcare professionals are continuously monitored. Any new safety signals identified will be reviewed and, if necessary, appropriate regulatory action will be taken. The MHRA has also put in place an additional proactive safety monitoring plan for all COVID-19 vaccines to enable rapid analysis of safety information which is important during a pandemic.

Other information about BNT162b2
Authorisation for the temporary supply of BNT162b2 was granted in the UK on 1 December 2020.

The full public assessment report for BNT162b2 follows this summary.

This summary was last updated in June 2021.

Please note that a marketing authorisation was granted for the Pfizer/BioNTech vaccine (Comirnaty) following a European Commission (EC) decision on 21 December 2020 (PLGB 53632/0002).

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I INTRODUCTION

This report is based on the information provided by the company in a rolling data submission procedure and it covers the authorisation for temporary supply of BNT162b2. At the time of writing, the main clinical study is still on-going and additional data is being collected. Due to differences in the collection date, the data and information in this report may differ from that contained in documents relating to BNT162b2 released by other regulatory authorities. Quality aspects of the vaccine are reviewed on a batch-specific basis.

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China and in January 2020, a novel coronavirus was discovered as the underlying cause. Infections by the virus, named 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.

At the time of this report, the number of COVID-19 cases in the UK is estimated at 1.64 million and more than 60,000 deaths have been attributed to the disease. These numbers continue to rise. The elderly and those with pre-existing medical conditions are at an increased risk of severe disease and death from COVID-19. Vaccination is the most effective medical intervention to decrease risk and reduce spread of the SARS-CoV-2 virus.

The Department of Health and Social Care (DHSC) is leading the Government's deployment of vaccinations against COVID-19. In order to save lives, and to reduce the number of people who need hospital treatment due to COVID-19, the DHSC have sought to deploy a safe and effective vaccination as soon as possible. In a letter dated November 17th 2020, the DHSC requested authorisation, on a temporary basis, of its proposed supply of a vaccine manufactured by Pfizer/BioNTech collaboration, named "COVID-19 mRNA Vaccine BNT162b2", under Regulation 174 of the Human Medicines Regulations 2012, ("the Regulations").

Following an extensive review of the quality, safety and efficacy data, COVID-19 mRNA Vaccine BNT162b2 has been authorised for temporary supply in the UK for the following indication: active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The active substance of the COVID-19 mRNA Vaccine BNT162b2 is a multi-dose concentrate of RNA-containing lipid nanoparticles formulated in saline and sucrose to be diluted for intramuscular (IM) administration. A single vial contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles).

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free *in vitro* transcription from the corresponding DNA templates.

COVID-19 mRNA Vaccine BNT162b2 encodes a mutant viral spike (S) protein of SARS-CoV-2, with two point mutations inserted to lock S in an antigenically preferred prefusion conformation (P2 S). It is formulated as an RNA-lipid nanoparticle of nucleoside-modified mRNA containing N1-methylpseudouridine instead of uridine. Encapsulation into lipid nanoparticles enables transfection of the mRNA into host cells after intramuscular injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the lipid nanoparticles are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated into the encoded viral protein. The viral spike (S) protein antigen induces an adaptive immune

response through neutralising antibodies. Furthermore, as the expressed spike (S) protein is being degraded intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus and infected cells.

The authorisation is for an identified batch of the vaccine (provided certain conditions are met), together with future batches, which will each be approved by MHRA on a batch-specific basis. These conditions are published on the MHRA website.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

This batch, and any future batches, of COVID-19 mRNA Vaccine BNT162b2 are subject to Qualified Person (QP) certification and batch evaluation by an independent control laboratory before the vaccine is released into the UK.

The COVID-19 Vaccine Benefit Risk Expert Working Group (Vaccine BR EWG) have met several times to review and discuss the quality, safety and efficacy aspects in relation to batches of COVID-19 mRNA Vaccine BNT162b2. The manufacturer, Pfizer/BioNTech, was also invited to a separate meeting with the quality subgroup of the Vaccine BR EWG to review and discuss questions related to manufacture and control of the product.

The Vaccine BR EWG gave advice to the Commission of Human Medicines (CHM) on 11th September 2020, 8th October 2020, 27th October 2020, 28th November 2020 and 30th November 2020, regarding the requirements for authorisation for the temporary supply of COVID-19 mRNA Vaccine BNT162b2. The requirements for quality, safety and efficacy were considered, taking into account the urgent public health need and risk to life, the pandemic situation and a lack of COVID-19 vaccines. As well as data on quality, safety and efficacy, specific mitigations and conditions on the product were discussed to ensure adequate standards of quality and safety are met.

The CHM concluded that the proposed supply of COVID-19 mRNA Vaccine BNT162b2 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older, is recommended to be suitable for approval under Regulation 174 provided the company meets the conditions set out by the MHRA.

Authorisation for the temporary supply of COVID-19 mRNA Vaccine BNT162b2 was granted in the UK on 1 December 2020. This report covers data received and reviewed for this authorisation only. This authorisation is valid until expressly withdrawn by MHRA or upon issue of a marketing authorisation.

Whilst an acceptable level of information has been received to provide assurance that appropriate standards of quality, safety and efficacy have been met for authorisation of specific batches for temporary supply under Regulation 174 of the Regulations, it should be noted that COVID-19 mRNA Vaccine BNT162b2 remains under review as MHRA continues to receive data from the company as it becomes available. This will include, for example, long-term follow-up efficacy and safety data. Further information that is received by the

MHRA will be reviewed as part of the ongoing assessment for this product and updates will be made to this PAR to reflect that in due course.

On 4 June 2021 the MHRA granted an extension of indication to 'the active immunisation to prevent COVID-19 caused by the SARS-CoV-2 virus, in individuals 12 years of age and older'.

II QUALITY ASPECTS

II.1 Introduction

This product is a white to off-white solution provided in a multidose vial and must be diluted before use. One vial contains 5 doses of 30 micrograms of BNT162b2 RNA embedded in lipid nanoparticles (LNPs). COVID-19 mRNA Vaccine BNT162b2 is provided in a pack size of 195 vials.

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) in lipid nanoparticles (LNPs). The mRNA is produced by cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

In addition to BNT162b2 RNA this product also contains the excipients ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3 phosphocholine, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water for injections.

The finished product is packaged in a 2 mL clear vial (type I glass) with a stopper (coated bromobutyl) and a plastic flip-off cap with aluminium seal. Container closure components comply with the relevant regulatory requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current Ph. Eur. quality standards

II.2 ACTIVE SUBSTANCE

Drug Substance (BNT162b2 RNA)
BNT162b2 drug substance is a single-stranded, 5'-capped mRNA encoding the full-length viral S (S1S2) protein of SARS-CoV-2. The optimised codon sequence encoding the spike glycoprotein antigen of the SARS-CoV-2 virus results in a protein expressed with two proline mutations that fix the S1S2 spike protein in a pre-fusion conformation to increase potential to elicit virus neutralising antibodies. In addition, the RNA contains common structural elements optimised for mediating high RNA stability and translational efficiency (5'-cap, 5'-UTR, 3'-UTR, poly(A) – tail). Uridine is replaced by modified N1-methylpseudouridine ($^{m1}\Psi$TP) in the RNA synthesis which increases RNA persistence *in-vivo* through dampening of innate immune response to itself. The 5 prime end is capped with a structure which will not activate the innate immune system.

Chemical Name: messenger RNA (mRNA), 5'-capped, encoding a full-length, codon-optimised pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 (severe acute respiratory syndrome

coronavirus 2, GenBank: MN908947.3) spike (S) glycoprotein, flanked by 5' and 3' untranslated regions and a 3' poly(A) tail; contains N1-methylpseudouridine instead of uridine (all-U>m1 Ψ). Immunological agent for active immunisation (anti-SARS-CoV-2)

Appearance: Clear to slightly opalescent, colourless to slightly brown liquid

BNT162b2 RNA is not the subject of a European Pharmacopoeia monograph (Ph. Eur.) or other pharmacopoeial monograph.
Overall, production of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and adequate starting material specifications are applied.

The starting materials are adenosine triphosphate, cytidine triphosphate, guanosine triphosphate, modified uridine triphosphate, 5’ Cap and the DNA template from which the RNA is transcribed.

The DNA template from which the RNA is transcribed is critical for the fidelity of the mRNA. The manufacture of the DNA template has been described. It is manufactured through fermentation in an established and well-controlled *Escherichia coli* cell line, extracted and purified. The specifications controlling the quality of the DNA template are satisfactory. Batch data for the DNA template have been supplied for several batches for which an acceptable level of batch to batch consistency is observed. The genealogy of the finished product can be traced back to the batch of originating DNA template.

The *in vitro* enzymatic RNA transcription process has been adequately described. The 5’cap and poly(A) tail are co-transcribed with the S1S2 spike protein codon. It is noted that the operating parameters for this process span a wide range however this does not raise any immediate concerns for the batch under review.

Full scale validation data for RNA transcription demonstrates consistency and repeatability of the process operation and is accepted as qualifying the process operated at its target set points.

The manufacturer has performed a comparability assessment of drug substance batches used in the clinical trial programme and batches representative of the subsequent manufacturing changes occurring during product development, such as introduction of new manufacturing sites, manufacturing process changes and increase in batch scale, including full scale validation batches. The drug substance batch release data for essential parameters that control the quality of the active RNA and several extended characterisation test parameters were considered. These data demonstrate consistency between the drug substance described for this application and those used in the pivotal clinical study.

Analytical procedure methods have been described and are considered appropriately qualified to control this batch in the context of a batch specific approval.

The shelf-life for BNT162b2 RNA (drug substance) has been provided and is satisfactory in relation to the cadence of drug substance to drug product manufacture.

II.3 DRUG PRODUCT

The data submitted to describe the drug product have been evaluated.

Pharmaceutical development

The manufacturer has described the finished product development strategy. This utilised principles described in ICH Q8 Pharmaceutical Development and was based on the available scientific knowledge and the manufacturer's prior experience with similar RNA-lipid nanoparticle vaccines, as well as risk assessments and development studies.

The characteristics of the drug product were provided, as well as formulation development and process characterisation studies. The development history, including process changes have been summarised. The manufacturer has described their approach to defining critical quality attributes and the rationale for their criticality decisions, as well as their process risk assessment strategy and methodology, which was accompanied by a description of the manufacturer's product development and characterisation strategy. Operating ranges have been defined and the manufacturer is working on the validation of the final commercial process, which follows process optimisation.

A quality target product profile for the finished product has been established taking into consideration the World Health Organization's "WHO Target Product Profiles for COVID-19 Vaccines".

Development studies have been submitted which support the compatibility of the vaccine with the container closure and the unpreserved sodium chloride 0.9% diluent as well as commonly used needles and syringes.

The manufacturer has performed a comparability assessment of batches used in the clinical trial programme and batches representative of manufacturing changes occurring during product development, such as introduction of new manufacturing sites, process changes and increase in batch scale. In addition to release testing, the manufacturer also investigated several extended characterisation test parameters. These data will be supplemented as further experience with the manufacturing process accumulates. The recommendation for the batch which is the subject of this assessment was based on a direct comparison of the batch release results with the results for the clinically qualified batches.

Manufacture of the product

A description of the manufacturing method for COVID-19 mRNA Vaccine BNT162b2 has been provided and consists of: thawing and dilution of the drug substance, lipid nanoparticle formation upon mixing organic and aqueous phases (where specialised equipment is used for LNP formation), buffer exchange, concentration, filtration, formulation, sterile filtration, aseptic filling, visual inspection, labelling and freezing, and storage packaging and shipment.

In-process monitoring and control are performed. In-process controls and process parameters for each manufacturing step are provided and criticality has been assigned. Further in-process details are expected from the manufacturer however the information provided to date are acceptable.

As part of the control of the product, once vials are manufactured, they undergo 100% visual inspection for defects.

A condition of authorisation under this regulation is that the manufacturer will provide further data on the drug product manufacturing process as it is scaled up.

Excipients
The excipients sucrose, sodium chloride, potassium chloride, dibasic sodium phosphate dihydrate, monobasic potassium phosphate and water for injection are all of Ph. Eur. grades, which are acceptable.

In addition to those excipients, the vaccine contains four lipids, of which two are used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine, hereafter termed DSPC) and two are considered novel in that they have not been used in an authorised medicinal product in the UK:

ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)) and ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

The lipids are intended to encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles.

ALC-0315 is the functional cationic lipid component of the drug product. When incorporated in lipid nanoparticles, it helps regulate the endosomal release of the RNA. During drug product manufacturing, introduction of an aqueous RNA solution to an ethanolic lipid mixture containing ALC-0315 at a specific pH leads to an electrostatic interaction between the negatively charged RNA backbone and the positively charged cationic lipid. This electrostatic interaction leads to encapsulation of RNA drug substance resulting with particle formation. Once the lipid nanoparticle is taken up by the cell, the low pH of the endosome renders the LNP fusogenic and allows the release of the RNA into the cytosol.

The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the LNP which contributes to storage stability and reduces non-specific binding to proteins. As higher PEG content can reduce cellular uptake and interaction with the endosomal membrane, PEG content is controlled.

Cholesterol is included in the formulation to support bilayer structures in the lipid nanoparticle and to provide mobility of the lipid components within the lipid nanoparticle structure. The specification for the conventional lipid, cholesterol, is considered acceptable for the purpose of this application.

DSPC is a phospholipid component intended to provide a stable bilayer-forming structure to balance the non-bilayer propensity of the cationic lipid. DSPC is a non-pharmacopeial excipient and an adequate specification has been provided.

The controls in place for the excipients are considered suitable for this application.

Excipients of human and animal origin
No excipients of animal or human origin are used in the finished product.

Novel excipients
ALC-0315 is a cationic lipid and is critical to the self-assembly process of the particle itself, the ability of the particle to be taken up into cells and the escape of the RNA from the endosome. ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid).

Finished Product Control
The product specification includes relevant control parameters considering the nature of the product and its manufacturing process.

Batch release data for this batch have been evaluated comparing the results with the clinically qualified ranges from batches used in the clinical trial programme.

Independent Batch testing
Independent batch testing is required for vaccines and provides additional assurance of quality before a batch is made available to the market. Independent batch testing is a function that is undertaken by an Official Medicines Control Laboratory (OMCL) and, under Regulation 174A, the UKs National Institute for Biological Standards and Control (NIBSC) is responsible for this function. Each batch will be independently tested prior to deployment.

Independent batch testing is product-specific and highly technical: it requires specific materials and documentation from the manufacturer and comprises laboratory-based testing and review of the manufacturer's test data. If all tests meet the product specifications a certificate of compliance is issued by the OMCL.

Characterisation of impurities
The impurity profile of the BNT162b2 drug product is based primarily on the impurity profile of the materials used for its manufacture.

The manufacturer has described four identified drug product manufacturing process-related impurities. A safety risk assessment for each of these four potential impurities has been performed and they are below the safety threshold given the intended product administration schedule.

Process-impurities from the sucrose, phosphate and chloride salts used in the final drug product formulation are controlled through testing and specifications ensuring compliance to relevant compendial monographs. This is acceptable.

The lipid impurities are controlled through the acceptance criteria used for their manufacture. No critical issues have been identified with respect to the lipids that would preclude the emergency use of the vaccine.

Reference standards or materials
The manufacturer has defined reference materials that are used in the determination of drug product content and in the determination of lipid content for the four lipids used for nanoparticle formation. These methods are considered conventional and uncomplicated to perform.

Container closure system
Overall, the container closure system has been well described and complies with the relevant quality standards of the Ph.Eur. The vaccine requires storage at ultra-low temperature conditions and the rubber septum is punctured at least 6 times to reconstitute the product and recover 5 doses from the vial. The manufacturer has provided details of adequate testing to provide evidence that the self-sealing capacity of the elastomeric closure is retained upon freezing and repeated thawing of product, even though the storage requirements do not permit this. The testing also accounted for the recommended needles for diluent addition.

Stability
The manufacturer has provided all stability data available to date. Information on the stability of batches used in clinical trials has been used to support conclusions on product storage and storage conditions.

Based on the stability information currently available, a shelf-life of 6 months at -80°C to -60°C can be accepted for this vaccine, with the following storage conditions: -

Store in a freezer at -80°C to -60°C.
Store in the thermal container at -90ºC to -60ºC.

Store in the original package in order to protect from light.

After removal from frozen storage, the undiluted vaccine can be stored for up to 5 days (120 hours) at 2°C to 8°C and up to 2 hours at temperatures up to 25°C, prior to use. Once thawed, the vaccine cannot be re-frozen.

During storage, it is recommended that exposure to room light is minimised, and exposure to direct sunlight and ultraviolet light avoided. Thawed vials can be handled in room light conditions.

After dilution with unpreserved normal saline, the vaccine should be stored at 2°C to 25°C and used as soon as practically possible. Since the vaccine does not contain a preservative, once the stopper has first been punctured on addition of the diluent, the vial should be used within 6 hours as is recommended by WHO guidance. After 6 hours, any unused vaccine left in the vial should be discarded.

Deployment of this vaccine is subject to the conditions of this Regulation 174 approval.

Suitable post approval stability commitments have been provided to continue stability testing on batches of COVID-19 mRNA Vaccine BNT162b2, including for the batch concerning this Regulation 174 application. The manufacturer has committed to provide these data to the MHRA on an on-going basis as it becomes available.

Handling of Pfizer Vaccine BNT162b2
Lipid nanoparticles (LNPs) are complex particles made of four lipid components that entrap the mRNA. Because of this complexity LNPs are potentially fragile to degradation and damage through inappropriate handling.

The published storage conditions are qualified by the data reviewed by the MHRA.
Long term storage: It must be stored frozen at ultra-low temperature (ULT).

After removal from frozen storage, it has a shelf life of up to 120 hours at 2-8 ºC before being diluted (label to be added once box removed from freezer).

In addition to the 120-hour period at 2-8 ºC, an undiluted vial can be stored for 2 hours at up to 25 ºC. This is intended to qualify removing the vial from the fridge for up to two hours immediately before it is diluted in preparation for use. It is not intended to qualify *ad hoc* removal from fridge within the 120-hour period with a view to then replacing back into stock were it not to be used.

Once thawed, the vaccine cannot be refrozen.
Before dilution the vial must be inverted gently 10 times without shaking (to avoid foaming).
Once the specified diluent is added, the vial must be inverted gently 10 times without shaking (to avoid foaming).

Once diluted, the vials should be marked with the dilution date and time.

Transportation by motor vehicle of diluted vaccine away from the site of dilution is not currently supported by any relevant stability data.
After dilution the vaccine should be used as soon as is practically possible and within 6 hours of dilution; it can be stored at 2-25 ºC during this period. It would not normally be considered good practice to store diluted product for 6 hours at 25ºC before being administered.

Similarly, there are no data supporting multiple temperature cycling within that 6 hours that would qualify the product being repeatedly removed and replaced into a fridge, as doses are administered over the course of 6 hours.

Following dilution, vials should be used in the shortest time period possible.

II.4 Regulation 174

Authorisation for temporary supply of COVID-19 mRNA Vaccine BNT162b2 under this Regulation 174 has been given following review of batch analytical data by MHRA.

Independent batch release by the National Institute for Biological Standards and Control (NIBSC) will be performed on all batches to be supplied to the UK.

The quality data currently available for COVID-19 mRNA Vaccine BNT162b2 can be accepted as sufficient with specific conditions in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174 of the Human Medicine Regulations.

