EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/CHMP/94082/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMEA/H/C/005735/II/0109/G

Invented name: COMIRNATY

International non-proprietary name: tozinameran

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

This application is in the area of: Quality

eCTD sequences related to the procedure: 0291

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	09 Feb 2022	09 Feb 2022
☐	CHMP Rapporteur Assessment Report	23 Feb 2022	23 Feb 2022
☐	CHMP members comments	28 Feb 2022	28 Feb 2022
☐	Updated CHMP Rapporteur Assessment Report	03 Mar 2022	N/A
☐	Start of written procedure	08 Mar 2022	08 Mar 2022
☒	Opinion	10 Mar 2022	10 Mar 2022

Procedure resources	
Rapporteur:	Filip Josephson
Contact person Rapporteur	[redacted]
Assessor Rapporteur	
EMA Product Lead	
Procedure Assistant	

Declarations

This application includes an Active Substance Master File (ASMF):

☐Yes ☒ No

☒The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, including in the Product Information, if any, unless there are previous contracts and/or agreements with the third party(ies).

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 31 January 2022 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	Type IB	None
B.II.b.2.b	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	Type II	None
B.II.b.2.b	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	Type II	None

Grouped variation:

Type II, B.II.b.2.b, To add [redacted] as an alternative site responsible for batch control/testing for Composition and Strength, Identity, Purity, Endotoxin of the biological finished product COMIRNATY 0.5 mg/ml Concentrate for dispersion for injection (EU/1/20/1528/001).

Type II, B.II.b.2.b, To add [redacted] as an alternative site responsible for batch control/testing for Purity of the biological finished product COMIRNATY 0.5 mg/ml Concentrate for dispersion for injection (EU/1/20/1528/001).

Type IB, B.II.d.2.a, Minor change to the High Performance Liquid Chromatography - Electronic Light Scattering Detection (HPLC-ELSD) test procedure for testing of lipids identity and content in the finished product to tighten the concentration ranges used for the calibration standard of ALC-0315 [redacted] ALC-0159 [redacted] cholesterol [redacted] and DSPC [redacted]

Editorial change:

The applicant takes the opportunity to provide the full validation reports and transfer reports, respectively, for the dynamic light scattering, fluorescence assay and capillary gel electrophoresis testing methods for the other testing sites at which these tests are carried out. In addition, the applicant is also taking the opportunity to delete 3.2.S.4.3 Overview (sequence 0049) and 3.2.P.5.3 Overview (sequence 0053) from the eCTD in line with deletions done for 3.2.S.4.2 Overview and 3.2.P.5.2 Overview as those sections are containing duplicated information.

The requested group of variations proposed no amendments to the Product Information.

GMP inspections

Not applicable.

Active substance master file

Not applicable.

2. Overall conclusion and impact on the benefit/risk balance

This is a grouped Type II variation to modify the HPLC-ELSD analytical procedure for testing of lipids identity and lipids content at mibe and Allergopharma, the introduction of Allergopharma as drug product release and stability testing site and introduction of BioNTech Marburg as a release and stability testing site for RNA integrity by capillary gel electrophoresis (purity). Both sites are authorised to perform these QC testing activities, and GMP compliance is confirmed.

In conclusion, the provided documentation included in this submission is found acceptable and no issues are raised. This grouped Type II variation for Comirnaty EMEA/H/C/005735/II/0109/G is recommended for approval. The benefit-risk balance of COMIRNATY, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	Type IB	None
B.II.b.2.b	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	Type II	None
B.II.b.2.b	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol	Type II	None

	method		

☒is recommended for approval.

Amendments to the marketing authorisation

The group of variations leads to no amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Not applicable

The information after this line is considered commercially confidential and may not be disclosed to third parties in accordance with the 'HMA/EMA guidance on the identification of commercially confidential information and personal data'.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The Applicant is submitting a grouped variation to support:

-The change of the HPLC-ELSD analytical procedure for testing of lipids identity and lipids content at mibe and Allergopharma:

- A Type IB (B.II.d.2.a) Change in the test procedure for the finished product. Minor changes to an approved test procedure (condition 4 not met).

-Introduction of Allergopharma as drug product release and stability testing site:

- A Type II (B.II.b.2.b) Replacement of addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed on the site is a biological/immunological method.

