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Decision

Summary of the Public Assessment Report for COVID-19 Vaccine Pfizer/BioNTech

Updated 16 August 2022

Applies to England, Scotland and Wales

Contents

This publication is available at https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

Summary of the Public Assessment Report

Authorisation for Temporary Supply, COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA) concentrate for solution for injection

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 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine) 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 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and the Information for UK recipients (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine) 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 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and the Information for UK recipients (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine), 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.

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

1. 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 (https://www.legislation.gov.uk/uksi/2012/1916/contents/made), ("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 nucleosidemodified 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 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine).

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'.

2. Quality aspects

2.1 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

2.2 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 (m1ΨTP) in the RNA synthesis which increases RNA persistence invivo 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, codonoptimised 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.

2.3 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 COVID19 Vaccines (https://www.who.int/publications/m/item/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))
- 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 nonspecific 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 UK’s 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.

2.4 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.

3. Non-clinical aspects

3.1 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).

3.2 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.

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 vaccineencoded 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 antispike protein antibodies in mice which has been reviewed as part of the ongoing assessment for this product. These data are not discussed here.

3.3 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 ALC0315, 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).

3.4 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 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 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and the Information for UK recipients (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine).

3.5 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 (https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-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.

3.6 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.

Further information

The rest of this document, including sections on clinical aspects, user consultation, and the overall conclusion, can be found in the PDF (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/944544/COVID-19_mRNA_Vaccine_BNT162b2__UKPAR___PFIZER_BIONTECH__15Dec2020.pdf).

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