III NON-CLINICAL ASPECTS

III.1 Introduction

COVID-19 mRNA Vaccine BNT162b2 has been developed for use in healthy subjects to prevent COVID-19 on exposure to SARS-CoV-2. The vaccine has as its active agent messenger ribonucleic acid (mRNA), made by transcription of a DNA template, encoding for the full-length spike (S) protein of SARS CoV-2 with two point mutations, to lock S in an antigenically preferred prefusion conformation.

COVID-19 mRNA Vaccine BNT162b2 is given as two intramuscular injections (IM), 21 days apart, of the same dose of 30 μg mRNA.

COVID-19 mRNA Vaccine BNT162b2 is made up of the mRNA component with 4 lipid components forming nanoparticles, of which two are novel and not used before in pharmaceutical products in the UK. The lipids function to encapsulate, stabilise the mRNA and mediate its delivery to cells.

The following non-clinical studies were submitted with this application:

Pharmacology
Study 20-0211: *In vitro* expression of BNT162b2 drug substance and drug product

Study R-20-0085: COVID-19: Immunogenicity of BNT162b2 in mice

Study R-20-0112: Characterizing the immunophenotype in spleen and lymph node of mice treated with SARS-CoV-2 vaccine candidates

Study VR-VTR-10671: BNT162b2 immunogenicity and evaluation of protection against SARS-CoV-2 challenge in rhesus macaques

Pharmacokinetics
Study PF-07302048: Single dose pharmacokinetics study of ALC-0315 and ALC-0159 following intravenous bolus injection of a nanoparticle formulation in rats

Study R-20-0072: Biodistribution of BNT162b2 using the luciferase protein as a surrogate marker protein after intramuscular injection in mice.

Toxicology
Study 38166: Repeat-dose toxicity study of three LNP-formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Wistar Han rats

Study 20GR142: 17-day Intramuscular Toxicity Study of BNT162b2 and BNT162b3 in Wistar Han Rats

These studies were conducted in accordance with current Good Laboratory Practice (GLP).

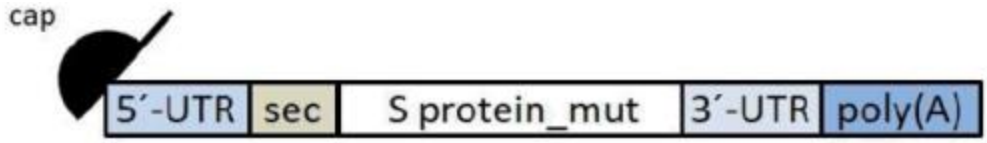
III.2 Pharmacology

This vaccine acts by intracellular translation of mRNA to the SARS-CoV-2 S protein to induce an immune response, a humoral neutralizing antibody response and Th1-type CD4+ and CD8+ cellular response, to block virus infection and kill virus infected cells, respectively.

The vaccine was tested for its ability to result in S protein expression in a mammalian cell population in vitro, for its immunogenicity in mice in two studies, and in one study in rhesus monkeys, including its capacity to prevent disease after challenge with SARS Cov-2 virus in rhesus monkeys. The vaccine also induced an immune response in rats in the two toxicity studies.

Physical chemistry

Figure 1: Structural schematic of the BNT162b2 RNA in the COVID-19 mRNA vaccine BNT162b2



Schematic illustration of the general structure of the RNA vaccine with 5'-cap, 5'- and 3'-untranslated regions, coding sequences with signal peptide, and poly(A)-tail. The individual elements are not drawn exactly true to scale compared to their respective sequence lengths.
UTR - untranslated region: sec-signal peptide; S protein mut – S protein sequence containing the two mutations K986P and V987P (P2 S). These two mutations ensure that the S protein remains in an antigenically optimum prefusion conformation.

Study 20-0211 analysed SARS-CoV-2 P2 S expression in HEK293T cells. The initial demonstration of *in vitro* expression in HEK293 cells confirmed that transfection and subsequent protein expression could take place, including in cells incubated with the nanoparticle presentation of the vaccine.

In Study R-20-085, four groups of eight female mice were immunised once by the IM route on day 0 with 0.2 µg, 1 µg or 5 µg RNA/animal of COVID-19 mRNA Vaccine BNT162b2, or with a control. Antibody response was assessed at days 7, 14, 21 and 28.

Study R-20-0112 aimed to characterise T- and B-cell responses in the spleen, lymph nodes and blood of BNT162b2 immunised mice. It characterised changes in the myeloid cell compartment, determined the ability of CD8+ T-cells to react to cells presenting the vaccine-encoded antigen, and determined antibody responses.

In Studies R-20-085 and R-20-0112 in mice, a dose-response effect was seen in the IgG responses specific for the SARS CoV-2 S1 protein fragment and its receptor binding domain. A high and dose-dependent pseudovirus neutralising antibody response was confirmed. $CD4^+$ and $CD8^+$ T cell cellular responses with a Th1 pattern of response (e.g. production of IFN-γ) were observed. Booster responses were not evaluated in these studies.

Study VR-VTR-10671 was performed in male rhesus macaques aged 2-4 years vaccinated with 30 µg COVID-19 mRNA Vaccine BNT162b2, 100 µg COVID-19 mRNA Vaccine BNT162b2 or a control.

Results showed COVID-19 mRNA vaccine BNT162b2 was immunogenic, eliciting IgG responses after a single dose, which were boosted by a second dose. It also showed a dose-response. At 30 µg BNT162, the neutralising geometric mean titre in a SARS-CoV-2 neutralization assay was compared to that seen in convalescent serum (HCS) from humans recovered from SARS CoV-2 infection/COVID-19 and found to be ~8-times higher. Seven days after Dose 2 of 100 µg, the neutralising GMT reached 18-times that of the HCS panel and

remained 3.3-times higher than this benchmark five weeks after the last immunisation. In monkeys, the cellular immune response was characterised as a strongly Th1-biased CD4+ T cell response with a concurrent interferon-γ (IFNγ)+ CD8+ T cell response.

For the challenge portion of the study, SARS-CoV-2 challenge was performed on the COVID-19 mRNA Vaccine BNT162b2-immunised animals (100 µg/animal dose level) and on animals dosed with a control. Upon challenge with SARS CoV-2, the resulting clinical pattern in monkeys was unremarkable and no signs of clinical illness resulted from this exposure. Total viral RNA (genomic and subgenomic RNA) was detected in bronchoalveolar lavage fluid of control monkeys but not detected in monkeys immunised with BNT162b2; in the nasal swabs viral RNA was detected in monkeys given BNT162 but clearance was faster than in controls. This is evidence of the beneficial effect of this vaccine. In lung tissues, control monkeys had evidence of some pulmonary disease indicated by their increased scores on computed tomography scans with a suggestion of recovery in those scores at day 10 that were less than those at day 3; in contrast, the monkeys given COVID-19 mRNA Vaccine BNT162b2 had lower scores than controls.

The absence of secondary pharmacology and safety pharmacology studies is acceptable for a vaccine and is in line with relevant regulatory guidance (WHO Guidelines on nonclinical evaluation of vaccines, 2005). The guidance does not mention secondary pharmacodynamics: however, it does state that if data from other studies suggest that the vaccine may affect physiological functions (central nervous system, renal, respiratory or cardiovascular system functions), safety pharmacology studies should be incorporated into the toxicity assessment. This does not apply for COVID-19 mRNA Vaccine BNT162b2.

There are no major public health concerns identified. Since this authorisation the manufacturer has provided further information on the methodology used to determine anti-spike protein antibodies in mice which has been reviewed as part of the ongoing assessment for this product. These data are not discussed here.

III.3 Pharmacokinetics

The active substance of COVID-19 mRNA Vaccine BNT162b2 is N1-methylpseudouridine instead of uridine containing mRNA expressing full-length SARS-CoV-2 spike protein with two proline mutations (P2 S) to lock the transmembrane protein in an antigenically optimal prefusion conformation. The vaccine is formulated in lipid nanoparticles (LNPs). The LNP is composed of 4 lipids: ALC-0315, ALC-0159, 1,2-distearoyl-sn-glycero-3-phosphocoline (DSPC), and cholesterol. Of the four lipids used as excipients in the LNP formulation, two are naturally occurring (cholesterol and DSPC) and will be metabolised and excreted like their endogenous counterparts.

Pharmacokinetic studies have not been conducted with COVID-19 mRNA Vaccine BNT162b2 and are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005; WHO, 2014).

The ADME profile of COVID-19 mRNA Vaccine BNT162b2 included evaluation of the PK and metabolism of the two novel lipid excipients (ALC-0315 and ALC-0159) in the LNP and potential in vivo biodistribution using luciferase expression as a surrogate reporter.

Absorption

No absorption studies were conducted for COVID-19 mRNA Vaccine BNT162b2 since the route of administration is intramuscular (IM).

The "Single dose pharmacokinetics study of ALC-0315 and ALC-0159 following intravenous bolus injection of a nanoparticle formulation in rats" was conducted to assess the PK and metabolism of the two novel lipid excipients (ALC-0315 and ALC-0159). This study used LNPs containing surrogate luciferase RNA, with the lipid composition being identical to BNT162b2, to investigate the *in vivo* disposition of ALC-0159 and ALC-0315.

Concentrations of ALC-0159 dropped approximately 8000- and >250-fold in plasma and liver, respectively, during this 2-week study. For ALC-0315, the elimination of the molecule from plasma and liver was slower, but concentrations fell approximately 7000- and 4-fold in two weeks for plasma and liver, respectively. Overall, the apparent terminal t½ in plasma and liver were similar in both tissues and were 2-3 and 6-8 days for ALC-0159 and ALC-0315, respectively. The apparent terminal t½ in plasma likely represents the re-distribution of the respective lipids from the tissues into which they have distributed as the LNP, back to plasma where they are eliminated.

Distribution

Study R-20-0072 evaluated the *in vivo* potential biodistribution of COVID-19 mRNA Vaccine BNT162b2 in mice using luciferase expression as a surrogate reporter. Protein expression was demonstrated at the site of injection and to a lesser extent, and more transiently, in the liver after mice received an IM injection of RNA encoding luciferase in an LNP formulation like BNT162b2. Luciferase expression was identified at the injection site at 6 hours after injection and diminished to near baseline levels by day 9. Expression in the liver was also present at 6 hours after injection and was not detected by 48 hours after injection. Information regarding the potential distribution of the test articles to sites other than the injection site following IM administration has been provided and is under review as part of the ongoing rolling assessment.

Metabolism

The *in vitro* metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver samples from the PK study. Metabolism of ALC-0315 and ALC-0159 appears to occur slowly *in vitro* and *in vivo*. ALC-0315 and ALC-0159 are metabolised by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

Excretion

No excretion studies have been conducted with COVID-19 mRNA Vaccine BNT162b2. In the PK study, it appears that 50% of ALC-0159 was eliminated unchanged in faeces. Metabolism played a role in the elimination of ALC-0315, as little to no unchanged material was detected in either urine or faeces. Investigations of urine, faeces and plasma from the rat PK study identified a series of ester cleavage products of ALC-0315. The manufacturer has proposed that this likely represents the primary clearance mechanism acting on this molecule, although no quantitative data is available to confirm this hypothesis. *In vitro*, ALC-0159 was metabolised slowly by hydrolytic metabolism of the amide functionality.

Pharmacokinetic drug interactions

No PK drug interaction studies have been conducted with COVID-19 mRNA Vaccine BNT162b2. This is acceptable and in line with relevant guidelines (WHO 2005; WHO 2014).

III.4 Toxicology

Single dose toxicity

No single dose toxicity studies have been performed. This is acceptable and in line with relevant guidelines (WHO 2005; WHO 2014).

Repeat-dose toxicity

Study 38166 was a GLP-compliant repeat-dose study performed in rats to evaluate toxicity of the LNP and mRNA platform used in BNT162b2.

Study 20GR142 was a GLP-compliant repeat-dose study performed in rats to evaluate toxicity of COVID-19 mRNA Vaccine BNT162b2.

In Study 38166, male and female Wistar rats were given BNT162b2 as IM injection(s) into the hind limb on three occasions each a week apart (dosing days 1, 8 and 15). Different doses (10, 30, and 100 μg) were tested; the lower doses were given as a single injection of 20-70 μL, while the highest dose (100 μg) and controls were given as two injections (one in each hindlimb) of 100 μL each. The control was phosphate buffered saline/300 mM sucrose, corresponding to the storage buffer of the vaccine product. Each group had 18 male and 18 female rats, assigned as 10 to the main study, 5 for recovery groups and 3 as additional animals for cytokine analyses. The recovery period was 3 weeks after the last dose. Necropsy was performed on study day 17, ~48 hours after the last dose, and after the 3-week recovery period.

No unscheduled deaths were observed.

Dosing was considered well tolerated and did not present any signs of systemic toxicity; there was a slight increase in body temperature in the hours after dosing and some loss in body weight over the same period but these were not of a magnitude to be considered adverse.

Local inflammatory reactions were observed at the intramuscular injection site. Injection site changes noted were of oedema, erythema, and induration, more severe and more frequent after the second and/or third doses compared to the first; however, these resolved prior to subsequent dosing and were fully recovered at the end of the 3-week recovery period.

Macroscopic findings at the injection sites included induration or thickening, occasionally accompanied by encrustation, which was noted for nearly all rats. This correlated microscopically with inflammation and variable fibrosis, oedema, and myofibre degeneration. Inflammation at the injection site was accompanied by elevations in circulating white blood cells and acute phase proteins (fibrinogen, alpha-2 macroglobulin, and alpha-1 acid glycoprotein).

Inflammation was occasionally evident extending into tissues adjacent to the injection site. There was enlargement of the draining (iliac) lymph nodes evident at the end of dosing. This correlated with increased cellularity of germinal centres and increased plasma cells in the draining (iliac) lymph node and is an anticipated immune response to the administered vaccine.

Enlargement of spleen and increased spleen weights correlated microscopically to increased haematopoiesis and increased haematopoiesis was also evident in the bone marrow. These findings are likely secondary to the immune/inflammatory responses to the vaccine.

At the end of the recovery period, injection sites were normal, clinical pathology findings and macroscopic observations had resolved and there was evidence of recovery of the injection site inflammation on microscopy.

Microscopic vacuolation of portal hepatocytes was present. There were no elevations in alanine aminotransferase (ALAT). There were elevations in gamma-glutamyltransferase (GGT) in all vaccinated rats, but there were no macroscopic or microscopic findings consistent with cholestasis or hepatobiliary injury to explain the increased GGT activity, which was completely resolved at the end of the 3-week recovery period.
The vacuolation may be related to hepatic distribution of the pegylated lipid in the LNP. No changes were seen in serum cytokine concentrations. Additional ADME data has been received since this authorisation and has been reviewed as part of the ongoing assessment for this product. This data is not discussed here.

There were no effects noted on ophthalmological and auditory assessments, nor on external appearance or behaviour; in particular, gait was normal meaning that the changes seen did not affect the rats' mobility. No vaccine-related changes were seen in serum cytokine concentrations.

Testing for immunogenicity showed that COVID-19 mRNA Vaccine BNT162b2 elicited a specific IgG antibody response to SARS CoV-2 spike protein directed against the S1 fragment and the receptor binding domain. A neutralizing antibody response was also observed with the vaccine in a pseudovirus neutralization assay.

In conclusion, COVID-19 mRNA Vaccine BNT162b2 was well tolerated, and produced inflammatory changes at the injection sites and the draining lymph nodes, increased haematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites. The findings in this study are typical of those expected with dosing of LNP encapsulated mRNA vaccines.
Study 20GR142 had the objective to determine toxicity in rats given COVID-19 mRNA Vaccine BNT162b2. This study was in compliance with Good Laboratory Practice. Two candidate vaccines were tested; however, results are presented here only for COVID-19 mRNA Vaccine BNT162b2.

Male and female Wistar Han rats were given BNT162b2 as an IM injection into the hind limb on three occasions, each a week apart (dosing days 1, 8 and 15). Necropsy was performed on study day 17, ~48 hours after the last dose, and after the 3-week recovery period. COVID-19 mRNA Vaccine BNT162b2 was supplied at 0.5 mg/ml, and the dose volume was 60 µL, to give 30 µg per dose. Control rats received saline. Each group contained 15 males and 15 females.

All rats given COVID-19 mRNA Vaccine BNT162b2 survived to their scheduled necropsy: there were no changes noted in clinical signs or body weight changes noted. A reduction in food intake was noted on days 4 and 11 (to 0.83x controls) and there was an increase in mean body temperature post-dose on day 1 (up to 0.54°C), day 8 (up to 0.98°C) and day 15 (up to 1.03°C) compared to controls.

At injection sites, there were instances of oedema and erythema on days 1 (maximum of slight oedema and very slight erythema), 8 (maximum of moderate oedema and very slight erythema) and 15 (maximum of moderate oedema and very slight erythema) which fully resolved and were not noted prior to dosing on days 8 and 15.

Haematological tests showed higher white blood cells (up to 2.95x controls), primarily involving neutrophils (up to 6.80x controls), monocytes (up to 3.30x controls), and large unstained cells, LUC, (up to 13.2x controls) and slightly higher eosinophils and basophils on days 4 and 17. White blood cells were higher on day 17 as compared with day 4. There were transiently lower reticulocytes on day 4 (to 0.27x controls) in both sexes and higher reticulocytes on day 17 (up to 1.31x controls) in females only. Lower red blood cell mass parameters (to 0.90x controls) were present on days 4 and 17. There were lower A:G ratios (to 0.82x) on days 4 and 17. Higher fibrinogen was noted on day 17 (up to 2.49x) compared to controls, consistent with an acute phase response. The acute phase proteins alpha-1-acid glycoprotein (up to 39x on day 17) and alpha-2 macroglobulin (up to 71x on Day 17) were elevated on days 4 and 17 with higher concentrations in males. There were no changes urinalysis parameters.

At post-mortem there were higher absolute and relative spleen weights in vaccinated rats (up to 1.42x in males and to 1.62x in females). There were no other changes in organ weights. Macroscopic findings included enlarged draining lymph nodes and pale/dark firm injection sites in a minority of vaccinated rats. The dosing is reported as tolerated without inducing any systemic toxicity and with all changes consistent with an inflammatory response and immune activation: findings are consistent with those typically associated with dosing of lipid nanoparticle-encapsulated mRNA vaccines. Since this authorisation the manufacturer has provided the final study report which has been reviewed as part of the ongoing assessment for this product and is not discussed here.

Toxicokinetics
No toxicokinetic studies have been performed with the vaccine. This is consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005).

Genotoxicity
No genotoxicity studies are planned for BNT162b2, as the components of all vaccine constructs are lipids and RNA that are not expected to have genotoxic potential (WHO, 2005).

Carcinogenicity
Carcinogenicity studies with BNT162b2 have not been conducted as the components of all vaccine constructs are lipids and RNA that are not expected to have carcinogenic or tumorigenic potential. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005).

Reproductive and developmental toxicity
Fertility and early embryonic development and embryofoetal development
In the general toxicity studies, macroscopic and microscopic evaluation of male and female reproductive tissues showed no evidence of toxicity.
A combined fertility and developmental study (including teratogenicity and postnatal investigations) in rats is ongoing.

Prenatal and postnatal development, including maternal function
No such studies have been done.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
No such studies have been done.

Local tolerance
No such studies have been done. The assessments made as part of the general toxicity study should suffice and a separate study is not needed.

Other toxicity studies
No such studies have been done.