-Introduction of BioNTech Marburg as a release and stability testing site for RNA integrity by capillary gel electrophoresis (purity):

- A Type II (B.II.b.2.b) Replacement of addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed on the site is a biological/immunological method.

The applicant wants to take the opportunity to provide the full validation reports and transfer reports, respectively, for the dynamic light scattering, fluorescence assay and capillary gel electrophoresis testing methods for the other testing sites at which these tests are carried out.

Assessor´s comments

The applicant has provided an acceptable background and overview to this grouped Type II variation to modify the HPLC-ELSD analytical procedure for testing of lipids identity and lipids content at mibe and Allergopharma, the introduction of Allergopharma as drug product release and stability testing site and introduction of BioNTech Marburg as a release and stability testing site for RNA integrity by capillary gel electrophoresis (purity).

A present and proposed table has been provided in module 1.

6. Quality aspects

3.2.S.4.3 Validation of Analytical Procedures – Capillary Gel Electrophoresis

CAPILLARY GEL ELECTROPHORESIS (CGE)

Overview

The capillary gel electrophoresis analytical procedure for the determination of RNA integrity has been validated for BNT162b2 drug substance (DS) and drug product (DP) in conformance with ICH Q2(R1) guidelines.

This section documents the testing, experimental design, method evaluation, acceptance criteria, and results for the validation of the analytical procedure. The type of validation, involved sites and reference to the validation reports are provided in Table 3.2.S.4.3-1.

Table 3.2.S.4.3-1. BNT162b2 Drug Substance and Drug Product Method Validation and Transfer Reports

Validation/Verification or Transfer	Site(s)	Report
Validation	Pfizer ARD	VAL100136603: Report for the Validation of the Method TM100010392: RNA integrity of mRNA drug substance and LNP-mRNA drug product samples by fragment analyzer (CGE)
Method transfer	PGS Andover	RPT-124539: Method Transfer Waiver Report for the Determination of RNA Integrity by Fragment Analyzer in Pfizer Global Supply Quality Control Analytical, Andover, MA
Method Transfer	PGS Puurs	INX100458163: Analytical Method Transfer Exercise (AMTE) Report for TM100010392 v5.0 Fragment Analyzer to test LNP-mRNA Drug Product from ARD to PGS Puurs, Belgium
Validation	BioNTech Mainz	MVR-20-0018: Determination of RNA integrity in DS samples (BNT162/CorVac)
		MVR-21-0004: Determination of RNA integrity in DP samples (BNT162/CorVac)
Validation	BioNTech IMFS	VAL-3022-VB-01: RNA integrity (CorVac DS/DP)
Validation	mibe	V-Q-125-01: RNA Integrity of mRNA-LNP vaccine BNT162b2 by Fragment Analyzer (capillary electrophoresis)
Method Transfer	Allergopharma	VAL-M-094_TB01_V01: Capillary Gel Electrophoresis for the Determination of the Purity of RNA
Validation	BioNTech Marburg	MVR-580946: Determination of mRNA Integrity through Fragment analysis of BNT162b2 DP Tris/ Sucrose Formulation and BNT162b2 DP PBS/ Sucrose Formulation

Abbreviations: ARD = Analytical Research & Development; PGS = Pfizer Global Supply

Assessor´s comments

Section S.4.3 has been updated with method validation and method transfer reports for CGE, respectively, from the different testing sites and the report from Allergopharma and BioNTech Marburg for the drug product.

This update of section S.4.3 is found acceptable.

3.2.P.3.1 Manufacturer

Table 3.2.P.3.1-1. Sites and Responsibilities for BNT162b2 Drug Product Manufacture

