3.2.P.2. PHARMACEUTICAL DEVELOPMENT – INTRODUCTION

In this section, the formulation and process development and (b) (4) control strategy for BNT162b2 drug product are described. The pharmaceutical development of BNT162b2 (b) (4) (b) (4) The pharmaceutical development section for drug product is organized as follows:

1. Components of the Drug Product
   The components of the drug product including (b) (4) physicochemical characteristics of the drug substance as relevant to the drug product are provided in this section (Section 3.2.P.2.1 Components of the Drug Product).

2. Drug Product
   A discussion of the approach, results and conclusions from the formulation development and characterization studies is provided in this section (Section 3.2.P.2.2 Drug Product).

3. Manufacturing Process Development

   a. Development History
   A summary of manufacturing process changes with justification for changes is provided in this section (Section 3.2.P.2.3 Development History). Comparability information is included (Section 3.2.P.2.3 Manufacturing Process Development – Comparability Assessment of PPQ Lots).

   b. Quality Attributes (QAs)
   This section includes the approach to defining the critical quality attributes (CQAs) and the rationale for the criticality decisions (Section 3.2.P.2.3 Quality Attributes).

   c. Process Risk Assessement Strategy
   The process risk assessment strategy and methodology are provided in this section (Section 3.2.P.2.3 Process Risk Assessment Strategy).

   d. Process Development and Characterization
   This section includes a discussion of the approach, results and conclusions from the process characterization studies completed for the manufacturing process, including how critical process parameters (CPPs) and critical material attributes (CMAs) of the process have been identified, as well as how the operating ranges have been defined in order to ensure product quality (Section 3.2.P.2.3 Process Development and Characterization).

   e. Lot Genealogy and Usage

This section includes a list of lots, along with their use and ingoing drug substance batch(es) (Section 3.2.P.2.3 Lot Genealogy and Usage).

f. Control Strategy
This (b) (4) control strategy section includes the approach to developing the control strategy, the description of elements of control, and the summary of the control strategy for QAs across drug substance and drug product. The summary of the control strategy for QAs includes the attributes, controls implemented and section references to where the controls are described in greater detail (Section 3.2.P.2.3 Control Strategy).

g. Analytical Method Evolution
This section describes the analytical testing strategy throughout drug product development history as (b) (4) (Section 3.2.P.2.3 Analytical Method Evolution).

4. Container Closure System
This section describes the selection and suitability of the container closure system (Section 3.2.P.2.4 Container Closure System).

5. Microbiological Attributes
As BNT162b2 is a sterile preservative-free multi-dose product, this section includes information supporting the integrity of the container closure system (Section 3.2.P.2.5 Microbiological Attributes).

6. Compatibility
This section includes results of testing the compatibility of BNT162b2 with the diluent (0.9% sodium chloride [saline] solution), components commonly used for preparation and intramuscular administration, as well as results of (b) (4) study (Section 3.2.P.2.6 Compatability).

Quality Target Product Profile (QTPP)

A QTPP was established to form the basis for development of BNT162b2. The development of the QTPP (b) (4) The QTPP describes the drug product in terms of quality characteristics, listing the intended product quality and performance characteristics to be achieved at the end of the drug substance and drug product manufacturing processes and linking these characteristics to the relevant CQAs. The QTPP for BNT162b2 with associated CQAs (both drug substance and drug product related) is provided in Table 3.2.P.2-1. Quality attributes with associated criticality assessment are discussed in Section 3.2.P.2.3 Quality Attributes.

Table 3.2.P.2-1. BNT162b2 Drug Product Quality Target Product Profile and Quality Attributes

Product Element	Product Quality and Performance Characteristics	Quality Attributes
Efficacy		
Product Type	Vaccine based on SARS-CoV-2 S glycoprotein antigens encoded in RNA	Identity of Encoded RNA Sequence In Vitro Expression RNA Integrity 5'-Cap Poly(A) Tail
Indication	Prevention of coronavirus disease 2019 (COVID-19), which is caused by the virus SARS-CoV-2, in individuals aged greater than 16 years old	
Dosage Form	Suspension for Intramuscular Injection Concentrate for solution for injection Injection, Lipid Complex Concentrate Dispersion for Dilution for Injection Concentrate for dispersion for injection	Appearance pH Lipid Identities LNP Size LNP Polydispersity RNA encapsulation RNA Integrity In Vitro Expression
Drug Product Shelf Life	Minimum of (b) (4) at -90 - -60 °C Including up to two weeks at -20 °C and Up to 1 month at 2 – 8 °C	
Formulation, Ingredients (Drug Product)	0.5 mg/mL BNT162b2 RNA formulated in lipid nanoparticles comprising 7.17 mg/mL ALC-0315, 0.89 mg/mL ALC-0159, 1.56 mg/mL DSPC, and 3.1 mg/mL cholesterol in a phosphate buffer comprising 1.08 mg/mL dibasic sodium phosphate dihydrate, 0.15 mg/mL monobasic potassium phosphate, with 103 mg/mL sucrose, 6 mg/mL sodium chloride and 0.15 mg/mL potassium chloride To be diluted with sterile 0.9% sodium chloride solution, Inj. prior to use.	ALC-0315 Content ALC-0159 Content DSPC Content Cholesterol Content
Dosage Strength	30 µg of RNA per 0.3 mL of diluted dosing solution; 30 µg per dose, 6 doses per vial	RNA Content Vial Content (Volume)
Safety		
Primary Package	Type I borosilicate glass vial with a bromobutyl stopper and an aluminum seal with flip-off cap	Appearance (Visible Particulates) Subvisible Particles Bacterial Endotoxins Sterility Container Closure Integrity
Drug Product Quality Requirements	Meets pharmacopoeial requirements for parenteral dosage form as well as product-specific requirements	
Type	Preservative-free, multi-dose vial	
Size	2 mL glass vial, 6 doses per vial	
Tolerability and Clinical Relevance		
Compatibility with Dosing Components	Diluted drug is stable for duration of dosage preparation and administration	Appearance pH Osmolarity RNA Integrity RNA Content In Vitro Expression Container Closure Integrity Vial Content (Volume)
Dosing Tolerability	Acceptable (local) toleration on intramuscular injection administration	
Compatibility with Co-administered Drugs	Not planned for co-administration	

Abbreviations: LNP = lipid nanoparticle; ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine

The 3.2.P.2 Pharmaceutical Development sections describe how the BNT162b2 drug product formulation, presentation, and manufacturing process were developed to ensure the drug product meets the requirements of the QTPP. CQAs are linked to the product attributes of the QTPP, bridging the QTPP to the control strategy. Because the drug substance is the source of the active component of the drug product, some of the QAs of the drug product are delivered in the drug substance process. The drug product control strategy, presented in Section 3.2.P.2.3 Control Strategy, is built on the assessment of CQAs for drug substance and drug product and considers how they are controlled in both the drug substance and drug product processes.

[1] WHO Target Product Profiles for COVID-19 Vaccines, Version 3 - 29 April 2020 available at https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true