Toxicity conclusions

The Public Assessment Report summarises the initial assessment at the time of approval in December 2020. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics on this page and the Summary of Coronavirus Yellow Card reporting.

The absence of reproductive toxicity data is a reflection of the speed of development to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need. In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available. In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time: however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination. Women who are breastfeeding should also not be vaccinated. These judgements reflect the absence of data at the present time and do not reflect a specific finding of concern. Adequate advice with regard to women of childbearing potential, pregnant women and breastfeeding women has been provided in both the Information for UK Healthcare Professionals and the Information for UK recipients.

III.5 Ecotoxicity/Environmental Risk Assessment

It is agreed that, in accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, due to their nature, vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, an environmental risk assessment is not provided in this application. This is acceptable.

III.6 Discussion and conclusion on the non-clinical aspects

The non-clinical data currently available for COVID-19 mRNA Vaccine BNT162b2 can be accepted as sufficient with specific mitigations in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

- **BNT162-01**: An on-going multi-site, Phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four different prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy adults.

- **C4591001**: An on-going phase 1/2/3, placebo-controlled, randomised, 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.

The product will be referred to as BNT162b2 in this clinical review for ease of reading.

Table 1: Overview of the 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)

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No pharmacokinetic data have been submitted for this application and none were required.

As the mode action of vaccines is dependent on immunologic processes and not pharmacological effects, studies to determine serum concentrations of antigens are not needed for an intramuscular COVID-19 vaccine.

IV.3 Clinical Immunogenicity

Bioanalytical assays

The qualification or validation reports for each bioanalytical assay have been provided. These

include the neutralising and binding antibody assays, ELISpot assay, intracellular cytokine staining and PCR. Overall, the methods are considered acceptable and fit for purpose.

Methods

Study BNT162-01

Part A of this study investigated the humoral and cell mediated immune responses to BNT162b2 in 60 participants aged 18-55 years who received 2 doses of either 1 µg, 3 µg, 10 µg, 20 µg or 30 µg separated by 21 days. Older adults aged 56-85 years are also enrolled.

Humoral immunogenicity assessments measured by neutralising and binding antibody assays are performed at baseline and at 7 and 21 days after Dose 1 and at 7, 14, 21, 28, 63, and 162 days after Dose 2.

Evaluation of the T cell response by ELISpot and by intracellular cytokine staining visualised with fluorescence is planned at baseline and at Day 29. Additional exploratory evaluation of the T-cell response is also planned at later time points up to 162 days after Dose 2.

The study population includes male and female adult participants deemed healthy and without COVID-19 symptoms or evidence of SARS-CoV-2 infection within 30 days prior to entering the study.

In Part B of this study expansion cohorts including healthy and immunocompromised adults (n=150) are planned, with additional blood draws up to 2 years including evaluation of the T cell response. ADCC activity will also be investigated as an exploratory objective.

Study C4591001

In phase 1 humoral immunogenicity responses to BNT162b2 were investigated in 90 participants aged 18-55 years and 65-85 years who were randomised to 10 µg, 20 µg, 30 µg or placebo, as a 2-dose schedule separated by 21 days. Neutralising titres and IgG antigen-binding levels (S1 and RBD) were measured on days 7 and 21 (pre-dose 2) after dose 1; 7 and 14 days and 1 month after Dose 2. Measurements will also be performed at 6, 12 and 24 months after Dose 2.

In Phase 2, immunogenicity was assessed at baseline and 1 month, after completion of vaccination in subjects aged 18-85 years. Assessments will also be performed at 6, 12 and 24 months after completion of vaccination. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months.

In addition, immune responses were measured 1 month after a visit due to COVID-19 illness.

To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalised.

Results

Immunogenicity data for BNT162b2 are currently available up to 1 month after the second vaccine dose.

Humoral response

Phase 1

The humoral immunogenicity results from phase 1 participants in study BNT162-01 and C4591001 reflected the results seen in the larger phase 2 population described below.

Phase 2

Three hundred and sixty subjects were enrolled in phase 2 of study C4591001. Of these, 335 were included in the post Dose 2 evaluable immunogenicity population: 168 in the BNT162b2 arm and 167 in the placebo arm.

In the Dose 2 evaluable immunogenicity population, 52% of participants were male; 85% were White and 10% were Black or African American. The median age was 56 years (range 18-85).

BNT162b2 elicited robust SARS-CoV-2 neutralisation and S1-binding antibody responses at 1 month after dose 2. SARS-Cov-2 neutralising titres and S1-binding antibody concentrations were higher in younger subjects (18-55years) compared with the older subjects (56-85years). Neutralising geometric mean titres (GMTs) for younger and older participants at 1 month after Dose 2 were comparable to panel of SARS-CoV-2 infection/COVID-19 human convalescent sera.

Table 2: Summary of Geometric Mean Titres/Concentrations – Dose 2 evaluable immunogenicity population

		Vaccine Group (as Randomized)							
		BNT162b2 (30 µg)						Placebo	
		18-55 Years		56-85 Years		18-85 Years		18-85 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT/GMC[c] (95% CI[c])	n[b]	GMT/GMC[c] (95% CI[c])	n[b]	GMT/GMC[c] (95% CI[c])	n[b]	GMT/GMC[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	80	10.1 (9.9, 10.4)	88	10.3 (9.9, 10.7)	168	10.2 (10.0, 10.5)	167	10.4 (10.0, 10.9)
	2/1 Month	80	399.4 (342.1, 466.2)	87	255.0 (205.7, 316.0)	167	316.1 (275.6, 362.6)	167	10.6 (10.0, 11.3)
S1-binding IgG level assay (U/mL)	1/Prevax	80	0.8 (0.6, 0.9)	88	0.8 (0.7, 1.1)	168	0.8 (0.7, 0.9)	167	0.8 (0.7, 0.9)
	2/1 Month	80	7122.8 (6217.4, 8160.2)	87	3960.7 (3007.2, 5216.6)	167	5246.5 (4460.3, 6171.4)	167	1.0 (0.8, 1.2)

Abbreviations: GMC = geometric mean concentration; GMT = geometric mean titer; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; S1 = spike protein S1 subunit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.

c. GMTs, GMCs, and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers or concentrations and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Table 3: Summary of Geometric Mean Fold Rises from before vaccination to each subsequent time point – Phase 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		BNT162b2 (30 µg)						Placebo	
		18-55 Years		56-85 Years		18-85 Years		18-85 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	80	39.4 (34.0, 45.6)	86	24.9 (20.2, 30.9)	166	31.1 (27.2, 35.5)	167	1.0 (1.0, 1.1)
S1-binding IgG level assay (U/mL)	2/1 Month	80	9167.2 (7452.8, 11276.0)	86	4975.5 (3655.9, 6771.4)	166	6679.4 (5511.6, 8094.7)	167	1.2 (1.0, 1.4)

Abbreviations: GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; S1 = spike protein S1 subunit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified assay at both prevaccination and the given dose/sampling time point.

c. GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

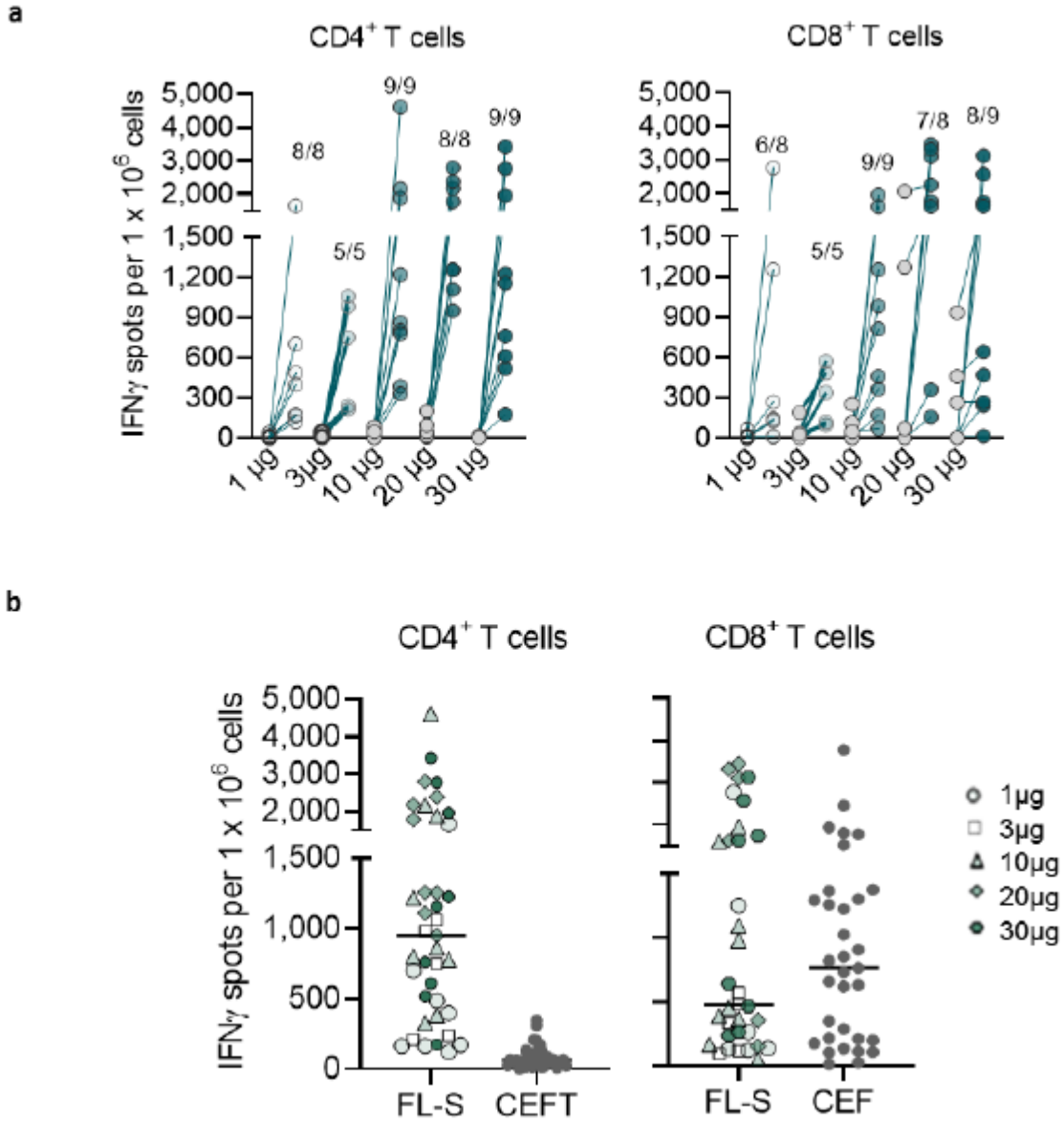
Cellular response

Cell mediated immunity data are available from study BNT162-01 in a limited number of subjects aged 18-55 years.

At the data-cut-off, evaluable ELISpot data were available from 39 participants across dose levels of BNT162b2. Evaluable intracellular cytokine staining and fluorescence-activated cell sorting data were available from 36 participants across dose levels.

The data, albeit with a limited number of subjects per cohort, suggest that BNT162b2 can induce de novo Class I and Class II T cell immune responses in most of the vaccinated subjects with a prime and booster regimen even at low vaccine dose levels as evidenced by an IFNγ ELISpot assay. The data suggest that the response may be attributed to various epitopes across the spike protein sequence, within and outside the RBD, but dose levels may not always directly correlate with the induced cellular immunogenicity and the existence of some reactivity at baseline in some participants may be due to a level of cross-reactivity with antigens to which those participants had previously been exposed, probably related to conserved regions in the sequence represented by the SARS-CoV-2-FL-S pool 2. For BNT162b2 dose levels of 10, 20 and 30 µg tended to induce higher CD4 and CD8 T cell responses that the lower dose levels. In some individuals, (3/9 for the 30 µg dose) CD8+ T cell responses to sequences in the S-protein peptide pool 2 prior to vaccination were detected indicating pre-formed cross-reactive T cells recognizing conserved epitopes in the SARS-CoV-2 spike protein.

Figure 5: Frequency and magnitude of BNT162b2-induced CD4+ and CD8+ T-cell responses across all dose levels



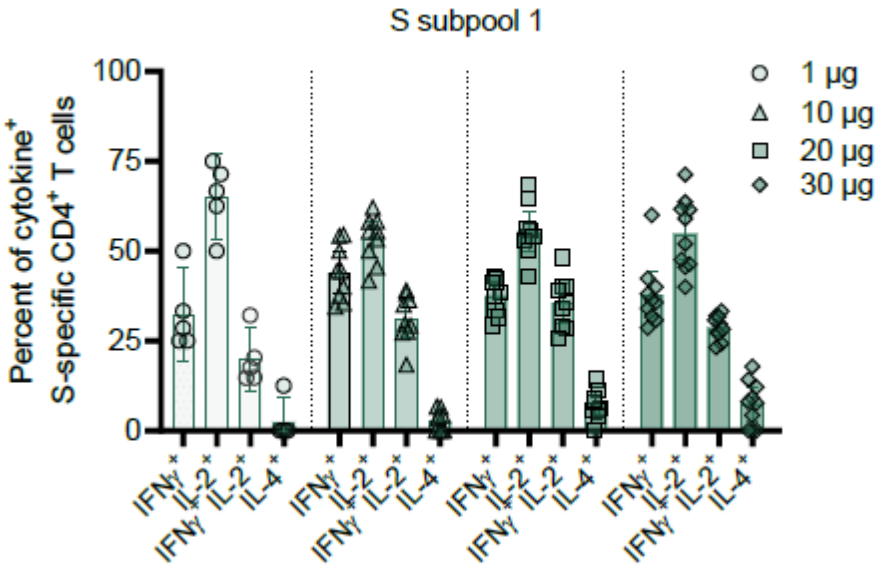
ex vivo INFγ ELISpot. Common pathogen T-cell epitope pools CEF (CMV, EBV, influenza virus HLA class I epitopes) and CEFT (CMV, EBV, influenza virus, tetanus toxoid HLA class II epitopes) served to assess general T-cell reactivity, cell culture medium served as negative control. Each dot represents the sum of normalised mean spot count from duplicate wells stimulated with two peptide pools corresponding to the full length of the wild type S protein for one participant, after subtraction of the medium-only control. ***a****, Ratios above post-dose data points are the number of subjects with detectable CD4+ or CD8+ T-cell response within the total number of tested participants per dose level.* ***b****, S protein-specific CD4+ and CD8+ T-cell responses in all participants with a positive response to S protein (n=22 for CD4+ and n=19 for CD8+ responses) and their baseline CEFT- and CEF-specific T-cell responses. Horizontal lines represent the median of each dose level.*
CMV = Cytomegalovirus; CEF and CEFT = epitope pools; EBV = Epstein-Barr-Virus; ELISpot = enzyme-linked immuno-spot; FL-S = Full-length spike protein; HLA = human leukocyte antigen; INF = interferon.

Most participants show a modest increase in cytokine-producing antigen-specific T cells reaching levels comparable to the levels observed in convalescent COVID-19 patients as measured by intracellular cytokine staining. A few outliers with a higher than average increase in cytokine-producing T cells skew the response above the levels observed in samples from convalescent COVID-19 patients.

There is high variability in the response as probably is to be expected but not much of a dose response between the 10, 20 and 30 µg groups for participants receiving BNT162b2.

The detection of IFNγ and IL-2, but only minor IL-4 production is reassuring, indicating a favourable Th1 profile.

Figure 6: S-specific CD4+ T cells producing the indicated cytokine in response to S protein sub-pool 1 as a fraction of total cytokine-producing S-specific CD4+ T cells



IV.4 Clinical efficacy

The clinical efficacy is supported by the phase 2/3 of the ongoing pivotal study C4591001, a multicentre, multi-national, randomised, placebo-controlled, observer-blind trial to evaluate the safety, tolerability and efficacy of BTN162b2 against COVID-19 in healthy individuals.

Methods

Study participants were subjects ≥ 12 years of age (with at least 40% > 55 years of age); healthy or with pre-existing stable disease; at higher risk of acquiring COVID-19 (e.g. use of mass transportation, relevant demographics, frontline essential workers). The main causes for exclusion were a previous clinical or microbiological diagnosis of COVID-19, a known or suspected immunodeficiency, therapy with immunosuppressants, pregnancy or breastfeeding.

Subjects with a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g. anaphylaxis) to any component of the study intervention(s) were also excluded from the study.

The primary objective was to evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of SARS-CoV-2 infection before vaccination and in all participants (with and without evidence of infection before vaccination). One key secondary objective was to evaluate the efficacy against confirmed severe COVID-19 in the same populations. The presence of SARS-CoV-2 infection was determined on the basis of a positive nasal swab using a nucleic acid amplification test (NAAT) and/or a serum sample positive for N-binding antibodies.

Subjects were randomised in a 1:1 ratio to BNT162b2 vaccine (2 doses of 30 μg by intramuscular injection into the deltoid muscle separated by 21 days) or a placebo (2 doses of 0.9% sodium chloride solution for injection) A site-based randomisation was stratified by age (≤55 vs >55 years). In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the test products were unblinded but all other study and site personnel, including the investigator, staff, and participants, were blinded to study product assignment.

The first primary endpoint was the incidence of confirmed COVID-19 per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of SARS-CoV-2 infection. The second primary endpoint was identical except the incidence was calculated in all participants (with and without evidence of SARS-CoV-2 infection up to 7 days after receipt of the last dose). Confirmed COVID-19 was defined as the presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive test during, or within 4 days before or after, the symptomatic period: 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; vomiting.

Confirmed severe COVID-19 was defined as confirmed COVID-19 and the presence of at least 1 of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute; SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg); respiratory failure; shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; death.

All participants were provided with a thermometer and asked to complete a COVID-19 illness e-diary. If a participant developed acute respiratory illness symptoms (or other specified symptoms), they were instructed to contact the site, and a COVID-19 illness and subsequent convalescent visit occurred. A nasal swab was taken for SARS-CoV-2 antigen. All potential COVID-19 illness events were reviewed by 3 blinded case reviewers.

The statistical analysis of vaccine efficacy (VE) used a Bayesian approach, with decisions based on the posterior probability of VE > 30%. With assumptions of a true VE of 60% after the last dose of investigational product, a total of approximately 164 first confirmed COVID-19 cases provide approximately 90% power to conclude true VE >30% with high probability. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomised in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection.

The primary analysis set was the Evaluable efficacy (7 days), defined as all eligible randomised participants who received all vaccination(s) as randomised, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. A secondary analysis set was the Evaluable efficacy (14 days), which was defined in a similar way and used for analyses of efficacy 14 days after Dose 2.

VE was estimated using the formula 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group.

The posterior probability (P[VE >30%|data]) was computed using a beta-binomial model and a specified minimally informative beta distribution as prior. Missing efficacy data were not imputed. The 2-sided 95% confidence interval for VE was derived using the Clopper-Pearson method as described by Agresti (the exact method).

Four interim analyses (IA) were initially planned and were to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. For administrative reasons the first interim analysis was removed in a protocol amendment. At these IAs, futility and VE with respect to the first primary endpoint were to be assessed.

Results

The study enrolled participants in the USA, Argentina, Brazil, Germany, South Africa and Turkey. The date of first subject first visit of the phase 1 of the study occurred on 29 April 2020.