Site	Responsibility
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium	LNP production and bulk drug product formulation Fill and finish Primary packaging Secondary packaging Release and stability testing (Composition and Strength, Identity, Purity, Endotoxin, Sterility, including rapid sterility test, Container Closure Integrity) Batch release by Qualified Person in EEA [European Economic Area][a]
BioNTech Manufacturing Marburg GmbH Emil-von-Behring-Straße 76 35401 Marburg Germany	LNP production and bulk drug product formulation Release and stability testing (Composition and Strength, Identity, Purity, Endotoxin)
Polymun Scientific Immunbiologische Forschung GmbH Donaustraße 99 3400 Klosterneuburg Austria	LNP production and bulk drug product formulation
Allergopharma GmbH & Co. KG Hermann-Körner-Straße 52[a] 21465 Reinbek Germany	LNP production and bulk drug product formulation Release and stability testing (Composition and Strength, Identity, Purity, Endotoxin)
mibe GmbH Arzneimittel Münchener Straße 15 06796 Brehna Germany	LNP production and bulk drug product formulation Fill and finish Primary packaging Secondary packaging Release and stability testing (Composition and Strength, Purity, Identity, Endotoxin, Sterility, Container Closure Integrity)
Baxter Oncology GmbH Kantstraße 2 33790 Halle/Westfalen Germany	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Extractable Volume, Endotoxin, Sterility, Container Closure Integrity)
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein Switzerland	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Extractable Volume, Endotoxin, Sterility)

Table 3.2.P.3.1-1. Sites and Responsibilities for BNT162b2 Drug Product Manufacture

Site	Responsibility
Delpharm Saint Remy Rue de l'Isle 28380 Saint Remy sur Avre France	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Extractable Volume, Endotoxin, Sterility)
Sanofi-Aventis Deutschland GmbH – Bereich Handelsprodukte Industriepark Hoechst-Brueningstrasse 50 H500, H590, H600, H750, H785, H790 65926 Frankfurt am Main Germany	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Extractable Volume, Sterility, Container Closure Integrity)
Siegfried Hameln GmbH Langes Feld 13 31789 Hameln Germany	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible Particles, Vial Content, Sterility, Container Closure Integrity)
Patheon Italia S.p.A. Viale G.B. Stucchi, 110 20900 – Monza (MB) Italy	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Vial Content, Sterility, Bacterial Endotoxin)
Catalent Agnani S.R.L. Località Fontana del Ceraso SNC Strada Provinciale 12 Casilina, N. 41 03012 Anagni FR Italy	Fill and finish Primary packaging Secondary packaging Release testing (Appearance, pH, Osmolality, Visible and Subvisible Particles, Vial Content, Endotoxin, Sterility)
BioNTech IMFS GmbH Vollmersbachstraße 66 55743 Idar-Oberstein Germany	Release and stability testing (Composition and Strength, Identity, Potency, Purity)
BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany	Release and Stability Testing (Identity, Purity)
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC [b] 1 Burtt Road Andover, MA 01810 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Container Closure Integrity)
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Container Closure Integrity)
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22	Release and stability testing (Identity, Composition, Potency)

Table 3.2.P.3.1-1. Sites and Responsibilities for BNT162b2 Drug Product Manufacture

Site	Responsibility
Ireland	
Hospira Zagreb Ltd.[c] Prudnička cesta 60 10291 Prigorje Brdovečko Croatia	Release testing (Sterility)
SGS Lab Simon SA Vieux Chemin du Poète 10 Wavre, 1301 Belgium	Release testing (Sterility)
Labor LS SE & Co.KG Mangelsfeld 4, 5, 6 97708 Bad Bocklet-Großenbrach, Germany	Release testing (Sterility)
Eurofins Pharma Quality Control 9 Avenue de Laponie ZI de Courtaboeuf 91940 Les Ulis France	Stability testing (Appearance, Visible Particles, pH, Container Closure Integrity)
Eurofins Pharma Quality Control SAS 16 rue Clément Ader 68127 Sainte Croix en Plaine France	Release and stability testing (Subvisible particles, Endotoxin, Sterility)
BioNTech Manufacturing GmbH Kupferbergterrasse 17-19 55116 Mainz Germany	Batch release by Qualified Person in EEA [European Economic Area]

a. Batch release of commercial lots utilizing drug substance from Wyeth (Pfizer) site in Andover, MA, US only.
b. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD.
c. Hospira is a wholly owned subsidiary of Pfizer Inc.
d. The GMP certificate and manufacturing license list additional sites. Operations for BNT162b2 drug product are carried out in building 10, Hermann-Körner-Straße 54.

Assessor´s comments

Section 3.2.P.3.1 has been updated with addition of Allergopharma as release and stability testing site and BioNTech Marburg as purity testing site.

This is found acceptable.

3.2.P.3.5 Process Validation and or Evaluation - Verification of In-Process Test Methods (Allergopharma)

Assessor´s comments

Section 3.2.P.3.5 has been updated to delete information on verification of analytical procedures used for some in-process tests.