The first efficacy interim analysis was performed after 94 COVID-19 cases had accrued and the data cut-off for this analysis was 4 November 2020, by which point 43325 participants had been randomised in the phase 2/3 (21653 BNT162b2 vs 21672 placebo). The pre-specified criterion for overwhelming efficacy was met; the posterior probability that VE>30% was >0.9999, higher than the success threshold of 0.995 required to declare overwhelming efficacy at an interim analysis. The point estimate for VE was 95.5% with a 95% credible interval ranging from 88.8 to 98.4%.

The second and final analysis was performed after 170 COVID-19 cases had accrued and the data cut-off for this analysis was 14 November 2020, by which point 43651 participants had been randomised (21823 BNT162b2 vs 21828 placebo).

Only the data relevant to the final analysis are described here.

<u>Study population</u>

Table 4: Participant disposition

	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.

The study enrolled about half male and half female participants (Table 4). These were mainly White (83%), with a small proportion of Black or African American (9%). The vast majority of the recruitment was in the US (77%), followed by Argentina (14%) and Brazil (7%). As site-based randomisation was used to ensure balance of vaccine group assignment within each site, vaccine allocation was balanced within countries.

The population included a very small number of children and adolescents 12 to 15 years old (88; 0.2%), a larger number of adolescents 16-17 year old (283; 0.8%) and 22% (N=8018) elderly subjects ≥ 65 years, up to 91 years (89 years in the vaccine arm). The median age was 52 years.

Overall, 46% of the participants had at least one comorbidity that increases the risk of severe COVID-19 disease: e.g. asthma, BMI ≥ 30 kg/m2, chronic pulmonary disease, diabetes mellitus, hypertension; 35% of the participants were obese and another 35% were

overweight. The demographics were well-balanced across the vaccine and placebo arms (Table 5).

Table 5: Demographic 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)

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, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

Primary efficacy endpoint

Out of the 170 COVID-19 cases, 8 were reported in the vaccine arm and 162 in the placebo arm (Table 6). The pre-specified criterion for success was met; the posterior probability that VE>30% was >0.9999, higher than the success threshold of 0.986 required to declare success at the final analysis. The point estimate for VE was 95.0% with a 95% credible interval ranging from 90.3-97.6%. The 95% confidence interval ranged from 90.0-97.9%.

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

	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

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.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
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. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Similar results were observed in the all-available efficacy population, which included subjects who did not receive Dose 2 within the predefined window (within 19-42 days after Dose 1) or had another important protocol deviation on or before 7 days after Dose 2. Three additional COVID-19 cases were reported in the placebo arm but none in the vaccine arm.

Similar results were also shown in the all-comer population (second primary endpoint), including all participants with and without evidence of SARS-CoV-2 infection up to 7 days after receipt of the last dose; the VE was 94.6% with a 95% credible interval ranging from 89.9 to 97.3%.

The results were consistent across various subgroups, with VE>90% in almost all analyses, and the confidence interval lower bounds demonstrated efficacy independently in all subgroups including subjects ≥ 65 years, Black/African American subjects, obese subjects and subjects at risk due to comorbidities.

Secondary efficacy endpoints

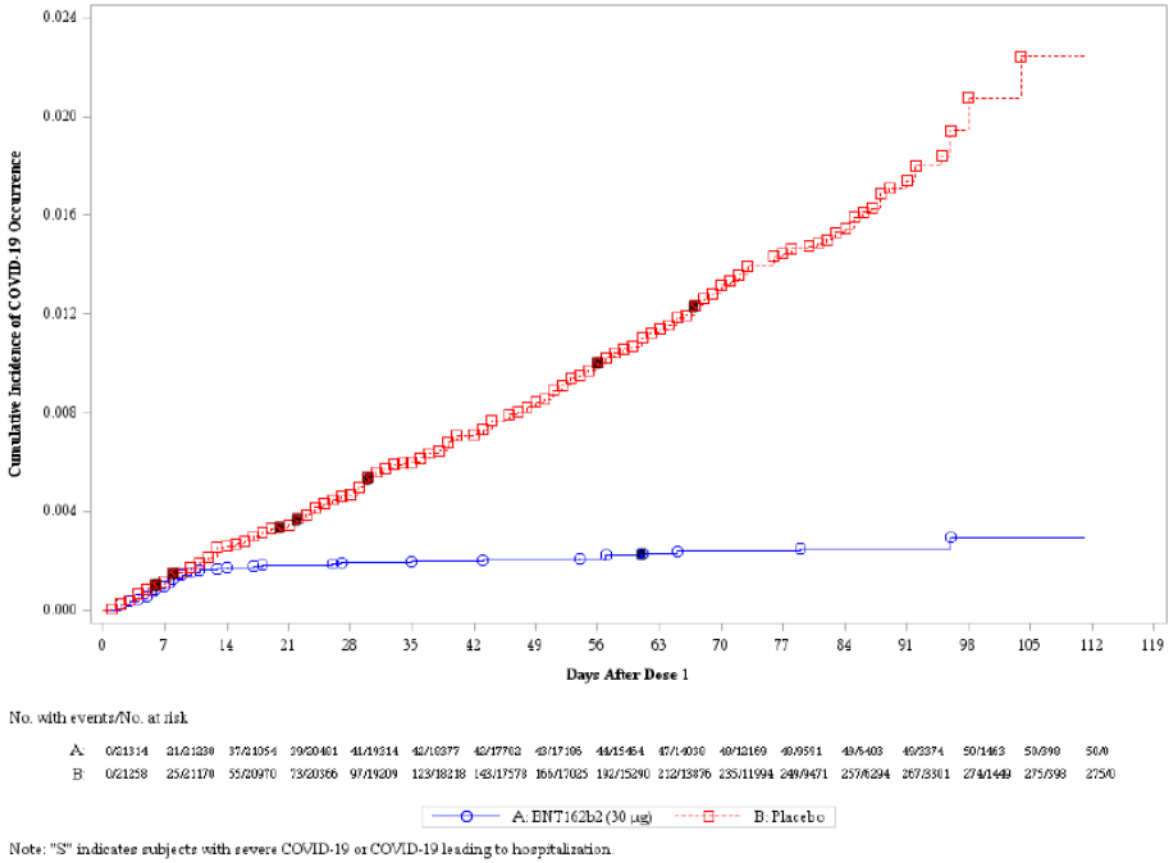
The first two secondary endpoints included only cases observed from 14 days after Dose 2 in populations comparable to those of the primary endpoints. In subjects without evidence of infection prior to 14 Days after Dose 2, VE was 94.2% with a 95% credible interval of 88.7 to 97.2%; similar results were shown in subjects with or without evidence of prior infections.

The total number of severe cases in the Evaluable efficacy population (7 days) of subjects without evidence of infection prior to 7 Days after Dose 2 is very small: 1 in the vaccine arm vs 3 in the placebo arm (VE = 66.4% with a broad 95% credible interval of -124.8 to 96.3%). However, considering all cases after the first dose (1 vs 9 cases, respectively) also provides evidence of an effect on severe cases (VE = 88.9% with a 95% confidence interval ranging from 20.1 to 99.7%).

Additional analysis

The early onset of protection is illustrated in the figure below, which displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants. Disease incidence is similar in the vaccine and placebo arms until approximately 12 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo arm while remaining virtually flat in the vaccine arm.

Figure 7: Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.

IV.5 Clinical safety

Safety population and exposure

Clinical safety data were submitted from the Phase 2/3 part of study c4591001. Non-serious adverse events (AEs) were actively elicited until 1 month after Dose 2. Serious AEs (SAEs) will be actively elicited until 6 months after Dose 2. AEs and SAEs will be collected as appropriate until 24 months after Dose 2. In the Phase 2/3 part, 43,448 participants had received at least one dose of study intervention, of which 21,720 participants had received at least one 30 µg dose of BNT162b2. Of the Phase 2/3 safety population, 34,532 participants had at least one month of safety follow-up post-Dose 2 (17,274 participants received BNT162b2) and 19,067 participants had at least 2 months of safety follow-up post-Dose 2 (9531 received BNT162b2). In addition, safety data were submitted from the Phase 1 study BNT162-01 and the Phase 1 part of Study c4591001; a total of 36 participants received at least one 30 µg dose of BNT162b2 during Phase 1. The baseline demographic characteristics of the safety population are presented below in Table 7.

Table 7: Demographic characteristics – Phase 2/3 (All Subjects) - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=21720) n[b] (%)	**Placebo (N[a]=21728) n[b] (%)**	**Total (N[a]=43448) n[b] (%)**
Sex			
Male	11183 (51.5)	10942 (50.4)	22125 (50.9)
Female	10537 (48.5)	10786 (49.6)	21323 (49.1)
Race			
White	17839 (82.1)	17857 (82.2)	35696 (82.2)
Black or African American	2091 (9.6)	2107 (9.7)	4198 (9.7)
American Indian or Alaska native	160 (0.7)	159 (0.7)	319 (0.7)
Asian	934 (4.3)	930 (4.3)	1864 (4.3)
Native Hawaiian or other Pacific Islander	57 (0.3)	31 (0.1)	88 (0.2)
Multiracial	536 (2.5)	514 (2.4)	1050 (2.4)
	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=21720) n[b] (%)	**Placebo (N[a]=21728) n[b] (%)**	**Total (N[a]=43448) n[b] (%)**
Not reported	103 (0.5)	130 (0.6)	233 (0.5)
Ethnicity			
Hispanic/Latino	5672 (26.1)	5668 (26.1)	11340 (26.1)
Non-Hispanic/non-Latino	15928 (73.3)	15940 (73.4)	31868 (73.3)
Not reported	120 (0.6)	120 (0.6)	240 (0.6)
Country			
Argentina	2883 (13.3)	2881 (13.3)	5764 (13.3)
Brazil	1452 (6.7)	1448 (6.7)	2900 (6.7)
Germany	249 (1.1)	250 (1.2)	499 (1.1)
South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Turkey	249 (1.1)	249 (1.1)	498 (1.1)
USA	16486 (75.9)	16501 (75.9)	32987 (75.9)
Age group			
16-55 Years	12780 (58.8)	12822 (59.0)	25602 (58.9)
>55 Years	8940 (41.2)	8906 (41.0)	17846 (41.1)
Age at vaccination (years)			
Mean (SD)	50.1 (15.68)	49.9 (15.78)	50.0 (15.73)
Median	51.0	51.0	51.0
Min, max	(16, 89)	(16, 91)	(16, 91)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	247 (1.1)	275 (1.3)	522 (1.2)
Normal weight (≥18.5 kg/m^2 - 24.9 kg/m^2)	6363 (29.3)	6357 (29.3)	12720 (29.3)
Overweight (≥25.0 kg/m^2 - 29.9 kg/m^2)	7614 (35.1)	7513 (34.6)	15127 (34.8)
Obese (≥30.0 kg/m^2)	7488 (34.5)	7575 (34.9)	15063 (34.7)
Missing	8 (0.0)	8 (0.0)	16 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Data for subjects randomized on or after 10OCT2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

In the subgroup > 55 years of age, the median age was 65 years. Data on baseline co-morbidities were also submitted according to the Charlson Comorbidity Index. Around 21% of the safety population had any co-morbidity, including diabetes (8.4%), chronic pulmonary disease (7.8%) and any malignancy (3.7%).

Baseline SARS-CoV-2 positive status was defined as having a positive N-binding antibody test result or positive nucleic acid amplification test (NAAT) result on the day of Dose 1. A total of 1125 participants in Phase 2/3 were identified as baseline SARS-CoV-2 positive, of which 545 received BNT162b2 and 580 received placebo.

The baseline characteristics of the safety population are sufficiently generalisable to the UK population.

The safety population, exposure and length of follow-up are acceptable for authorisation for temporary supply under Regulation 174. Safety data corresponding to longer follow-up will be submitted as laid out in the Risk Management Plan (RMP).

Local and systemic reactogenicity

Local and systemic reactogenicity data were planned to be collected by e-diary for at least the first 6000 participants enrolled in Phase 2/3. The final subset included 8214 participants, of whom 4108 had received BNT162b2. E-diary transmission rates were above 90% in the BNT162b2 arm for each of the 7 days post-Dose 1, and above 80% for each of the 7 days post-Dose 2 (except the day of Dose 2 which was 76%).

Local reaction events were solicited for up to 7 days following each dose according to FDA criteria (Table 8):

Table 8: Local reaction grading scale (FDA criteria)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

Table 9: Local Reactions, by Maximum Severity, Within 7 Days After Any 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])
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)
		BNT162b2 (30 µg)			Placebo		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	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.

The commonest local reaction (Table 9) was pain, reported by more than 84% of the reactogenicity subset after BNT162b2, and mostly mild or moderate. The frequencies of local reactions were similar after Doses 1 and 2. The median onset of the solicited local reactions was the day of vaccination until 2 days post-Dose, and the median duration was 1 to 2 days.

The local reactogenicity results were analysed by age (16-55 years; >55 years). The profiles were generally similar. However, the frequency of moderate pain after any dose was increased for younger participants compared to older participants (40.4% vs 23.6%). Local reactions were also solicited in 100 participants aged 12 to 15 years: 48 participants after Dose 1 and Dose 2 of BNT162b2 and 52 participants after Dose 1 and Dose 2 of placebo. The available local reactogenicity profile in the aged 12 to 15 years group was consistent with that observed in the 16 to 55 years group.

The reactogenicity subset included 318 baseline SARS-CoV-2 positive participants of whom 154 received BNT162b2 and 164 received placebo. The local reactogenicity profile in this subgroup was consistent with that of the overall reactogenicity subset.

Based on the local reactogenicity data, the following local reactions are considered to be adverse drug reactions (ADRs) and have been included in the Information for Healthcare

Professionals and the Information for UK recipients: Injection site pain (very common), injection site swelling (common) and injection site erythema (common).

Systemic events were solicited for up to 7 days following each dose according to FDA criteria (Table 10):

Table 10: Systemic event grading scale (FDA criteria)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

In addition, participants took their own oral temperature daily (and additionally when fever was suspected) during the 7-day reporting period. Fever was defined as follows: Mild (38.0 to 38.4°C); Moderate (>38.4 to 38.9°C); Severe (>38.9 to 40.0°C) and Grade 4 (> 40.0°C). The use of antipyretic or pain medication was also documented.

Table 11: Systemic Events, by Maximum Severity, Within 7 Days After Any 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])
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)
	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)

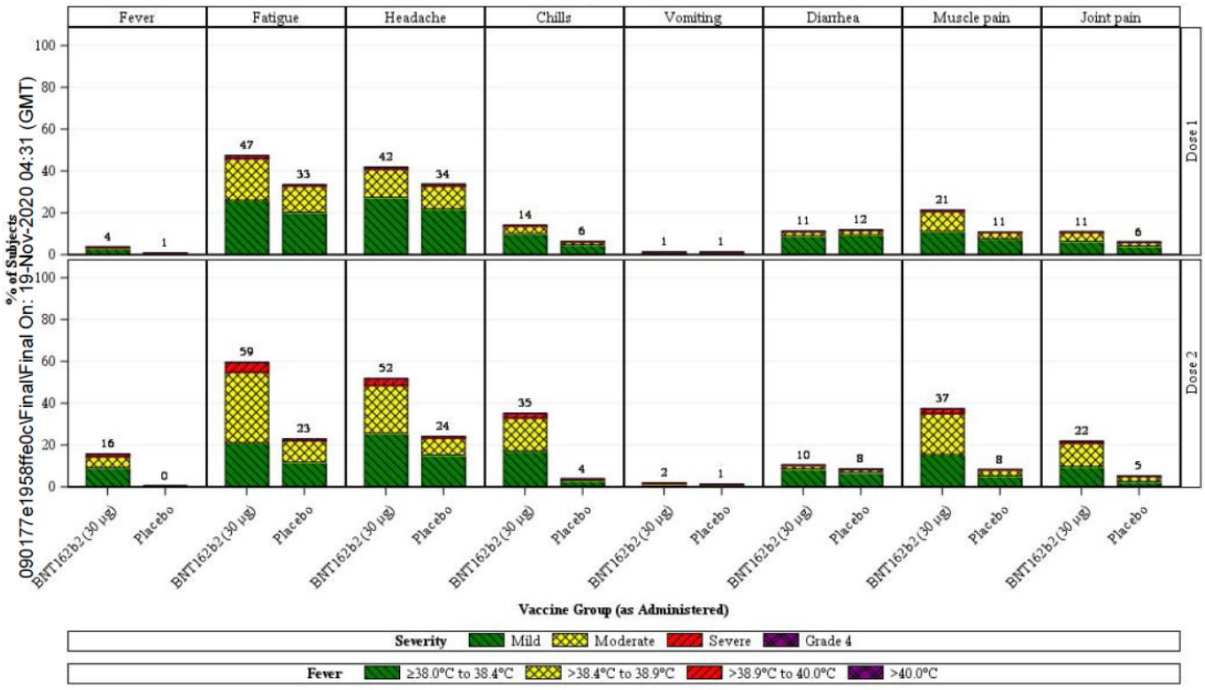
Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose. Grade 4 events were classified by the investigator or medically qualified person.

a. N = number of subjects reporting at least 1 yes or no response for the specified event 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: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.

Apart from vomiting and diarrhoea, all the solicited systemic events were reported significantly more frequently after BNT162b2 compared to placebo. Anti-pyretic or pain medication was also used more often. The median onset for most systemic events after either dose of BNT162b2 was 1 to 2 days post-Dose and median duration was one day.

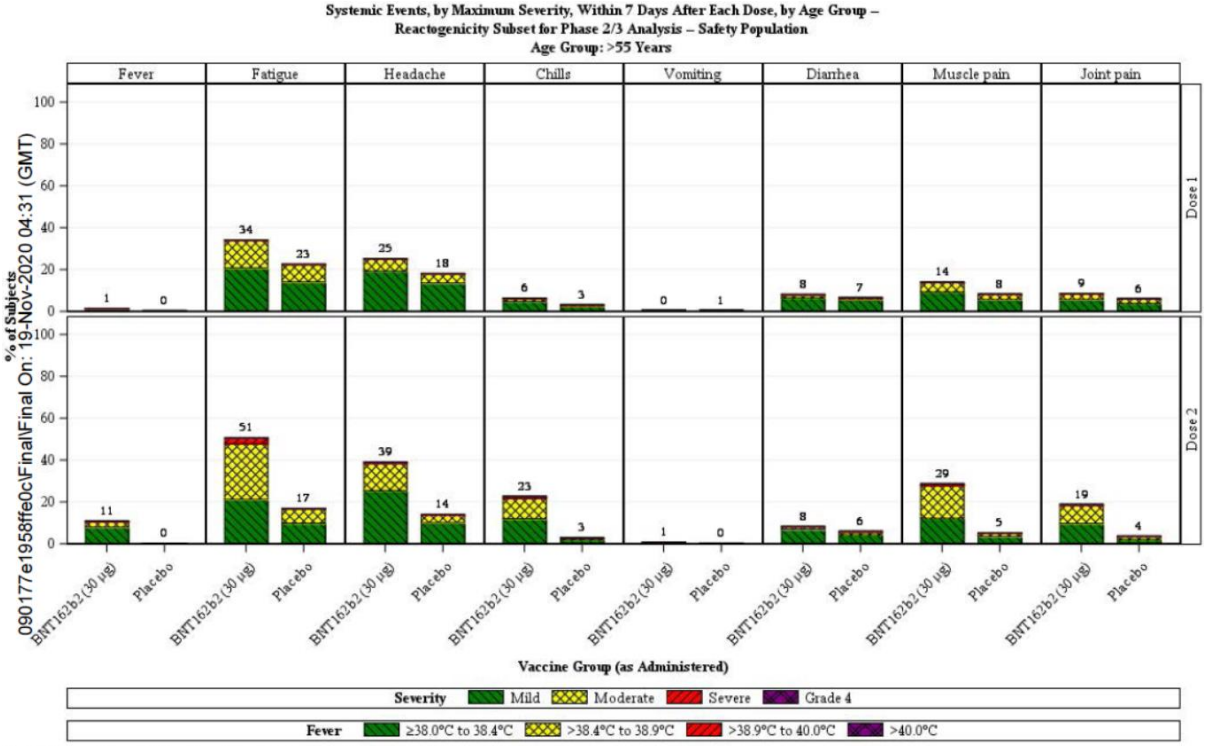
The systemic reactogenicity results were analysed by age (16-55 years; >55 years). The frequency and severity of systemic events were increased in the younger group compared to the older group, and post-Dose 2 compared to post-Dose 1 as shown below:

Figure 8: 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.