The proposed update of section 3.2.P.3.5 is found acceptable.

3.2.P.5.1 Specification

Table 3.2.P.5.1-1. BNT162b2 Drug Product Specifications

Quality Attribute	Analytical Procedure[a]	Procedure Number(s)	Acceptance Criteria
Composition and Strength			
Appearance	Appearance (Visual)	TM100010539 [g] TM9002A [j] SOP-10173 [i] A-Q-082 [n] 10032.01 [p] 042I01VIAL [q] FRA-A-MET-004054 [r] 1PV03161 [s] 21ACE213R [t] ACHIM201 [x] P6-0258 [w]	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles)	Ph Eur. 2.9.20, USP <790>, JP 6.06	May contain white to off-white opaque, amorphous particles
Subvisible Particles	Subvisible Particulate Matter *(USP <787>, light obscuration method)*	TM100010541 [g] SOP-13114 [i] PV-Q-1279 [n] QK TM 47872e [o] 37301.01 [p] FRA-A-MET-004070 [r] 042I01VIAL [q] EB21AA1543 [u] ARIC608 [v] P6-0258 [w]	[redacted]
pH	Potentiometry	Ph. Eur. 2.2.3, USP <791>	[redacted]
Osmolality	Osmometry[b][c] *(USP <785>)*	TM100010540 [g] TM8209A [j] SOP 7040133 [i] QK TM 47872e [o] 13711.01 [p] 042I01VIAL [q] 1PV03146 [s] FRA-A-MET-004057 [r] ARIC612 [v] P6-0258 [w] PM-6.255 [x]	[redacted]
LNP Size	Dynamic Light Scattering (DLS)	TM100010649 [g] PV-Q-1270 [n] SOP-10021 [i] TM9119A [j] PAN-1288-K [m] PM-6.257 [x]	[redacted]

Table 3.2.P.5.1-1. BNT162b2 Drug Product Specifications

Quality Attribute	Analytical Procedure[a]	Procedure Number(s)	Acceptance Criteria
LNP Polydispersity	Dynamic Light Scattering (DLS)	TM100010649 [g] PV-Q-1270 [n] SOP-10021 [i] TM9119A [j] PAN-1288-K [m] PM-6.257 [x]	[redacted]
RNA Encapsulation	Fluorescence assay	TM100011182 [g] PV-Q-1272 [n] SOP-10013 [i] TM9130A [j] PAN-1331-K [m] PM-6.259 [x]	[redacted]
RNA content	Fluorescence assay	TM100011182 [g] PV-Q-1272 [n] SOP-10013 [i] TM9130A [j] PAN-1331-K [m] PM-6.259 [x]	[redacted]
ALC-0315 content	HPLC-CAD HPLC-ELSD[e]	TM100010322 [g] SOP-10186 [i] PV-Q-1269 [n] TM8891A [j] PAN-1287-K [m] PM-6.256 [x]	[redacted]
ALC-0159 content			
DSPC content			
Cholesterol content			
Vial content (volume)	Container content[c]	TM100011129 [g] TM9125A [j] QK TM 47872e [o] 12301.01 [p] 042I01VIAL [q] FRA-A-MET-004056 [r] 1PV03155 [s] ARIC619 [v] P6-0258 [w]	
Identity			
Lipid identities	HPLC-CAD[e] HPLC-ELSD[e]	TM100010322 [g] PV-Q-1269 [n] SOP-10186 [i] TM8891A [j] PAN-1287-K [m] PM-6.256 [x]	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR[e]	TM100010407 [g] SOP-111956 [i] PAN-1235-K [m] TM-072-038 [k] LAB-37698 [h] PV-QM-038 [n]	Identity confirmed
Potency			
In Vitro Expression	Cell-based flow cytometry	TM100010380 [g] SOP-113198 [i] PAN-1215-K [m] PAN-1216-K [m] LAB-38621 [h]	[redacted]

Table 3.2.P.5.1-1. BNT162b2 Drug Product Specifications

Quality Attribute	Analytical Procedure[a]	Procedure Number(s)	Acceptance Criteria
Purity			
RNA Integrity	Capillary Gel Electrophoresis	TM100010392 [g] PAN-1234-K [m] PV-Q-1271 [o] TM9089A [j] TM-072-039 [k] PM-6.258 [s] SOP-522160 [t]	[redacted]
Adventitious Agents			
Bacterial Endotoxin	Endotoxin (LAL)	Ph. Eur. 2.6.14, USP <85>, JP 4.01	[redacted]
Sterility	Sterility	Ph. Eur. 2.6.1, USP <71>, JP 4.06 LAB-37663 [f,i]	No Growth Detected
Container Closure Integrity	Dye incursion[d]	TM100010635 [g] PV-Q-1280 [o] QKM TM 47847e [u] FRA-A-MET-004066 [v] 1PV03160 [x] 21ACE329R [l] TM8999A [j]	Pass

a. All assays performed on stability unless otherwise noted.
b. In accordance with Ph. Eur. 2.2.35, with minor difference in instrument calibration
c. Assay not performed on stability.
d. Tested at time 0 for stability batches only
e. Test used at mibe instead of HPLC-CAD
f. Rapid Sterility Test, which is performed in accordance with the compendia with the exception of incubation duration and detection method (see Section 3.2.P.5.2 Sterility), may also be used.
g. Analytical procedure at Pfizer, Analytical Research and Development
h. Analytical procedure at Pfizer Global Supply, Andover, MA, USA
i. Analytical procedure at Pfizer Global Supply, Grange Castle, Ireland
j. Analytical procedure at Pfizer Global Supply, Puurs, Belgium
k. Analytical procedure at BioNTech, Mainz
l. Analytical procedure at BioNTech, Marburg
m. Analytical procedure at BioNTech IMFS
n. Analytical procedure at mibe (for pharmacopoeial standard methods no internal procedure numbers are available)
o. Analytical procedure at Baxter (for appearance (visual) no test method is in place)
p. Analytical procedure at Novartis
q. Analytical procedure at Delpharm
r. Analytical procedure at Sanofi
s. Analytical procedure at Siegfried
t. Analytical procedure at Eurofins, Les Ulis
u. Analytical procedure at Eurofins, Sainte Croix en Plaine
v. Analytical procedure at Catalent
w. Analytical procedure at Patheon Monza
x. Analytical procedure at Allergopharma

Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; ELSD = evaporative light scattering detector; RT-PCR = reverse transcription polymerase chain reaction; FACS = fluorescence activated cell sorter; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amebocyte lysate; EU = endotoxin unit

Assessor´s comments

Section 3.2.P.5.1 has been updated with method reference numbers for Allergopharma and BioNTech Marburg.

This is found acceptable.

3.2.P.5.2 Analytical Procedures – HPLC-ELSD

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY – ELECTRONIC LIGHT SCATTERING DETECTION

Principle and Scope

The purpose of this reverse phase high performance liquid chromatography (RP-HPLC) analytical procedure is to confirm the identity of BNT162b2 drug product (DP) and to quantify the ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide), ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl) bis(2-hexyldecanoate), cholesterol and DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) lipids in BNT162b2 DP.

The chromatography technique separates bound molecules based on hydrophobicity using a column containing a non-polar stationary phase and polar solvents. The separated molecules are detected simultaneously by electronic light scattering (ELS) and quantitated using a multipoint standard curve.

3.2.P.5.2.5. Standard, Control Solutions and Blank Preparation

3.2.P.5.2.5.1. Mixed Lipid Stock Solution

The lipids ALC-0315, ALC-0159, cholesterol and DSPC are prepared in methanol to a final concentration of [redacted], respectively.

3.2.P.5.2.5.2. Mixed Lipid Working Standard

Five calibration standards are prepared by diluting the mixed lipid stock solution in methanol to the following ranges:

- ALC-0315: [redacted]
- ALC-0159: [redacted]
- Cholesterol: [redacted]
- DSPC: [redacted]

3.2.P.5.2.5.3. Mixed Lipid Assay Control

The mixed lipid assay control is prepared for analysis by diluting the mixed lipid stock solution [redacted] in methanol.

3.2.P.5.2.5.4. Blank

Methanol is analyzed as a blank.

Assessor´s comments

This section 3.2.P.5.3 has been updated for the amended analytical procedures for the determination of lipids identity and lipids content (HPLC-ELSD).

The analytical procedure for determination of lipids content by HPLC-ELSD has been slightly changed by tightening the concentration ranges used for the calibration standards of each lipid. As described below, the analytical procedure has been revalidated.