Figure 9: 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.

Systemic reactogenicity events were also solicited in 100 participants aged 12 to 15 years, 48 participants after Dose 1 and Dose 2 of BNT162b2 and 52 participants after Dose 1 and Dose 2 of placebo. The available systemic reactogenicity profile in the aged 12 to 15 years group was consistent with that observed in the 16 to 55 years group.

The reactogenicity subset included 318 baseline SARS-CoV-2 positive participants of whom 154 received BNT162b2 and 164 received placebo. The systemic reactogenicity profile in this subgroup was consistent with that of the overall reactogenicity subset.

Based on the systemic reactogenicity data, the following systemic events are considered to be ADRs and have been included in the Information for Healthcare Professionals and the Information for UK recipients: headache, myalgia, arthralgia, fatigue, chills and pyrexia (all very common).

Adverse events

An adverse event (AE) was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. A summary of adverse events (AEs) is shown below:

Table 12: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020) – Phase 2/3 (All Subjects) - Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=21621)	Placebo (N[a]=21631)
Adverse Event	n[b] (%)	n[b] (%)
Any event	5770 (26.7)	2638 (12.2)
Related[c]	4484 (20.7)	1095 (5.1)
Severe	240 (1.1)	139 (0.6)
Life-threatening	21 (0.1)	24 (0.1)
Any serious adverse event	126 (0.6)	111 (0.5)
Related[c]	4 (0.0)	0
Severe	71 (0.3)	68 (0.3)
Life-threatening	21 (0.1)	23 (0.1)
Any adverse event leading to withdrawal	37 (0.2)	30 (0.1)
Related[c]	16 (0.1)	9 (0.0)
Severe	13 (0.1)	9 (0.0)
Life-threatening	3 (0.0)	6 (0.0)
Death	2 (0.0)	4 (0.0)

Note: Data for subjects randomized on or after 10OCT2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.

AE data are also provided for the safety population of 37,586 participants with a median of 2 months follow-up after Dose 2, and 19,067 participants with at least 2 months follow-up after Dose 2. The AE summary profiles in these populations were consistent with that of the 'All subjects' population. This suggests that most of the related AEs occurred soon after vaccination. AE summary profiles were provided by age (16-55 years; >55 years); AEs were

reported more frequently in the younger group than the older group, with a greater difference after BNT162b2 compared to after placebo: 28.8% vs 12.6%. This reflects the reactogenicity profile. For the subgroup of Black or African American participants (9.1%), the AE summary profile was consistent with that of the overall safety population.

AE data were evaluated at the preferred term level, and with reference to AE listings which included information on onset, duration, severity, seriousness, relatedness and resolution, as well as investigator free text. AEs by System Organ Class (SOC) are summarised below:

Table 13: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020), by System Organ Class – Phase 2/3 (All subjects) - Safety Population

System Organ Class	Vaccine group (as administered)	
	BNT162b2 (30 µg) (N = 21621) n (%)	Placebo (N = 21631) n (%)
Any event	5770 (26.7)	2638 (12.2)
Blood and lymphatic system disorders	90 (0.4)	17 (0.1)
Cardiac disorders	52 (0.2)	44 (0.2)
Congenital, familial and genetic disorders	2 (0.0)	0
Ear and labyrinth disorders	61 (0.3)	41 (0.2)
Endocrine disorders	12 (0.1)	4 (0.0)
Eye disorders	54 (0.2)	44 (0.2)
Gastrointestinal disorders	617 (2.9)	403 (1.9)
General disorders and administration site conditions	4007 (18.5)	829 (3.8)
Hepatobiliary disorders	14 (0.1)	5 (0.0)
Immune system disorders	26 (0.1)	22 (0.1)
Infections and infestations	322 (1.5)	320 (1.5)
Injury, poisoning and procedural complications	184 (0.9)	220 (1.0)
Investigations	145 (0.7)	40 (0.2)
Metabolism and nutrition disorders	86 (0.4)	61 (0.3)
Musculoskeletal and connective tissue disorders	1511 (7.0)	435 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (0.1)	31 (0.1)
Nervous system disorders	1277 (5.9)	501 (2.3)
Pregnancy, puerperium and perinatal conditions	0	2 (0.0)
Product issues	1 (0.0)	1 (0.0)
Psychiatric disorders	84 (0.4)	58 (0.3)
Renal and urinary disorders	30 (0.1)	24 (0.1)
Reproductive system and breast disorders	35 (0.2)	36 (0.2)
Respiratory, thoracic and mediastinal disorders	187 (0.9)	169 (0.8)
Skin and subcutaneous tissue disorders	196 (0.9)	136 (0.6)
Social circumstances	3 (0.0)	0
Surgical and medical procedures	29 (0.1)	21 (0.1)

Uncoded term	38 (0.2)	23 (0.1)
Vascular disorders	65 (0.3)	69 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: Data for subjects randomised on or after 10OCT2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.
N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event", n = number of subjects reporting at least 1 occurrence of any event.

The imbalance in the SOC of *Blood and lymphatic system disorders* was driven by lymphadenopathy events, reported by 70 (0.3%) participants after BNT162b2 vs 7 (0.0%) after placebo. Most events were transient and non-serious. Lymphadenopathy is known to be associated with vaccines and is related to the immune response. In the non-clinical rat repeat dose toxicity studies, there was enlargement of the draining lymph nodes at the end of dosing. Lymphadenopathy has been included as an ADR in the Information for Healthcare Professionals and the Information for UK recipients with a frequency of uncommon.

The imbalance in the SOC of *Gastrointestinal disorders* was driven by nausea events, reported by 238 (1.1%) participants after BNT162b2 vs 75 (0.3%) after placebo. Nausea has been included as an ADR in the Information for Healthcare Professionals and the Information for UK recipients with a frequency of common.

The imbalance in the SOC of *General disorders and administration site conditions* was driven by the following events: injection site pain, fatigue, pyrexia, chills, pain, injection site erythema, injection site swelling and malaise. Based on the local and systemic reactogenicity data (see above under ‘Local and systemic reactogenicity’) the following events from this SOC are considered ADRs: Injection site pain (very common), fatigue (very common), chills (very common), pyrexia (very common), injection site swelling (common) and injection site erythema (common). These events have been included as ADRs in the Information for Healthcare Professionals and the Information for UK recipients. Malaise was reported by 104 (0.5%) participants after BNT162b2 vs 18 (0.1%) after placebo and is included as an ADR in the Information for Healthcare Professionals and the Information for UK recipients with a frequency of uncommon.

The imbalances in the SOCs of *Musculoskeletal and connective tissue disorders* and *Nervous system disorders* are driven by myalgia, arthralgia and headache. These are considered ADRs and are included in the Information for Healthcare Professionals and the Information for UK recipients at frequencies that correspond to the solicited systemic reactogenicity events.

Within the SOC of *Immune system disorders*, six participants reported Drug hypersensitivity after BNT162b2 compared to one after placebo. One participant reported Drug hypersensitivity and Urticaria on the day of Dose 1 of BNT162b2; both events were of moderate severity and lasted one day. Another participant reported a Drug hypersensitivity event 23 days after Dose 1 of BNT162b2. The other five Drug hypersensitivity events were documented by investigators as reactions to other drugs. Five participants reported Immunisation reactions after BNT162b2 compared to none after placebo; all were associated with other systemic reactogenicity events and none were associated with events that would indicate hypersensitivity. Post -authorisation monitoring for hypersensitivity events will be conducted.

Severe events were reported by 240 (1.1%) participants after vaccination with BNT162b2 compared to 139 (0.6%) participants after placebo arm. The imbalance in the proportion of

participants reporting at least one severe AE was driven by the SOCs of *General disorders and administration site conditions*, *Musculoskeletal and connective tissue disorders* and *Nervous system disorders*, and within these SOCs, the events of pyrexia, fatigue, injection site pain, chills, pain, myalgia and headache. These AEs reflect the local and systemic reactogenicity profile and are considered ADRs. The proportion of participants who reported at least one Grade 4 (life-threatening) AE was low and balanced between the treatment groups: 21 (0.1%) after BNT162b2 vs 24 (0.1%) after placebo. After evaluation, no specific concerns were raised.

Immediate AEs were those collected within 30 minutes hours after administration. Immediate AEs were reported after Dose 1 by 101 (0.5%) participants after BNT162b2 vs 77 (0.4%) after placebo. Immediate AEs were reported after Dose 2 by 57 (0.3%) participants after BNT162b2 vs 46 (0.2%) after placebo. The predominant immediate event was injection site pain. No participant reported an immediate allergic reaction after either dose of BNT162b2.

The safety population included 1125 baseline SARS-CoV-2 positive participants of whom 545 received BNT162b2 and 580 received placebo. On comparison of AE data with that of the 'All subjects', there is no indication of a worse safety profile in baseline positive participants.

Serious adverse events

A serious adverse event (SAE) was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention, that resulted in death, was life-threatening, required inpatient hospitalisation, resulted in persistent disability/incapacity or was a congenital abnormality/birth defect. SAE reporting may have also been appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

Two deaths were reported in participants that received BNT162b2 in Phase 2/3 of study c4591001; narratives were provided. A participant died 3 days after Dose 1; the provisional cause of death was atherosclerotic disease. A participant experienced cardiac arrest 60 days after Dose 2 and died 3 days later. There were 4 deaths in participants that received placebo in Phase 2/3. There were no deaths during study BNT162-01 or phase 1 of study c4591001.

During Phase 2/3 of study c4591001, SAEs were reported by 126 (0.6%) participants after BNT162b2 compared to 111 participants (0.5%) after placebo. SAE data were evaluated at the preferred term level, and with reference to AE listings which included information on onset, duration, severity, relatedness and resolution, as well as investigator free text. There was one SAE of anaphylaxis 9 days after Dose 2 of BNT162b2; this was due to a bee sting. No significant concerns are raised. On comparison of SAE data of baseline SARS-CoV-2 positive participants with the 'All subjects' SAE data, there is no indication of a worse safety profile in baseline positive participants.

Laboratory findings

Routine laboratory testing of haematology and clinical chemistry parameters was only conducted for Study BNT162-01 and Phase 1 of study c4591001. Transient increases in C-reactive protein and transient decreases in lymphocyte count were observed in a dose

dependant manner, and no clinical impact was observed. These effects are related to the mode of action of the vaccine. No related investigational AEs were reported during Phase 2/3.

Safety in special populations

Pregnancy is reported for a total of 23 participants during study c4591001; no outcome data are available. The results of the non-clinical developmental and reproductive toxicity study will not be available until early 2021. Therefore, BNT162b2 is not recommended during pregnancy. However, use in women of childbearing potential can be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination. As a precautionary measure, women of childbearing potential are advised to avoid becoming pregnant until at least 2 months after vaccination.

It is unknown whether BNT162b2 is excreted in breast milk. Therefore, it is recommended that BNT162b2 should not be administered to women who are breastfeeding. Information for Healthcare Professionals and the Information for UK recipients reflect these recommendations. Use in pregnancy and lactation is included as missing information in the RMP. Use in pregnancy will be investigated as part of the pharmacovigilance plan.

Adolescents aged 16 to 17 years were eligible for Study c4591001 following protocol amendment 6, and adolescents aged 12 to 15 years were eligible for Study c4591001 following protocol amendment 7. The safety population included 283 participants aged 16 to 17 years. Furthermore, the reactogenicity profile was characterised in 100 participants aged 12 to 15 years, the results of which can be extrapolated to adolescents aged 16 to 17 years. These data support use in recipients over 16 years of age.

Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or were planned to receive such treatment, were not eligible for inclusion in Study c4591001. Although 120 participants with HIV were included in the phase 3 part of Study c4591001, analyses of safety are not yet available for this subgroup. Use in immunosuppressed individuals will be investigated as part of the pharmacovigilance plan.

Safety related to interactions

No data are available on use with concomitant vaccines, including influenza vaccines. According to the protocol for Study c4591001, administration of vaccine or placebo was not permitted within 14 days before or after influenza vaccines, or within 28 days before or after other non-study vaccines.

Discontinuations due to adverse events

During the phase 2/3 part of Study c4591001, 37 (0.2%) participants were discontinued due to adverse events after at least one dose of BNT162b2 compared to 30 (0.1%) participants after at least one dose of placebo. Evaluations of AEs that resulted in discontinuation raise no significant concerns.

IV.6 Risk Management Plan (RMP)

Every new medicine that is authorised has a Risk Management Plan (RMP) in place to ensure

the medicine is used as safety as possible. An RMP details important risks for the medicine and how more information can be obtained about these. This includes important identified risks which have been demonstrated to be associated with the medicine and require additional measures as part of the authorisation to minimise any potential risk to users. Important potential risks are those where there is a potential association with the product but that this has not been confirmed and further information needs to be collected to establish whether this risk exits. Missing information topics are typically those which have not been fully evaluated in the clinical trials and are relevant to the use of the product and require further information to be gathered.

The following section describes the RMP that has been agreed for the safe use of COVID-19 mRNA Vaccine BNT162b2. In addition to routine pharmacovigilance and risk minimisation measures, the MHRA has requested that all COVID-19 vaccines carry out further *ad hoc* pharmacovigilance activities specific to the pandemic situation. This includes more frequent safety signal detection with additional epidemiological analysis of potential safety signals and targeted safety events, frequent pharmacovigilance meetings with the MHRA, monthly pharmacovigilance safety update reports and batch specific surveillance.

In addition to these routine pharmacovigilance activities, the following additional risks and safety measures have been proposed:

Important identified risks	None
Important potential risks	Vaccine associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and lactation Vaccine effectiveness

There are no important identified risks for BTN162b2.

Vaccine associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD) has been included as a potential risk. This is a theoretical risk which is relevant to all COVID-19 vaccines based on VAED having been seen in animal models for vaccines developed for SARS-CoV-1 (a similar but not identical virus to SARS-CoV-2, the virus responsible for COVID-19) and also seen in association with use of another respiratory virus vaccine, the Respiratory syncytial virus (RSV) vaccine. There is currently no evidence from non-clinical or clinical data of an association of VAED/VAERD with COVID-19 mRNA Vaccine BNT162b2; this potential risk will be further investigated as part of the pharmacovigilance plan of this vaccine.

Use in pregnancy and lactation are included as missing information because this group was excluded from the clinical trials and further data needs to be collected on the safety and efficacy of this use.

Vaccine efficacy for BTN162b2 has been clearly demonstrated in clinical trials. Vaccine effectiveness relates to how well a vaccine works in the “real world” setting outside of clinical trials and being used in a wider variety of people. Therefore, long-term real-world data on vaccine effectiveness needs to be collected and this has been included as a missing information topic.

The following studies have been proposed to gather more information on these topics:

Study	**Country**	**Summary of Objectives**	**Safety concerns addressed**	**Status (Planned, Ongoing)**
C4591001 A Phase 1/2/3, placebo controlled, randomised, 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	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. Surveillance is planned for 2 years following Dose 2.	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)	*Ongoing*
C4591008 Post-Emergency Use Authorization Observational Cohort Study to evaluate the safety of SARS-COV-2 RNA Vaccine in Healthcare Workers: A primary data collection active surveillance study	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD) Use in Pregnancy and Lactation	Planned
C4591011 Safety Surveillance of the Pfizer COVID-19 Vaccine in the U.S. Department of Defence Population Following Emergency Use Authorization	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in a cohort of people within the Department of Defence Healthcare System	Safety events of interest including vaccine associated enhanced disease Use in Pregnancy and Lactation	Planned
C4591012 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	US	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 disease in real world use of COVID-19 mRNA vaccine	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD) Use in Pregnancy and Lactation	Planned

C4591010 A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of the Pfizer-BioNTech COVID-19 vaccine in the EU	EU	Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in real-world use of COVID-19 mRNA vaccine	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)	Planned
C4591015 A Phase 2/3, Placebo-Controlled, Randomised, 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	Not available	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine	Use in Pregnancy and Lactation	Planned
C4591014 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	EU, US	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	Planned
BNT162-01 Cohort 13 COVID-19 mRNA vaccine in immunocompromised subjects, including assessment of antibody responses and cell mediated responses	EU	To assess potentially protective immune responses in immunocompromised adults	Vaccine effectiveness	Ongoing
ACCESS/VAC4EU	EU	Planned non-interventional study	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)	Planned

IV.7 Discussion on the clinical aspects

Clinical Immunogenicity

Immunogenicity data for BNT162b2 in subjects aged 18-85 years of age are currently available up to 1 month after the second vaccine dose.

Humoral immunogenicity data from study BNT162-01 and phase 1/2 of study c4591001 show that BNT162b2 elicits robust SARS-CoV-2 neutralisation and S1-binding antibody responses at 1 month after dose 2. The neutralising titres and binding antibody concentrations are higher in younger subjects (18-55y) compared with the older subjects (56-85y). Nevertheless, neutralising GMTs for younger and older participants at 1 month after Dose 2 are comparable to the GMTs of a panel of SARS-CoV-2 infection/COVID-19 human convalescent serum.

Cell mediated immunity data are available from study BNT162-01 in a limited number of subjects aged 18-55 years. These indicate that antigen-specific CD4+ and CD8+ T cell responses are induced by the vaccine, with a favourable Th1 profile.

Longer-term antibody data at 6, 12 and 24 months after completion of vaccination (including analysis by baseline serostatus); and additional T-cell response data up to 24 months, including in older subjects, immunocompromised adults and HLA typing of the subjects are being collected. This is addressed via the RMP and proposed conditions for the Regulation 174 approval.

Clinical Efficacy

The results from the phase 2/3 of the pivotal trial support vaccine efficacy in the population most at risk of severe COVID-19 as reflected in the study population which comprises high proportions of subjects who are obese or overweight or have relevant comorbidities.

The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.

However, the current data do not address the following questions.

- Data on vaccine protection beyond 2-3 months are currently lacking. These will be generated as the study follow-up is continuing and in effectiveness studies as reflected in the RMP.

- Data in individuals above 75 years of age are limited (about 1500 in total, half vaccinated). In this subgroup, the VE estimate is 100% with a 95%CI lower bound of –13%, which reflects the current uncertainty around vaccine efficacy in this age group. This information will be generated in effectiveness studies as reflected in the RMP.

- Regarding COVID-19 cases, no viral genomic sequencing data of the isolated strains and no immunogenicity data in these vaccine failures are currently available. This will be addressed at a broader level by the COVID-19 Genomics UK (COG-UK) Consortium and in the follow-up immunogenicity report requested in the RMP.

- There are no data on concomitant immunisation, in particular influenza vaccination, or concomitant medications. Flu vaccination was prohibited 2 weeks before and 2 weeks after the study vaccination. In the safety database of the first 6610 participants, a small percentage of participants in either group (4-5%) received any concomitant vaccine after Dose 1, and most concomitant vaccines received were influenza vaccines (3-4%). Analyses of immunogenicity may be available in the future in subgroups defined by concomitant influenza vaccination as well as by concomitant immunosuppressive treatment, if any (RMP).

- There are no data in pregnant women and immunosuppressed patients as these subjects were excluded from the trial. These will be generated in effectiveness studies as reflected in the RMP.

- There are currently no data in adolescents (12 to 15 years old) as these have only been recently enrolled. These data will be submitted when available.

Clinical Safety

Clinical safety data are available from more than 43,000 participants aged over 16 years, of which more than 19,000 have been followed up for at least 2 months after Dose 2 of BNT162b2 or placebo. The baseline characteristics of the safety population are sufficiently generalisable to the UK population.

Local and systemic reactogenicity data were collected by e-diary for more than 8000 participants. The commonest local reaction was pain, mostly mild or moderate. The median onset of the solicited local reactions was the day of vaccination until 2 days post-Dose, and the median duration was 1 to 2 days. The commonest systemic events were fatigue, headache, chills and myalgia. Severity was mostly mild or moderate; antipyretic or pain medication was often needed. Systemic reactions were more frequent and severe in the 16 to 55 years age group. The median onset for most systemic events after either dose of BNT162b2 was 1 to 2 days post-Dose and median duration was one day.

At least one adverse event (AE) was reported by 27% of participants after BNT162b2 compared to 12% of participants after placebo. AEs were reported more frequently in the younger group (16 to 55 years) than the older group (>55 years), reflecting the reactogenicity profile. Lymphadenopathy, nausea and malaise were reported more frequently after BNT162b2 than placebo. Assessment of severe, life-threatening or immediate AEs raises no specific concerns. At present, there is no evidence that BNT162b2 is associated with hypersensitivity or anaphylaxis, but post-authorisation monitoring for these events will be conducted. No significant concerns are raised on assessment of serious AEs or AEs leading to discontinuation. AEs of special interest (AESIs) have been defined by MHRA for COVID-19 vaccines. Interrogation of the AE data did not identify any rare AESIs, or imbalances between treatment groups for incidences of more common AESIs.

The data to support safety in pregnancy are insufficient. Therefore, BNT162b2 is not recommended during pregnancy. However, use in women of childbearing potential can be supported provided healthcare professionals are advised to rule out known or suspected

pregnancy prior to vaccination. As a precautionary measure, women of childbearing potential are advised to avoid becoming pregnant until at least 2 months after vaccination.

The safety data support use in adults and adolescents aged 16 to 17 years.

The safety population included baseline SARS-CoV-2 positive participants defined as having a positive N-binding antibody test result or positive nucleic acid amplification test (NAAT) result on the day of Dose 1. There is no indication of a worse safety profile in baseline positive participants. Therefore, BNT162b2 can be used irrespective of COVID-19 history or SARS-CoV-2 serological status.

Based on the solicited local and systemic reactogenicity data, and the adverse event data, the following adverse drug reactions (ADRs) have been included in the Information for Healthcare Professionals and the Information for UK recipients:

- Very common (≥ 10%): injection site pain, fatigue, headache, myalgia, chills, arthralgia and pyrexia
- Common (≥ 1% to < 10%): injection site swelling, injection site erythema and nausea
- Uncommon (≥ 0.1% to < 1%): malaise and lymphadenopathy

The safety population, exposure and length of follow-up are acceptable for authorisation for temporary supply under Regulation 174. Safety data corresponding to longer follow-up will be submitted as laid out in the Risk Management Plan (RMP).

Overall conclusion on the clinical aspects

The data for BNT162b2 available to date are considered favourable. From a clinical aspect, based on the reviewed information, there is no objection to the temporary supply of BNT162b2 under a Regulation 174.

V USER CONSULTATION

Evaluation of the patient information for readability via a user consultation study is currently deferred in the context of emergency supply under a Regulation 174.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable in the context of batch specific release under Regulation 174. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of COVID-19 mRNA Vaccine BNT162b2 should be in accordance with official guidance.

The Information for UK Healthcare Professionals and the Information for UK recipients and labelling are satisfactory.

The Information for UK Healthcare Professionals and the Information for UK recipients for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
Extension of indication	Extension of indication to include patients aged 12 to 15 years.	Information for Healthcare Professionals on Pfizer/BioNTech COVID-19 vaccine; Information for UK recipients on Pfizer/BioNTech COVID-19 vaccine	4 June 2021	Granted	Y

Annex 1

Reference: PL 53632/0001
Product: COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection
Type of Procedure: National route
Submission category: Extension of indication

As well as the conditions of authorisation already in place for COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection**,** the extension of indication has the condition that Pfizer BioNTech must provide 6-month safety follow-up data in subjects aged 12-15 years from Study C4591001 once available.

Further data in 12-15-year olds will be gathered in existing post-authorisation safety and effectiveness studies, and the results of these will be provided to the MHRA for assessment.

Reason
Extension of indication to expand the target population to include adolescents 12-15 years of age.

Supporting evidence
Updated information for healthcare professionals (HCPs) and for UK recipients has been provided along with results from the pivotal Phase 1/2/3 study (C4591001), which has been amended to enrol adolescents 12–15 years of age.

Evaluation
The indication for COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection is active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. The posology is the same in adolescents and adults. BNT162b2 is administered intramuscularly after dilution as a series of two doses (0.3 mL each) at least 21 days apart.

The protocol of the Phase 1/2/3 study (C4591001), which provided the basis for the Regulation 174 and Conditional Marketing Authorisation of BNT162b2 vaccine in subjects aged ≥ 16 years, was amended in October 2020 to enrol adolescents 12–15 years of age in a separate age stratum (approximately 2,200 subjects). These participants were all enrolled in the US and most remain currently blinded. This report describes the immunogenicity results as well as efficacy and safety results with a data cut-off of 13-03-2021.

1. Clinical Immunogenicity

An immunogenicity objective was added to the study in order to demonstrate non-inferiority (NI) of the immune response to BNT162b2 in a subset of participants 12-15 years of age compared to a subset of participants 16-25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. This NI analysis was performed to provide immunobridging between these younger adolescents and young adults 16-25 years of age using a validated SARS-CoV-2 neutralisation assay.

Methods
A random sample of 280 participants who received BNT162b2 and 50 participants who received placebo was initially selected for each of the two age groups (660 participants in total) as a subset for immunogenicity assessment. The placebo participants were selected for serology testing to maintain blinding of the laboratory personnel. This sample size was originally estimated to provide a power of 90.4% to declare NI in the specified analysis. Immunogenicity analyses were finally performed on a set of participants who had the required tests completed using the same

available viral reagent lot for the neutralising assay. A blinded review of the samples tested at that time suggested a sufficient sample size properly balanced across age groups to perform the planned NI analysis. It was estimated that if the true geometric mean ratio (GMR) is ≥0.88, there was approximately 90% power to demonstrate NI and >99% power if the true GMR is 1. This approach was agreed with the US FDA.

Endpoints
The primary immunogenicity endpoint was the geometric mean titre (GMT) in each age group and the ratio (GMR) of 12-15 years group to 16-25 years group at 1 month after Dose 2. Other endpoints were the geometric mean-fold rise (GMFR) and percentage of participants with a ≥4-fold rise in neutralising titres (seroresponse) from before vaccination to 1 month after Dose 2 in each age group.

Statistical analysis
NI was assessed based on the GMR of SARS-CoV-2 neutralizing titres at 1 month after Dose 2 using a 1.5-fold margin. The GMR and its 2-sided 95% confidence interval (CI) were derived by calculating differences in means ([12-15 years of age] – [16-25 years of age]) and CIs on the natural log scale of titres based on Student's t-distribution, then exponentiating the results. NI was declared if the lower bound of the 2-sided 95% CI for the GMR was >0.67.
A supportive analysis was conducted to assess the seroresponse rate. The difference in percentages (12-15 years of age – 16-25 years of age) and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided.

Results

Data set analysed
The Dose 2 evaluable immunogenicity subset for adolescents 12-15 years of age included 209 participants in the BNT162b2 arm and 36 participants in the placebo arm, and the subset for young adults 16-25 years of age included 186 participants in the BNT162b2 arm and 32 participants in the placebo arm. The majority of exclusions were due to participants not having at least one valid and determinate immunogenicity result after Dose 2 and were generally balanced across age and vaccine groups.

Demographics
In the adolescent immunogenicity BNT162b2 arm, 51% of participants were male, most (88%) were White and the median age was 14 years. About 5% of participants were SARS-CoV-2 positive at baseline. Obese adolescents (based on age- and sex-specific body mass index) made up for 11.5% of this age group. Demographics were generally similar in BNT162b2 and placebo arms, and between adolescents and young adults 16-25 years of age (Table 1).

Table 1: Demographics (Immunogenicity Subset)

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N[a]=209) n[b] (%)	16-25 Years (N[a]=186) n[b] (%)	12-15 Years (N[a]=36) n[b] (%)	16-25 Years (N[a]=32) n[b] (%)
Sex				
Male	106 (50.7)	92 (49.5)	21 (58.3)	14 (43.8)
Female	103 (49.3)	94 (50.5)	15 (41.7)	18 (56.3)
Race				
White	184 (88.0)	147 (79.0)	31 (86.1)	28 (87.5)
Black or African American	16 (7.7)	15 (8.1)	3 (8.3)	2 (6.3)
American Indian or Alaska Native	1 (0.5)	3 (1.6)	0	1 (3.1)
Asian	5 (2.4)	10 (5.4)	1 (2.8)	1 (3.1)
Native Hawaiian or other Pacific Islander	0	3 (1.6)	0	0
Multiracial	3 (1.4)	6 (3.2)	1 (2.8)	0
Not reported	0	2 (1.1)	0	0
Age at vaccination (years)				
Mean (SD)	13.5 (1.12)	20.6 (3.09)	13.4 (1.17)	20.3 (3.05)
Median	14.0	21.0	13.0	19.5
Min, max	(12, 15)	(16, 25)	(12, 15)	(16, 25)
Baseline SARS-CoV-2 status				
Positive[c]	10 (4.8)	8 (4.3)	2 (5.6)	1 (3.1)
Negative[d]	194 (92.8)	178 (95.7)	33 (91.7)	31 (96.9)
Missing	5 (2.4)	0	1 (2.8)	0
Body mass index (BMI) Obese[e]				
Yes	24 (11.5)	43 (23.1)	3 (8.3)	4 (12.5)
No	185 (88.5)	143 (76.9)	33 (91.7)	28 (87.5)

Abbreviation: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but analyzed and reported separately.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
e. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm. For 16 through 25 years age group, obesity is defined as BMI≥30.0 kg/m^2.

Neutralising antibody results

- **Participants without prior evidence of SARS-COV-2 infection**

This analysis was conducted in subjects who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at baseline and SARS-CoV-2 not detected by nucleic acid amplification test [nasal swab] at any visit up to 1 month after Dose 2).

Table 2: Summary of Geometric Mean Ratio (Immunogenicity Subset) – Participants with baseline negative status

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		12-15 Years/16-25 Years	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Noninferiority Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12-15 years] – Group 2 [16-25 years]) and the corresponding CI (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

Table 3: Summary of seroresponse rates (Immunogenicity Subset) – Participants with baseline negative status

		Vaccine Group (as Randomized)					
		BNT162b2 (30 µg)					
		12-15 Years		16-25 Years		Difference	
Assay	Dose/ Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	%[e]	(95% CI[f])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	143	140 (97.9) (94.0, 99.6)	124	124 (100.0) (97.1, 100.0)	-2.1	(-6.0, 0.9)

Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (12-15 years – 16-25 years).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

- **All participants**

Table 4: Summary of GMTs (Immunogenicity Subset) by baseline status

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	ALL	155	11.2 (10.3, 12.3)	136	10.5 (9.9, 11.2)	29	11.2 (8.9, 14.0)	24	10.0 (10.0, 10.0)
		POS	8	54.1 (19.7, 148.7)	5	38.6 (6.4, 232.9)	1	251.0 (NE, NE)	0	NE (NE, NE)
		NEG	146	10.3 (9.7, 10.9)	131	10.0 (10.0, 10.0)	27	10.0 (10.0, 10.0)	24	10.0 (10.0, 10.0)
	2/1 Month	ALL	207	1283.0 (1139.6, 1444.5)	185	730.8 (646.7, 825.8)	36	15.1 (10.7, 21.4)	32	10.7 (9.3, 12.4)
		POS	10	2342.2 (1308.7, 4191.8)	8	1439.2 (727.1, 2848.7)	2	191.0 (1.2, 30873.6)	1	10.0 (NE, NE)
		NEG	192	1239.2 (1096.6, 1400.5)	177	708.7 (626.4, 802.0)	33	13.1 (9.7, 17.7)	31	10.8 (9.3, 12.5)

Abbreviations: COVID-19 = coronavirus disease 2019; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status.
c. n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.
d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Table 5: Summary of GMFRs (Immunogenicity Subset) by baseline status

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])	n[c]	GMFR[d] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	118.3 (101.4, 137.9)	135	71.2 (61.3, 82.7)	29	1.4 (1.0, 1.9)	24	1.1 (0.9, 1.3)
		POS	8	47.6 (26.4, 86.0)	5	47.1 (3.1, 721.4)	1	1.1 (NE, NE)	0	NE (NE, NE)
		NEG	145	125.0 (106.9, 146.2)	130	72.3 (62.9, 83.2)	27	1.4 (1.0, 2.0)	24	1.1 (0.9, 1.3)

Abbreviations: COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status.
c. n = Number of subjects with valid and determinate assay results for the specified assay both prevaccination time points and at the given dose/sampling time point.
d. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Table 6: Summary of seroresponse (Immunogenicity Subset) by baseline status

			Vaccine Group (as Randomized)							
			BNT162b2 (30 µg)				Placebo			
			12-15 Years		16-25 Years		12-15 Years		16-25 Years	
Assay	Dose/ Sampling Time Point[a]	Baseline SARS-CoV-2 Status[b]	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	ALL	154	151 (98.1) (94.4, 99.6)	135	134 (99.3) (95.9, 100.0)	29	1 (3.4) (0.1, 17.8)	24	1 (4.2) (0.1, 21.1)
		POS	8	8 (100.0) (63.1, 100.0)	5	4 (80.0) (28.4, 99.5)	1	0 (0.0) (0.0, 97.5)	0	0 (NE) (NE, NE)
		NEG	145	142 (97.9) (94.1, 99.6)	130	130 (100.0) (97.2, 100.0)	27	1 (3.7) (0.1, 19.0)	24	1 (4.2) (0.1, 21.1)

Abbreviations: LLOQ = lower limit of quantitation; NE = not estimable; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Baseline assay results below the LLOQ were set to LLOQ in the analysis.
a. Protocol-specified timing for blood sample collection.
b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. ALL = irrespective of baseline SARS-CoV-2 status, including missing baseline status
c. N = number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
d. n = Number of subjects with ≥4-fold rise from before vaccination for the given assay at the given dose/sampling time point.
e. Exact 2-sided CI based on the Clopper and Pearson method.

Conclusions on clinical immunogenicity

The objective of this immunogenicity analysis was to provide immunobridging between adolescents (12–15 years old) and young adults (16-25 years old). The data establish non-inferiority of neutralising antibody levels in adolescents compared to young adults. In baseline seronegative subjects, a robust neutralising response was shown after the second vaccine dose in both adolescents (GMFR=118) and young adults (GMFR=71), with seroresponse rates of almost 100% in both age groups. The response of adolescents is formally non inferior to that of young adults but, actually, the GMT appears almost twice higher (1.76-fold) in adolescents compared to young adults. There are very few seropositive subjects at baseline, and as expected, their GMT after vaccination is notably higher than the GMT in baseline seronegative subjects, almost twice higher in both age groups. Based on these immunogenicity data, similar efficacy is anticipated in adolescents and adults.

2. Clinical efficacy

Methods

The same selection criteria and vaccine regimen as in adults were applied to the adolescent stratum of the Phase 1/2/3 study (C4591001).

Outcomes/endpoints

The same primary endpoints and COVID-19 case definition as presented for the adult population were used for adolescents:

- first primary endpoint: 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 last dose) of past SARS-CoV-2 infection;
- second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT regardless of past infection.

Sample size

There was no independent sample size calculation based on demonstration of efficacy in adolescents. It was anticipated that approximately 2,000 adolescents could be enrolled.

Blinding (masking)
Starting 14 December 2020, individuals 16 years of age and older have been progressively unblinded in the study to receive BNT162b2 vaccination when eligible per protocol. However, adolescents 12-15 years of age remain blinded in this study, as BNT162b2 vaccination eligibility in all regions is currently for 16 years of age and older; a few participants in the 12-15 years of age group turned 16 years of age after study enrolment and thus became eligible for unblinding to treatment assignment and vaccination. Sponsor and site personnel responsible for the ongoing conduct of the study remain blinded to individual participants' randomisation for those who have not been unblinded.

Statistical methods
The point estimate of vaccine efficacy (VE) and associated 2-sided 95% CI were derived using the Clopper-Pearson method adjusted for surveillance time and provided as descriptive statistics. No formal hypothesis testing was performed.
The following populations are used for the presented efficacy analyses:
- Evaluable efficacy (7 days): All eligible randomised participants who receive all vaccinations as randomised, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.
- Dose 1 all-available efficacy 1: All randomised participants who receive at least 1 vaccination.

Results

Participant flow
Out of the 2,264 adolescents randomised, 4 were not vaccinated. Out of the 2,260 subjects that received Dose 1, 2,241 (> 99%) received Dose 2. The reason for not receiving Dose 2 was an adverse event (AE) in 2 cases of the BNT162b2 arm (see Table 18): pyrexia (related) and anxiety, depression (considered unrelated). The most frequent reason was a COVID-19 positive test, which was reported more frequently in the placebo arm. Overall, a high level of compliance was observed in these adolescents up to 1-month post-Dose 2 visit.

Table 7: Disposition of all randomised subjects through 1 month after Dose 2

	Vaccine Group (as Randomized)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N[a]=1134) n[b] (%)	16-25 Years (N[a]=1875) n[b] (%)	12-15 Years (N[a]=1130) n[b] (%)	16-25 Years (N[a]=1913) n[b] (%)
Randomized	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Dose 1	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Dose 2	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Completed 1-month post–Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continue in the study up to 1-month post–Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	7 (0.6)	12 (0.6)	10 (0.9)	36 (1.9)
Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	1 (0.1)	7 (0.6)	6 (0.3)
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria	3 (0.3)	4 (0.2)	10 (0.9)	26 (1.4)
Withdrawal by subject	0	6 (0.3)	1 (0.1)	1 (0.1)
Pregnancy	0	1 (0.1)	0	3 (0.2)
Adverse event	2 (0.2)	1 (0.1)	0	0
Physician decision	1 (0.1)	0	0	2 (0.1)
Protocol deviation	0	0	1 (0.1)	2 (0.1)
Lost to follow-up	0	0	0	1 (0.1)
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)
Withdrawn from the study before 1-month post–Dose 2 visit	0	45 (2.4)	2 (0.2)	56 (2.9)
Withdrawn after Dose 1 and before Dose 2	0	25 (1.3)	1 (0.1)	34 (1.8)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	0	20 (1.1)	1 (0.1)	22 (1.2)
Reason for withdrawal from the study				
Lost to follow-up	0	29 (1.5)	0	32 (1.7)
Withdrawal by subject	0	14 (0.7)	0	19 (1.0)
Protocol deviation	0	0	1 (0.1)	1 (0.1)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.1)	0
Adverse event	0	0	0	1 (0.1)
Physician decision	0	0	0	1 (0.1)
Other	0	1 (0.1)	0	2 (0.1)

Note: Human immunodeficiency virus (HIV)-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects randomized but did not sign informed consent or had a significant quality event due to lack of PI oversight are not included in any analysis population.
a. N = number of randomized subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

Baseline data

Since the efficacy population includes nearly the same number of participants in each arm as in the safety population, the demographics of the efficacy population is essentially the same as in the safety population. It is presented in Table 8 in parallel with the demographics of the young adult (16-25 years) population.

Most adolescent participants are White (86%), with 5% Black and 6% Asian participants. Half are male and 12% are obese. The median age is 14 years. Finally, 4% have positive SARS-CoV-2 baseline status. The demographic characteristics are well-balanced across the vaccine and placebo arms. The population of young adults is more racially diverse as they were also enrolled outside the US and the proportion of obese is notably higher (about 20%).

Table 8: Demographics (Safety Population)

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=1131) n^b (%)	16-25 Years (N^a=1867) n^b (%)	12-15 Years (N^a=1129) n^b (%)	16-25 Years (N^a=1903) n^b (%)
Sex				
Male	567 (50.1)	921 (49.3)	585 (51.8)	882 (46.3)
Female	564 (49.9)	946 (50.7)	544 (48.2)	1021 (53.7)
Race				
White	971 (85.9)	1443 (77.3)	962 (85.2)	1510 (79.3)
Black or African American	52 (4.6)	189 (10.1)	57 (5.0)	179 (9.4)
American Indian or Alaska Native	4 (0.4)	32 (1.7)	3 (0.3)	18 (0.9)
Asian	72 (6.4)	108 (5.8)	71 (6.3)	108 (5.7)
Native Hawaiian or other Pacific Islander	3 (0.3)	10 (0.5)	0	3 (0.2)
Multiracial	23 (2.0)	76 (4.1)	29 (2.6)	74 (3.9)
Not reported	6 (0.5)	9 (0.5)	7 (0.6)	11 (0.6)
Racial designation				
Japanese	5 (0.4)	3 (0.2)	2 (0.2)	6 (0.3)
Ethnicity				
Hispanic/Latino	132 (11.7)	604 (32.4)	130 (11.5)	575 (30.2)
Non-Hispanic/non-Latino	997 (88.2)	1259 (67.4)	996 (88.2)	1322 (69.5)
Not reported	2 (0.2)	4 (0.2)	3 (0.3)	6 (0.3)
Country				
Argentina	0	282 (15.1)	0	287 (15.1)
Brazil	0	160 (8.6)	0	142 (7.5)
Germany	0	11 (0.6)	0	20 (1.1)
South Africa	0	69 (3.7)	0	75 (3.9)
Turkey	0	12 (0.6)	0	15 (0.8)
USA	1131 (100.0)	1333 (71.4)	1129 (100.0)	1364 (71.7)
Age at vaccination (years)				
Mean (SD)	13.6 (1.11)	21.0 (2.99)	13.6 (1.11)	21.0 (2.98)
Median	14.0	22.0	14.0	21.0
Min, max	(12, 15)	(16, 25)	(12, 15)	(16, 25)
Baseline SARS-CoV-2 status				
Positive[c]	46 (4.1)	100 (5.4)	47 (4.2)	104 (5.5)
Negative[d]	1028 (90.9)	1754 (93.9)	1023 (90.6)	1789 (94.0)
Missing	57 (5.0)	13 (0.7)	59 (5.2)	10 (0.5)
Body mass index (BMI) Obese[e]				
Yes	143 (12.6)	353 (18.9)	128 (11.3)	385 (20.2)
No	988 (87.4)	1514 (81.1)	1001 (88.7)	1518 (79.8)

a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
d. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
e. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html charts/bmiagerev.htm. For 16 through 25 years age group, obesity is defined as BMI≥30.0 kg/m^2.

Outcomes and estimation

- **First primary efficacy endpoint**

An analysis has been performed with all accrued cases in adolescents during blinded follow-up to a data cut-off date of 13 March 2021, by which time the median duration of follow-up after Dose 2 was greater than 2 months (Table 9). This is a descriptive analysis and no formal hypothesis tests were performed. Nevertheless, the point estimate for VE is greater than 50% and the 95% CI is entirely above 30%, so the WHO criteria for VE have been satisfied independently for the 12-15 years age group (Table 10).

Table 9: Follow-up time after Dose 2 (Safety Population)

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
Subjects (%) with length of follow-up of:			
Total exposure from Dose 2 to cutoff date			
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Note: Follow-up time was calculated to the cutoff date or the date of unblinding, whichever date was earlier.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.

Table 10: First COVID-19 occurrence from 7 days after Dose – Evaluable Efficacy Population (7 days) – without evidence of infection prior to 7 days after Dose 2

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1005)		Placebo (N[a]=978)			
Efficacy Endpoint	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	0	0.154 (1001)	16	0.147 (972)	100.0	(75.3, 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.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
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.

- **Second primary efficacy endpoint**

There were an additional 2 cases in the placebo arm if participants with prior evidence of infection were also considered. The incidence of infection in those with and without prior evidence of infection was similar: 2/122 (1.64%) vs. 16/972 (1.64%), respectively.

Table 11: First COVID-19 occurrence from 7 days after dose – Evaluable Efficacy Population (7 days) – with or without evidence of infection prior to 7 days after Dose 2

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1119)		Placebo (N[a]=1110)			
Efficacy Endpoint	**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	0	0.170 (1109)	18	0.163 (1094)	100.0	(78.1, 100.0)

- **Severe cases**

No severe COVID-19 cases were reported in adolescents (12-15 years of age) as of the data cut-off date. Therefore, there is no information to allow independent inferences about VE against severe infection in adolescents to be made.

- **All confirmed cases of COVID-19 after Dose 1**

The results demonstrate that, consistent with what was observed in adults, the vaccine provides protection even before the administration of Dose 2. There were no cases reported in the vaccine arm from 11 days after Dose 1 and the lower bound of the 95% CI is above 30% for the period from 11 days after Dose 1 to Dose 2; 11 days was approximately the time point where the cumulative incidence curves for the vaccine and placebo arms began to diverge in the analysis of the adult data.

Table 12: First COVID-19 occurrence after Dose 1 – All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=1131)		Placebo (N[a]=1129)			
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	3	0.257 (1120)	35	0.250 (1119)	91.6	(73.5, 98.4)
After Dose 1 to before Dose 2	3		12		75.0	(7.4, 95.5)
After Dose 1 to <11 days after Dose 1	3		4		25.0	(-343.3, 89.0)
≥11 Days after Dose 1 to before Dose 2	0		8		100.0	(41.4, 100.0)
Dose 2 to 7 days after Dose 2	0		5		100.0	(-9.1, 100.0)
≥7 Days after Dose 2	0		18		100.0	(77.3, 100.0)
≥7 days after Dose 2 to <2 Months after Dose 2	0		16		100.0	(74.1, 100.0)
≥2 Months after Dose 2 to <4 Months after Dose 2	0		2		100.0	(-432.5, 100.0)

Abbreviation: 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 Dose 1 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 for overall row).

Conclusions on clinical efficacy
In the pivotal Phase 1/2/3 study (C4591001), a cohort of about 2,200 adolescents 12-15 years of age was randomised to placebo or the same vaccination regimen as adults with a median duration of follow-up superior to 2 months, which is considered acceptable. The data show a high level of vaccine efficacy against symptomatic disease (100%; 95%CI [75.3, 100]) after 2 vaccine doses, consistent with immunogenicity results and adult data. Furthermore, this level of efficacy was already observed from 11 days after Dose 1.

Overall, the data currently available show a very high level of short-term efficacy in adolescents, supporting an extension of indication to this age group.

3. Clinical safety
Safety results are presented for 2,260 adolescents aged 12-15 years, of which 1131 received at least one dose of BNT162b2 up to the data cut-off 13 March 2021. In-line with immunogenicity, the main comparison presented is with young adults aged 16-25 years up to 1-month post Dose 2 (1097 subjects in the reactogenicity subset, of which 536 received at least 1 dose of BNT162b2).

Comparative data beyond 1 month post Dose 2 have not been provided as young adults had a different follow-up time up to the data cut-off due to enrolment starting time into the study and due to unblinding of individuals ≥ 16 years of age as per the protocol for vaccination under emergency use authorisation.

Patient exposure

The median duration of follow-up for adolescents was >2 months after Dose 2 (see Table 9).

All adolescent subjects were enrolled in US study sites compared with 81% of young adults. Otherwise, with the exception of a higher proportion of Hispanic/Latino subjects in the young adult group, the demographics were generally well balanced across the two vaccine arms.

Table 13: Demographic characteristics – subjects 12-15 years and 16-25 years (Reactogenicity Subset)

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
	12-15 Years (N^a=1131) n^b (%)	16-25 Years (N^a=537) n^b (%)	12-15 Years (N^a=1129) n^b (%)	16-25 Years (N^a=561) n^b (%)
Sex				
Male	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)
Female	564 (49.9)	282 (52.5)	544 (48.2)	292 (52.0)
Race				
White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Black or African American	52 (4.6)	47 (8.8)	57 (5.0)	50 (8.9)
American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Racial designation				
Japanese	5 (0.4)	0	2 (0.2)	0
Ethnicity				
Hispanic/Latino	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Non-Hispanic/non-Latino	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Country				
Argentina	0	20 (3.7)	0	28 (5.0)
Brazil	0	24 (4.5)	0	19 (3.4)
Germany	0	11 (2.0)	0	20 (3.6)
South Africa	0	34 (6.3)	0	45 (8.0)
Turkey	0	12 (2.2)	0	15 (2.7)
USA	1131 (100.0)	436 (81.2)	1129 (100.0)	434 (77.4)
Age at vaccination (years)				
Mean (SD)	13.6 (1.11)	19.4 (3.26)	13.6 (1.11)	19.6 (3.33)
Median	14.0	18.0	14.0	19.0
Min, max	(12, 15)	(16, 25)	(12, 15)	(16, 25)
Baseline SARS-CoV-2 status				
Positive[c]	46 (4.1)	30 (5.6)	47 (4.2)	34 (6.1)
Negative[d]	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)
Body mass index (BMI) Obese[e]				
Yes	143 (12.6)	80 (14.9)	128 (11.3)	101 (18.0)
No	988 (87.4)	457 (85.1)	1001 (88.7)	460 (82.0)

Reactogenicity

All participants aged 12-15 years and a subset of participants ≥16 years of age (young adults 16-25 years of age) were asked to record local and systemic reactions and antipyretic/pain medication use from Day 1 through Day 7 after each dose. This was done each evening using prompts from an electronic diary (e-diary).

Adolescent participants (12-15 years of age) with e-diary data included N=1131 in the BNT162b2 arm and N=1129 in the placebo arm post Dose 1, and N=1124 in the BNT162b2 arm and N=1117 in the placebo arm post Dose 2.

Young adult participants (16-25 years of age) in the reactogenicity subset with e-diary data included N=539 in the BNT162b2 arm and N=564 in the placebo arm post Dose 1, and N=526 in the BNT162b2 arm and N=537 in the placebo arm post Dose 2.

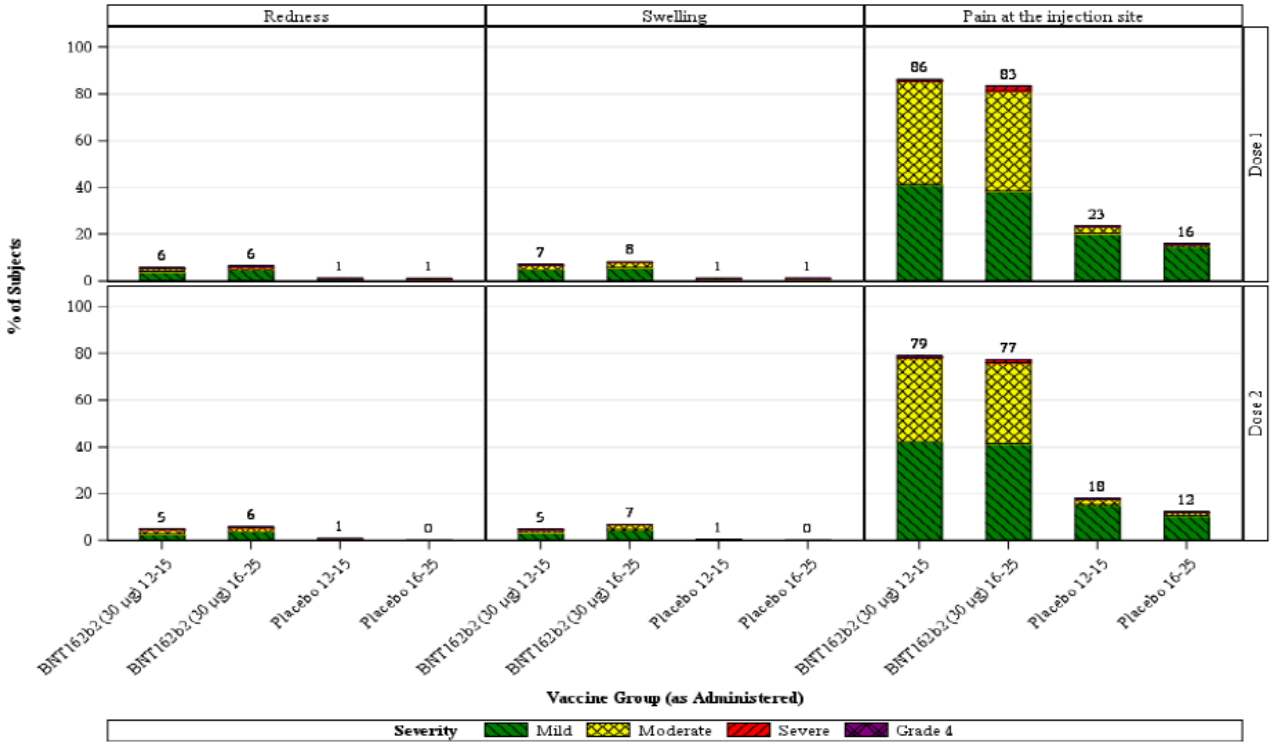
Local reactions

Local reactogenicity was similar in adolescents aged 12- 15 years and young adults aged 16-25 years.

In line with local reactogenicity data previously reported in adults, in the BNT162b2 arm, pain at the injection site was the most frequently reported local reaction in adolescents and young adults. The frequency was similar after Dose 1 and after Dose 2 in adolescents (86.2% vs 78.9%) and in young adults (83.4% vs 77.5%). After the first and second dose and in both age groups, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently and at lower incidence in adolescents (≤1.5%) compared with young adults (≤3.4%) across the BNT162b2 and placebo arms after any dose. No Grade 4 local reactions were reported in either age group.

Across age groups, median onset for all local reactions after either dose of BNT162b2 was Day 1 to Day 3 (Day 1 was the day of vaccination) and they resolved with a median duration of 1-3 days.

Figure 1: Participants reporting local reactions, by maximum severity, within 7 days after each dose – Reactogenicity Subset: 12-15 years and 16-25 years



Note: Number above each bar denotes percentage of subjects reporting the reaction with any severity.

A comparison of the local reactogenicity data in adolescents with data in adult subjects 16-55 years old was also provided. Generally, the data in these two age groups are similar, with the exception of an increased frequency of moderate pain reported in adolescents. This is in-keeping with the same trend that was seen in the adult population, where it was noted that the frequency

of moderate pain after any dose was increased for younger participants aged 16-55 years compared to older participants aged >55 years.

Systemic events
Systemic reactogenicity was generally similar between adolescents aged 12-15 years and young adults aged 16-25 years.

Systemic events in the adolescent group compared with the young adult group, in decreasing order of frequency by dose (Dose 1 vs Dose 2) in subjects that received BNT162b2, were:

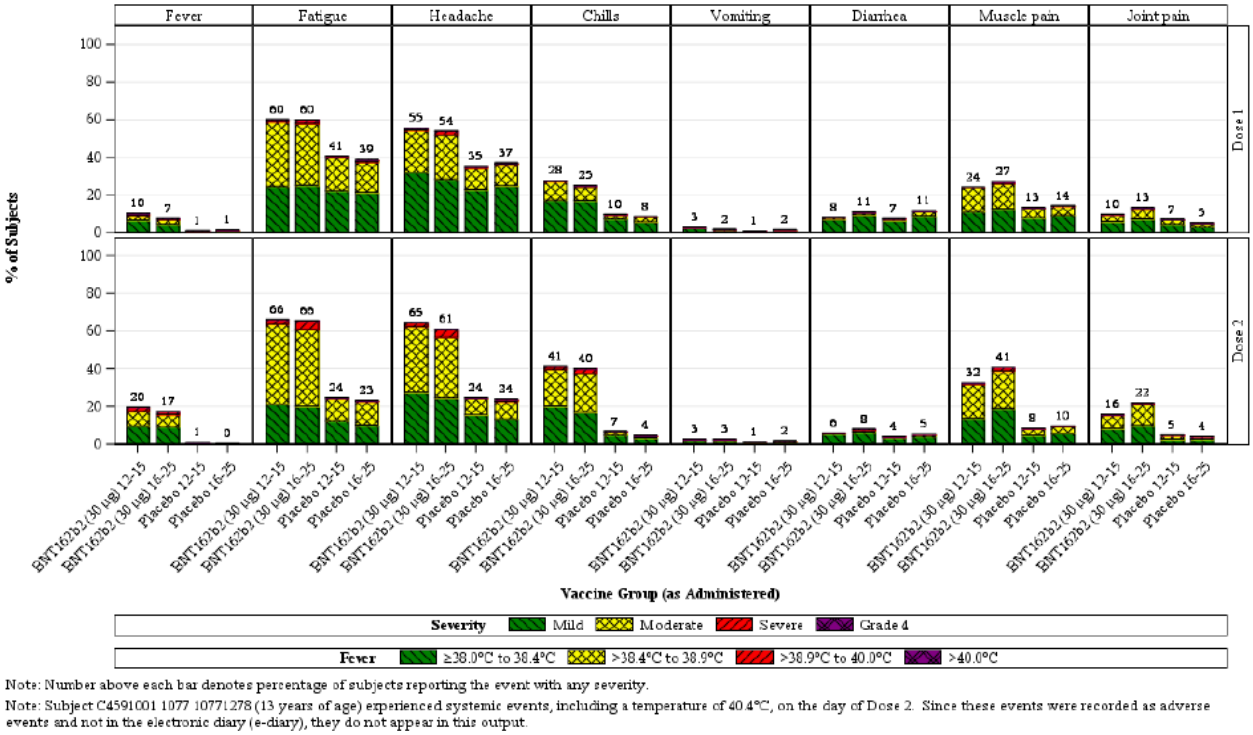
- fatigue: adolescents (60.1% vs 66.2%) compared to young adults (59.9% vs 65.6%)
- headache: adolescents (55.3% vs 64.5%) compared to young adults (53.9% vs 60.9%)
- chills: adolescents (27.6% vs 41.5%) compared to young adults (25.0% vs 40.0%)
- muscle pain: adolescents (24.1% vs 32.4%) compared to young adults (26.9% vs 40.8%)
- joint pain: adolescents (9.7% vs 15.8%) compared to young adults (13.2% vs 21.9%)
- fever: adolescents (10.1% vs 19.6%) compared to young adults (7.3% vs 17.2%)
- vomiting: reported infrequently in both age groups and similar after either dose
- diarrhoea: reported infrequently in both age groups and similar after either dose

In line with systemic reactogenicity data previously reported in adults, the frequency and severity of systemic reactions increased with number of doses for most events, the most frequent systemic reactions were fatigue and headache, and most systemic events were mild or moderate in severity. Severe systemic reactions were reported infrequently and at lower incidence in adolescents (≤3.5%) compared with young adults (≤6.0%) that received BNT162b2 after any dose. One adolescent in the BNT162b2 arm had Grade 4 pyrexia (40.4 °C) on Day 2 after Dose 1, with temperature returning to normal within 2 days; it was also reported as an adverse event (AE) leading to withdrawal.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication in subjects that received BNT162b2 was slightly higher in adolescents (37% and 51%) compared with young adults (32% and 46%). Similar to the data previously seen in adults, medication use increased in both age groups after Dose 2 compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo arm than in the BNT162b2 arm and was similar after Dose 1 and Dose 2 in the adolescent and young adult placebo arms (ranging from 10% to 12%).

Median onset and duration for systemic reactions after either dose of BNT162b2 was similar between the adolescent and young adult groups. Across age groups, median onset for all systemic events after either dose of BNT162b2 was Day 1 to Day 4 (Day 1 was the day of vaccination). Systemic events resolved after each dose with a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days.

Figure 2: Participants reporting systemic events, by maximum severity, within 7 days after each dose – Reactogenicity Subset: 12-15 years and 16-25 years



Note: Number above each bar denotes percentage of subjects reporting the event with any severity.

Note: Subject C4591001 1077 10771278 (13 years of age) experienced systemic events, including a temperature of 40.4°C, on the day of Dose 2. Since these events were recorded as adverse events and not in the electronic diary (e-diary), they do not appear in this output.

A comparison of the systemic reactogenicity data in adolescents with data in adult subjects 16-55 years old was also provided. Overall, the frequency of solicited systemic events and proportion of moderate events was increased in adolescents compared to adults. However, the frequency of severe systemic events was low and similar in the adolescent and 16-55 years age groups. Duration of symptoms was similar in both age groups. Use of antipyretic/pain medication was higher in the adolescents compared with those aged 16-55 years, although this difference was mainly after Dose 1 (Dose 1: 37% vs 28%, Dose 2: 51% vs 45%). This is in keeping with the same trend that was seen in the adult population where it was noted that the frequency and severity of systemic events was increased in subjects aged 16-55 years compared with those aged > 55 years.

Unsolicited adverse events

Overview of adverse events

The percentage of participants with any unsolicited adverse event up to 1-month post Dose 2 was similar in the BNT162b2 and placebo arms for both age groups.

An overview of AEs for adolescents and young adults reported from Dose 1 to 1 month after Dose 2 is provided in Table 14.

Table 14: Number (%) of subjects reporting at least 1 AE from Dose 1 through 1 month after Dose 2 – Reactogenicity Subset: 12-15 years and 16-25 years

	Vaccine Group (as Administered)			
	BNT162b2 (30 µg)		Placebo	
Adverse Event	12-15 Years (N[a]=1131) n[b] (%)	16-25 Years (N[a]=536) n[b] (%)	12-15 Years (N[a]=1129) n[b] (%)	16-25 Years (N[a]=561) n[b] (%)
Any event	68 (6.0)	58 (10.8)	67 (5.9)	45 (8.0)
Related[c]	33 (2.9)	33 (6.2)	21 (1.9)	12 (2.1)
Severe	7 (0.6)	9 (1.7)	2 (0.2)	3 (0.5)
Life-threatening	1 (0.1)	0	1 (0.1)	0
Any serious adverse event	4 (0.4)	2 (0.4)	1 (0.1)	2 (0.4)
Related[c]	0	0	0	0
Severe	2 (0.2)	2 (0.4)	0	1 (0.2)
Life-threatening	0	0	1 (0.1)	0
Any adverse event leading to withdrawal	2 (0.2)	1 (0.2)	0	2 (0.4)
Related[c]	1 (0.1)	1 (0.2)	0	0
Severe	1 (0.1)	1 (0.2)	0	0
Life-threatening	1 (0.1)	0	0	0
Death	0	0	0	0

Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary

An overview of AEs from Dose 1 to the cut-off date for 2,260 adolescents 12-15 years of age during the blinded safety follow-up is presented in Table 15.

Table 15: Number (%) of subjects reporting at least 1 AE from Dose 1 through cut-off date (13MAR2021): Subjects 12-15 years

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)
Any event	72 (6.4)	71 (6.3)
Related[c]	33 (2.9)	21 (1.9)
Severe	9 (0.8)	3 (0.3)
Life-threatening	1 (0.1)	1 (0.1)
Any serious adverse event	5 (0.4)	2 (0.2)
Related[c]	0	0
Severe	4 (0.4)	1 (0.1)
Life-threatening	0	1 (0.1)
Any adverse event leading to withdrawal	2 (0.2)	0
Related[c]	1 (0.1)	0
Severe	1 (0.1)	0
Life-threatening	1 (0.1)	0
Death	0	0

Note: Adverse events that occurred on the day of or after subjects were unblinded are excluded from this summary

Analysis of adverse events
Adverse events reported in adolescents were generally similar to young adults within the respective BNT162b2 and placebo arms.

Most of the AEs after Dose 1 up to 1 month after Dose 2 were reactogenicity events reported as AEs. In adolescents, AE frequencies in these reactogenicity System Organ Classes (SOCs) were (BNT162b2 vs placebo):

- general disorders and administration site conditions (1.4% vs 1.0%)
- musculoskeletal and connective tissue disorders (0.8% vs 0.7%)
- nervous system disorders (1.1% vs 0.6%)
- gastrointestinal disorders (1.2% vs 0.3%)

In young adults, AE frequencies in these reactogenicity SOCs (BNT162b2 vs placebo) were:

- general disorders and administration site conditions (3.9% vs 1.8%)
- musculoskeletal and connective tissue disorders (2.2% vs 1.4%)
- nervous system disorders (2.4% vs 1.2%)
- gastrointestinal disorders (0.9% vs 1.1%)

AEs reported in adolescents through the data cut-off date were similar in the BNT162b2 and placebo arms. The most frequently reported AEs in adolescents through the data cut-off date included lymphadenopathy (0.8%), injection site pain (0.6%), fatigue (0.6%), pyrexia (0.4%), nausea (0.4%), and headache (0.4%). These are all listed adverse drug reactions for BNT162b2.

Related adverse events
From Dose 1 to 1 month after Dose 2, AEs assessed as related by the investigator in adolescents and young adults were similar in the BNT162b2 arm and in the placebo arm (adolescents 2.9% vs 1.9%, young adults 6.2% vs 2.1%). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 15 adolescents (1.3%) and 19 young adults (3.5%) in the BNT162b2 arm compared with 9 adolescents (0.8%) and 9 young adults (1.6%) in the placebo arm. Related events of lymphadenopathy were reported in 7 adolescents in the BNT162b2 arm and 1 adolescent in the placebo arm, compared with 1 young adult in the BNT162b2 arm and none in the placebo arm.

Immediate adverse events
Immediate AEs were those collected within 30 minutes hours after administration. No immediate AEs occurred after the 1st dose of BNT162b2 in either age group. Following the 2nd dose, the incidence of immediate AEs was very low in both age groups and comparable with the placebo arms (12-15 years 0.2% vs 0.3%, 16-25 years 0.2% vs 0.4%). No allergic AEs were reported after either dose of BNT162b2 within 30 minutes after vaccination.

Severe or life-threatening events
From Dose 1 to 1 month after Dose 2, severe AEs reported in adolescents and young adults were overall low in frequency: 0.6% in the BNT162b2 arm versus 0.2% in the placebo arm among adolescents, and 1.7% in the BNT162b2 arm versus 0.5% in the placebo arm among young adults.

Among adolescents, 2 participants (1 each in the BNT162b2 and placebo arms) had at least 1 life-threatening (or Grade 4) AE from Dose 1 to 1 month after Dose 2. These included:

- Focal peritonitis and appendicitis reported in 1 adolescent in the placebo arm, both events were reported as serious adverse events (SAEs), resolved, and the participant continued in the study.
- Pyrexia (40.4 °C) reported as Grade 4 in 1 adolescent in the BNT162b2 arm, occurred 2 days after Dose 1 with a duration of 3 days (i.e. temperature returned to normal within 2 days), and was considered by the investigator as related to study intervention; the event was reported by the investigator as non-serious, resolved, and the participant withdrew from the study (also recorded in the e-diary as reactogenicity systemic event).

Additionally, 2 participants in the adolescent age group had life-threatening AEs that occurred after they turned 16 years of age during the study and were unblinded to receive BNT162b2 and were therefore not included in analyses of blinded data:

- Anaphylactoid reaction reported in 1 participant originally randomised to the placebo arm, 3 days after receiving the first dose of BNT162b2 with a duration of 1 day, considered by the investigator as related to study intervention; the event was reported as an SAE, resolved, and the participant withdrew from the study.
- Depression reported in 1 participant originally randomised to the placebo arm, 7 days after receiving the first dose of BNT162b2 reported as ongoing at the time of the data cut-off date, considered by the investigator as not related to study intervention; the event was reported as an SAE due to hospitalisation and reported as resolving, and the participant continued in the study.

Among young adults, there were no life-threatening AEs reported from Dose 1 to 1 month after Dose 2.

Serious adverse events and deaths

Deaths
No deaths were reported in adolescents aged 12-15 years of age or young adults aged 16-25 years up to the data cut-off 13 March 2021.

Serious adverse events
Up to 1-month post Dose 2, the incidence of serious AEs in subjects that received BNT162b2 was very low in both age groups (0.4%) and none of the SAEs were considered related to treatment by the investigator.

The incidence of SAEs in the 12-15 years group that received BNT162b2 remained low up to the data cut-off (0.4%).

In subjects that received BNT162b2, the only SAE that occurred in more than one subject was ‘Depression’, which was reported in 3 subjects in the 12-15 years group and none in the 16-25 years group; 2 non-serious events of depression occurred in the placebo arm of the 12-15 years group. All 3 subjects with an SAE of ‘Depression’ had a significant past medical history that included depression, 2 of the 3 cases resolved after 5 days and none of the cases were considered related to treatment.

Two adolescents originally randomised to the placebo arm had SAEs that occurred after they turned 16 years of age during the study and were unblinded to receive BNT162b2. These events were also considered as life-threatening and are described above: an anaphylactoid reaction reported in 1 participant and depression reported in 1 participant

Hypersensitivity reactions and anaphylaxis have been observed post-authorisation in subjects aged ≥ 16 years and are a recognised risk with BNT162b2.

Adverse events of special interest (AESIs)
AESIs, such as those in the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders, were considered in the review of reported events for the adolescent group in addition to programme defined targeted medical events.

The only AESI that was reported in subjects aged 12-15 years that received BNT162b2 was lymphadenopathy.

Anaphylaxis
No cases of anaphylaxis or anaphylactoid reactions were reported during blinded follow-up in the adolescent (12-15 years of age) or young adult (16-25 years of age) groups as of 13 March 2021. One young adult participant who was originally randomised to the placebo arm and unblinded to receive BNT162b2 had an anaphylactoid reaction 3 days following their first dose of BNT162b2[1], with an event duration of 1 day; the event was reported as an SAE, reported as resolved, and the participant withdrew from the study.

Lymphadenopathy
In the BNT162b2 treated arms, up to 1-month post Dose 2, nine subjects (0.8%) reported 10 events of lymphadenopathy in the 12-15 years group, of which 7 events in 7 subjects (0.6%) were considered related to treatment. The majority of these events occurred in the arm and neck region, were mild (grade 1), reported within 2-10 days after vaccination, and half of events resolved within 1-10 days (4 events were ongoing at the time of the data cut-off date). In young adults (16-25 years of age), 1 related event of lymphadenopathy was reported up to the data cut-off date, occurring in the axilla within 1 day of Dose 2 and resolved within 5 days.

The frequency of lymphadenopathy events in subjects 12-15 years is within that expected based on the frequency designation in the product information, and the frequency of related events is similar to that seen in adults 16-55 years. Lymphadenopathy is considered an adverse reaction to vaccine and is included in section 4.8 of the information for HCPs with a frequency designation 'Uncommon (≥ 1/1,000 to < 1/100)'.

Appendicitis
In adolescents (12-15 years of age), 2 participants in the placebo arm had events of appendicitis reported as SAEs and considered as not related to study intervention.
In young adults (16-25 years of age), 1 participant in the BNT162b2 arm had an event of appendicitis reported as an SAE and considered as not related to study intervention.

Bell's Palsy/Facial paralysis/Facial paresis
No cases of facial paralysis were reported in adolescents (12-15 years of age) as of 13 March 2021.

Severe Covid-19 illness
As of 13 March 2021, no severe COVID-19 cases were reported in adolescents 12-15 years of age in Study C4591001.

[1] This case was not included in the summary safety tables as these only included blinded follow-up data

Laboratory findings
No laboratory data have been provided with this extension of indication.

Safety in special populations

Pregnancy
As of the data cut-off of 13 March 2021, no pregnancies were reported in participants 12-15 years of age. Four pregnancies were reported in the young adults (16-25 years of age) that led to discontinuation from the vaccination period in Study C4591001, and 1 additional participant in the young adult group withdrew from the study due to a reported AE of exposure during pregnancy; none of these participants has given birth as of the data cut-off date.

Safety related to interactions
No new data have been provided with this extension of indication.

Discontinuation due to adverse events
From Dose 1 to 1 month after Dose 2, few adolescents and young adults in the BNT162b2 arm (≤0.2%) and in the placebo arm (≤0.4%) were withdrawn due to AEs.

Of these events, in the adolescent group, 1 participant in the BNT162b2 arm had an AE leading to withdrawal that was considered by the investigator as related to study intervention (pyrexia), and none in the placebo arm. In the young adult group, 1 participant in the BNT162b2 arm a had an AE leading to withdrawal that was considered by the investigator as related to study treatment (severe injection site pain that started 2 days after Dose 1 and resolved after 1 day), and none in the placebo arm.

No additional subjects discontinued due to AEs in the 12-15 years group up to the data cut-off 13 March 2021. However, one young adult subject who was originally randomised to the placebo arm and unblinded to receive BNT162b2 had an anaphylactoid reaction (see AESI) and withdrew from the study.

Conclusions on clinical safety
The safety database comprises of 2,260 adolescents aged 12-15 years who were randomised 1:1 to placebo or the same vaccination regimen as adults with a median duration of follow-up > 2 months. This is the same duration of follow-up that was agreed for subjects aged 16 years and over and is considered acceptable, particularly given the significant post-marketing data now available for this vaccine.

Reactogenicity in adolescents was mostly mild to moderate, resolved within a few days and was similar to that seen in young adults. When the reactogenicity data in adolescents aged 12-15 years were compared to those in adults 16-55 years old, an increased frequency of moderate pain at the injection site was seen, and overall, the frequency of events and proportion of moderate events was increased in adolescents. This is in keeping with the same trend that was seen previously in subjects 16-55 years compared with those aged > 55 years of age. Section 4.8 of the Information for UK HCPs has been updated to reflect the following wording that is already included in the EU SmPC *'A slightly lower frequency of reactogenicity events was associated with greater age.'*

Unsolicited adverse events were generally similar in adolescents and young adults, with the majority of AEs relating to reactogenicity events. No new adverse drug reactions have been identified.

Currently available short-term safety data in adolescents aged 12-15 years reflect a similar safety profile to that in young adults and support an extension of indication to this age group. Provision of 6-month safety follow-up data in subjects 12-15 years, once available, has been added as a new condition of the Regulation 174 approval.

Risk Management Plan
The company submitted an updated RMP (version 2.0) with the extension which includes data on use in individuals aged 12-15 years. No changes to the summary of safety concerns or risk minimisation measures were required; the safety profile of BNT162b2 in adolescent subjects was similar to that of young adults. The company will gather further data in 12-15-year olds in existing post-authorisation safety and effectiveness studies, and the results of these will be provided to the MHRA for assessment. The company has agreed to provide age-stratified analysis on the post-authorisation safety data for 12-15-year olds in the summary monthly safety reports.

4. Benefit/risk evaluation

Benefits
Immunogenicity data from adolescent participants show robust neutralising GMTs after vaccination with 2 doses of BNT162b2 at 30 μg. This response is evident in the 50% neutralising GMTs of participants with negative baseline SARS-CoV-2 status and is further supported by the boosting effect observed in the small number of subjects with positive baseline SARS-CoV-2 status. The neutralising GMT in adolescents is formally non-inferior to that in young adults, but in fact largely exceeds that of young adults. Therefore, these data provide reassurance that the vaccine provides a robust immune response to SARS-CoV-2 in the adolescent population, at least comparable to the response that has been associated with vaccine efficacy in adults.
Descriptive efficacy analyses in adolescents, based on confirmed COVID-19 cases reported from at least 7 days after Dose 2 through the data cut-off date (13 March 2021), show a short-term (at least 2 months) observed VE of 100% (95% CI lower bound 75.3%) in individuals without evidence of prior SARS-CoV-2 infection as well as overall in individuals with/without evidence of prior SARS-CoV-2 infection. No severe COVID-19 cases were reported in the adolescents enrolled in the cohort, and therefore, prevention of severe cases cannot be assessed.
Taken together, efficacy and immunogenicity data strongly support a positive benefit in adolescents 12-15 years of age for the same BNT162b2 regimen as in adults.

Risks
The safety profile of BNT162b2 in adolescent subjects appears similar to that of young adults. Reactogenicity in adolescents was mostly mild to moderate, had an onset date 1-3 days post vaccination and generally resolved within a few days. Local reactions were predominantly injection site pain and occurred with a similar frequency after Dose 1 and 2. The most frequent systemic reactions were fatigue and headache. For most systemic events, frequency and severity increased with number of doses. Severe local or systemic reactions were reported infrequently. When the reactogenicity profile of adolescents was compared with adults aged 16-55 years, an increased frequency of moderate pain at the injection site was seen, and overall, the frequency of events and proportion of moderate events was increased in adolescents. This is in keeping with the same trend that was seen previously in subjects 16-55 years compared with those aged > 55 years of age.

The adverse event profile in adolescents mainly reflected reactogenicity events and no new adverse drug reactions have been identified. No deaths were reported and the incidence of serious

adverse events and adverse events leading to withdrawal was very low. The only AESI reported was lymphadenopathy.

Whilst the number of events was small, a slight imbalance in serious adverse events of depression was noted in adolescents compared to placebo and to young adults. All 3 adolescent subjects that had an SAE of 'depression' and were treated with BNT162b2 had a significant past medical history that included depression. Two of the 3 cases resolved after 5 days and none of the cases were considered related to treatment.

Balance of benefits and risks
The benefit risk balance of COVID-19 mRNA Vaccine BNT162b2 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus is considered positive in subjects aged 12-15 years.

Conclusion
The data provided by the company support the proposed extension of indication.

In accordance with legal requirements, the information for healthcare professionals (HCPs) and for UK recipients is available on the MHRA website.

Decision: Grant
Date: 4 June 2021