This is found acceptable.

3.2.P.5.3 Validation of Analytical Procedures – HPLC-ELSD

The HPLC-ELSD analytical procedure is validated as a quantitative procedure for the determination of lipid identity and content in BNT162b2 drug product (DP) and includes assessments of precision (repeatability-system, repeatability method and intermediate precision), accuracy, specificity, linearity, range and robustness.

This section documents the testing, experimental design, method evaluation, acceptance criteria, and results for the validation of the analytical procedure. The results of the validation of the analytical procedure for each of the sites, where this procedure is conducted, are provided in validation reports listed in Table 3.2.P.5.3-1.

Table 3.2.P.5.3-1. BNT162b Drug Product Method Validation Reports for HPLC-ELSD

Validation or Transfer	Site(s)	Report
Validation of the procedure	mibe	V-Q-169-01_Lipid determination (ELSD)_VR: Identification and Quantification of ALC-0159 (PEG A), Cholesterol, DSPC and ALC-0315 in LNP vaccine BNT162b2 by RP-HPLC with ELSD detection.
Validation of the procedure	Allergopharma	VAL-M-092_VB01_V01: Analytical procedure PM-6.256_V02 "Identity and Content of ALC-0159 (PEG A), Cholesterol, DSPC and ALC-0315 in LNP-mRNA Vac-cine BNT162b2 (Comirnaty®) by means of RP-HPLC and ELSD Detection.

Abbreviations: 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; LNP = lipid nanoparticle; ELSD = evaporative light scattering detection

Assessor´s comments

This section has been updated with reference to the updated method validation reports from mibe and Allergopharma for the lipids identity and lipids content by HPLC-ELSD.

The analytical procedure for determination of lipids content by HPLC-ELSD has been changed by tightening the concentration ranges used for the calibration standards of each lipid. The re-validation of the analytical procedure has been conducted and the results presented in this section. The validation confirms that the predefined acceptance criteria were met and the performance of the HPLC-ELSD is confirmed at mibe and Allergopharma.

This is found acceptable.

3.2.P.5.3 Validation of Analytical Procedures – Endotoxin

3.2.P.5.3.10. Verification of Bacterial Endotoxin - Allergopharma

Suitability of the determination of bacterial endotoxins in LNP bulk drug product on the basis of the chromogenic-kinetic method is validated at Allergopharma. The results of the verification of the endotoxin test for three bulk drug product batches are presented in Table 3.2.P.5.3-24, Table 3.2.P.5.3-48 and Table 3.2.P.5.3-49.

Table 3.2.P.5.3-47. Verification of Endotoxin Test for Batch 210101

Test solution	Reference value (EU/mL)	Endotoxin content (EU/mL)	Hard Spike Recovery (%)	CV Sample (%)	Spike recovery (%)	CV Spike (%)	pH
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							

Abbreviations: EU = endotoxin units; CV = coefficient of variation

Table 3.2.P.5.3-48. Verification of Endotoxin Test for Batch 210207

Test solution	Reference value (EU/mL)	Endotoxin content (EU/mL)	Hard Spike Recovery (%)	CV Sample (%)	Spike recovery (%)	CV Spike (%)	pH
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K2, rerun							
Control K3							
Control K3, rerun							

Table 3.2.P.5.3-48. Verification of Endotoxin Test for Batch 210207

Test solution	Reference value (EU/mL)	Endotoxin content (EU/mL)	Hard Spike Recovery (%)	CV Sample (%)	Spike recovery (%)	CV Spike (%)	pH
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
Sample (2nd measurement)							
Control K1 (2nd measurement)							
Control K2 (2nd measurement)							
Control K3 (2nd measurement)							
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
[redacted] EU/mL cartridges on [redacted]							
Sample	[redacted]						
Control K1							
Control K2							
Control K3							
Sample (2nd measurement)							
Control K1 (2nd measurement)							
Control K2 (2nd measurement)							
Control K3 (2nd measurement)							

Abbreviations: EU = endotoxin units; CV = coefficient of variation; na = not applicable

Assessor´s comments

This section has been updated with the method verification data for endotoxin from Allergopharma, these data has been moved from Section 3.2.P.3.5.

This is found acceptable.

3.2.P.5.3 Validation of Analytical Procedures – Fluorescence Assay

Overview

The fluorescence analytical procedure for the determination of total RNA concentration and percent encapsulation in BNT162b2 DP has been validated in conformance with ICH Q2(R1) guidelines.

This section documents the testing, experimental design, method evaluation, acceptance criteria, and results for the validation of the up-dated analytical procedure. Reference to the validation reports, type of validation and the involved sites are provided in Table 3.2.P.5.3-1.

Table 3.2.P.5.3-1. BNT162b2 Drug Product Method Validation and Transfer Reports

Validation/Verification or Transfer	Site(s)	Report
Validation	Pfizer ARD	VAL100140104: Report for Validation of Test Method TM100011182: Quantification of Total and Percent Encapsulated RNA in PF-07302048 (Drug Product) by RiboGreen Fluorescence
Method Transfer	Pfizer Global Supply, Puurs, Belgium (PGS-Puurs)	INX100457529: Analytical Method Transfer Exercise (AMTE) Report for the Transfer of TM100011182 (RiboGreen) from Pfizer Biotherapeutics Pharmaceutical Sciences Analytical Research & Development to Pfizer Global Supply (PGS) Kalamazoo and PGS Puurs

Abbreviations: ARD = Analytical Research & Development

Assessor´s comments

This section has been updated with reference to the method validation and method transfer reports for the fluorescence assay, from the different testing sites.

This is found acceptable.

3.2.P.5.3 Validation of Analytical Procedures – Dynamic Light Scattering

Overview

The DLS analytical procedure is validated as a quantitative procedure for the determination lipid nanoparticle (LNP) size and polydispersity in BNT162b2 drug product (DP) in conformance with ICH Q2(R1) guidelines.

This section documents the testing, experimental design, method evaluation, and results for the of the validation of the analytical procedure. The successful completion of the procedures defined in this section provides assurance that the analytical procedure is suitable for its intended use at each site. Reference to the validation reports, type of validation and the involved sites are provided in Table 3.2.P.5.3-1.

Table 3.2.P.5.3-1. BNT162b2 Drug Product Method Validation and Transfer Reports

Validation/Verification or Transfer	Site(s)	Report
Co-Validation	Pfizer ARD and PGS Kalamazoo	VAL100137959: Report for the Validation of Method TM100010649 for Testing Drug Product Samples: Analytical Method for Size and Polydispersity Index Measurement in mRNA LNP Samples by Dynamic Light Scattering (DLS) Malvern Zetasizer.
Method Transfer	PGS Puurs	INX100458821: Analytical Method Transfer Exercise (AMTE) Report for TM100010649 (DLS) from Pfizer Biotherapeutics Pharmaceutical Sciences Analytical Research & Development to Pfizer Global Supply (PGS) Puurs
Validation	BioNTech Marburg	ANMV_VALR_00562170: LNP size and Polydispersity Index Measurement of BNT 162b2/CorVac IPC6 using Dynamic Light Scattering
Validation	BioNTech IMFS	VAL-3123-VB-01: LNP size and PDI measurement in BNT162b2/CorVac by Dynamic Light Scattering
Validation	mibe	DER-BNT162b2-DLS: Determination of particle size and polydispersity index of LNP vaccine DER-BNT162b2 by Dynamic Light Scattering
Method Transfer	Allergopharma	VAL-M-093-TB01: Determination of particle size and polydispersity index (PDI) of the LNP-mRNA vaccine using Dynamic Light Scattering (DLS)

Abbreviations: ARD = Analytical Research & Development; PGS = Pfizer Global Supply; LNP = lipid nano particle; PDI = polydispersity index

Assessor´s comments

This section has been updated with reference to the method validation and method transfer reports for the dynamic light scattering, from the different testing sites.

This is found acceptable.

Assessor´s concluding comments

This is a grouped Type II variation to modify the HPLC-ELSD analytical procedure for testing of lipids identity and lipids content at mibe and Allergopharma, the introduction of Allergopharma as drug product release and stability testing site and introduction of BioNTech Marburg as a release and stability testing site for RNA integrity by capillary gel electrophoresis (purity).

In conclusion, the provided documentation included in this submission is found acceptable and no issues are raised. This grouped Type II variation for Comirnaty EMEA/H/C/005735/II/0109/G is recommended for approval.

Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion or 5 days after the submission by the MAH of the final language translations, when there is a linguistic review. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU