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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005735/II/0183

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Timetable	Date
Start of procedure	03 Jul 2023
CHMP Rapporteur Assessment Report	21 Aug 2023
CHMP members comments	23 Aug 2023
Updated CHMP Rapporteur Assessment Report	25 Aug 2023
Start of written procedure	28 Aug 2023
Opinion	30 Aug 2023

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 03 July 2023 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A

B.I.a.6.a (Type II): Addition of a new strain (Omicron XBB.1.5, raxtozinameran) resulting in four new monovalent presentations:

- Comirnaty Omicron XBB.1.5 (30 micrograms)/dose dispersion for injection
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose dispersion for injection
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose concentrate for dispersion for injection
- Comirnaty Omicron XBB.1.5 (3 micrograms)/dose concentrate for dispersion for injection

The Annex A, the SmPC, the Package Leaflet and Labelling are updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A.

2. Introduction

Pfizer and BioNTech have developed the COMIRNATY vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs).

There are several approved formulations of Comirnaty vaccine:

- PBS/Sucrose drug product, *Comirnaty, 30 micrograms/dose, concentrate for dispersion for injection* which received a conditional approval 21 December 2020 (EMA/H/C/005735)
- Tris/Sucrose drug product, *Comirnaty, 30 micrograms/dose, dispersion for injection*, approved 03 November 2021 (EMA/H/C/005735/X/0044)
- Tris/Sucrose drug product, *Comirnaty, 10 micrograms/dose, concentrate for dispersion for injection*, approved 26 November 2021 (EMA/H/C/005735/X/0077)
- Tris/Sucrose drug product, *Comirnaty Original/Omicron BA.1, (15/15 micrograms)/dose, dispersion for injection*, approved 01 September 2022 (EMA/H/C/005735/II/0140)
- Tris/Sucrose drug product, *Comirnaty Original/Omicron BA.4-5, (15/15 micrograms)/dose, dispersion for injection*, approved 12 September 2022 (EMA/H/C/005735/II/0143)

- Tris/Sucrose drug product, *Comirnaty*, 3 micrograms/dose, concentrate for dispersion for injection, approved 20 October 2022 (EMA/H/C/005735/X/0138)
- Tris/Sucrose drug product, *Comirnaty Original/Omicron BA.4-5*, (5/5 micrograms)/dose, concentrate for dispersion for injection, approved 10 November 2022 (EMA/H/C/005735/X/0147)
- Tris/Sucrose drug product, *Comirnaty Original/Omicron BA.4-5*, (1.5/1.5 micrograms)/dose, concentrate for dispersion for injection, approved 08 August 2023 (EMA/H/C/005735/X/176)
- Tris/Sucrose drug product, *Comirnaty Original/Omicron BA.4-5*, (5/5 micrograms)/dose, dispersion for injection, approved 08 August 2023 (EMA/H/C/005735/X/180)

The emergence of SARS-CoV-2 variants with multiple mutations have led Pfizer and BioNTech to develop variant vaccine constructs. To assist in the continued management of COVID-19, and taking into account the [ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants](#), a new BNT162b2 Omicron (XBB.1.5) monovalent variant vaccine is the subject of this variation.

The variant vaccine is manufactured at a subset of previously authorized Pfizer and BioNTech sites. The finished product is formulated at 0.1 mg/mL RNA in Tris buffer, sucrose, pH 7.4 or 0.033 mg/mL RNA in Tris buffer, sucrose, pH 7.4. The associated presentations are presented as multi-dose vials (MDV) and single dose vials (SDV) as presented in Table 2.3-1.

Table 2.3-1. Omicron (XBB.1.5) Variant Vaccine Presentations

Formulation	Total RNA Dose	Injection Volume (mL)	0.9% NaCl Dilution Volume (mL)	Fill Volume (mL)	# Doses per Vial
0.1 mg/mL RNA in [REDACTED] mM Tris buffer, [REDACTED] mM sucrose, pH 7.4	30 µg	0.3	N/A	2.25	6
	30 µg	0.3	N/A	0.48	1
	10 µg	0.2	1.3	1.3	10
	3 µg	0.2	2.2	0.4	10
0.033 mg/mL RNA in [REDACTED] mM Tris buffer, [REDACTED] mM sucrose, pH 7.4	10 µg	0.3	N/A	2.25	6
	10 µg	0.3	N/A	0.48	1

To demonstrate product quality, a batch of active substance and lots of finished product are manufactured at one approved manufacturing facility on approved manufacturing line(s) using the already validated manufacturing processes (linear DNA template, active substance and finished product). The active substance and finished product are tested according to the approved acceptance criteria and placed on stability.

There are no changes to the lipid nano particle (LNP) formation and stabilization, bulk drug product (intermediate) formulation, or authorized bulk drug product, thawing and pooling of the drug product intermediate, drug product (intermediate) filling, or packaging processes, including facilities, filling lines and components for the periodic updated vaccine when compared to the Original vaccines. All drug product process parameters, in-process tests and critical quality attributes will stay unchanged. A strategy is utilized to support the 30 µg (0.1 mg/mL) MDV and 10 µg (0.033 mg/mL) MDV presentations.

Table 2.3-2 represents a comparison between Omicron (XBB.1.5) variant vaccine in relation to the Original monovalent vaccine and Table 2.3-3 present the manufacturing and stability strategy.

Table 2.3-2. Comparison of [Omicron (XBB.1.5) Variant] Vaccine to Original Vaccine

	[Omicron (XBB.1.5)]
Manufacturing process	
MCB	Comparable to Original
Linear DNA Template	Comparable to Original
Drug Substance	No change from Original
Drug Product	No change from Original
Analytical Procedures	
MCB	No change from Original
Linear DNA Template	Comparable to Original
Drug Substance	Addition of alternate Identity method (ddPCR) and construct specific modifications to Identity by RT-PCR method
Drug Product	Addition of alternate Identity method (ddPCR) and construct specific modifications to Identity by RT-PCR and IVE methods

Abbreviations: ddPCR = Droplet digital polymerase chain reaction; IVE = In Vitro Expression; RT-PCR = reverse transcription polymerase chain reaction; RT-PCR = reverse transcription - polymerase chain reaction; ID = Identity

Table 2.3-3. Omicron (XBB.1.5) Confirmatory Batch Manufacturing and Stability Strategy

Drug Product Dose	30 µg		10 µg			3 µg
	MDV	SDV	MDV	MDV	SDV	MDV
Drug Product Presentation						
Drug Product Concentration	0.1 mg/mL		0.1 mg/mL	0.033 mg/mL		0.1 mg/mL
First Commercial Batch to be placed on stability (Y/N) ^a	Y		Y	Y		Y

a. Each presentation will be part of the annual stability protocol, independent of the seasonal variant. A bracketing approach is used to cover both SDV and MDV.

Abbreviations: MDV = Multidose Vial; SDV = Single Dose Vial; N = No; Y = Yes

3. Quality aspects

3.1. Introduction

The finished product is presented as a dispersion for injection or a concentrate for dispersion for injection containing raxtozinameran as active substance, embedded in lipid nanoparticles, in the following presentations:

- Comirnaty Omicron XBB.1.5 (30 micrograms)/dose dispersion for injection (EU/1/20/1528/018-020)
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose dispersion for injection (EU/1/20/1528/023-024)
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose concentrate for dispersion for injection (EU/1/20/1528/021)
- Comirnaty Omicron XBB.1.5 (3 micrograms)/dose concentrate for dispersion for injection (EU/1/20/1528/022)

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

Other ingredients are: ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), Cholesterol, Trometamol, Trometamol hydrochloride, Sucrose, Water for injections.

The product is available as type I clear glass single dose vials (SDV) or multidose vials (MDV) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal, in pack sizes of 10 or 195 vials as defined in SmPC section 6.5.

The 30 microgram/dose dispersion presentation is supplied as SDV or as MDV containing 6 doses, with a grey cap.

The 10 microgram/dose dispersion presentation is supplied as SDV or as MDV containing 6 doses, with a blue cap.

The 10 microgram/dose concentrate presentation is supplied as MDV with an orange cap containing 10 doses after dilution.

The 3 microgram/dose concentrate presentation is supplied as MDV with a maroon cap containing 10 doses after dilution.

3.2. Active substance – Raxtozinameran (XBB.1.5)

3.2.1. General information (CTD module 3.2.S.1)

Section 3.2.S.1 has been updated with information related to the Omicron XBB.1.5 variant. The RNA nucleotide Sequence of the Omicron (XBB.1.5) active substance is included. The information provided is considered adequate and acceptable.

3.2.2. Manufacture (CTD module 3.2.S.2)

3.2.2.1. Manufacturer(s) (CTD section: S.2.1)

All proposed active substance manufacturing and testing sites are already approved in the existing Comirnaty conditional marketing authorisation (EU/1/20/1528/001-017) for the manufacture of the active substances tozinameran (Original), riltozinameran (Omicron BA.1) and famtozinameran (Omicron BA.4-5). The GMP compliance of these sites has been previously confirmed.

3.2.2.2. Description of manufacturing process and process controls (CTD section: S.2.2)

The manufacturing process and process controls are the same as currently approved for the manufacture of tozinameran, riltozinameran and famtozinameran.

3.2.2.3. Control of materials (CTD section: S.2.3)

Manufacture of the BNT162b2 Omicron XBB.1.5 active substance is achieved using in vitro transcription that includes a linear DNA template as a starting material. The linear DNA template is produced via plasmid DNA from transformed Escherichia coli cells. The plasmid, , is designed for the production of Omicron XBB.1.5 variant. This plasmid was generated using a combination of gene synthesis and recombinant DNA technology. The antigen-encoding sequence was generated by gene synthesis and cloned into the vector. The plasmid) used in the manufacture of the original vaccine was generated using the same procedure. The nucleotide differences between Omicron XBB.1.5 and (Original) are all located within the gene encoding the spike sequence.

The plasmid map of Omicron XBB.1.5 was provided.

BNT162b2 Omicron (XBB.1.5) variant vaccine active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA () from transformed Escherichia coli cells. The functional elements of the Omicron XBB.1.5 are sufficiently described in graphic and tabular formats and the sequence is included. The information provided on the source and generation of the Omicron XBB.1.5 plasmid is considered sufficient, as the plasmid used in the manufacture of the original vaccine was generated using the same procedure, included in the original dossier, and as the nucleotide differences between Omicron XBB.1.5 and Original are located only within the gene encoding the spike sequence.

The sites involved in manufacturing, testing and storage of the plasmids are listed.

The master cell bank involved in the plasmid manufacturing process is described. MCB qualification tests are listed and include morphologic and genotypic identity, DNA sequencing, absence of contaminating bacteriophages and viability. Relevant specifications are set and data from the current MCB are provided. Restriction map analysis, plasmid retention and plasmid copy number are included. The approach is endorsed.

The plasmid MCB is enrolled in a cell bank stability program consisting of viability and plasmid retention assays conducted at all stability time points. The strategy is considered adequate.

A single-tier cell banking system consisting of only a MCB is proposed for the plasmid cell bank: As relatively few vials of the plasmid MCB are needed to prepare the desired quantity of XBB.1.5 plasmid and Omicron strain changes are expected in the future, the MCB inventory is expected to last for the lifetime of the product. The approach is acceptable.

Omicron XBB.1.5 plasmid is manufactured by a fed-batch fermentation process initiated from the bacterial master cell bank, identical to the process described in the original dossier.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are quantified routinely. Results from commercial-scale confirmatory batch are provided for the circular and linearized plasmid. All analytical methods used for the control of the linear DNA template obtained from Omicron XBB.1.5 plasmid are identical to the already provided methods used for testing of the DNA template except for the identity by restriction mapping and identity of the transgene region which is tested using a DNA Sanger sequencing method. These methods were updated to include Omicron XBB.1.5-specific reagents and sufficient descriptions and summary of the validation exercises are included.

A shelf life based on the data collected and on-going stability studies that have been initiated for the original circular plasmid DNA and linear DNA template. Stability data are not yet available for the specific Omicron XBB.1.5 variant. However, considering that no changes are included in the

manufacturing process of the DNA template as compared to the original variant, the shelf-life is considered sufficiently supported by the original data.

3.2.2.4. Control of critical steps and intermediates (CTD section: S.2.4)

The control of critical steps and intermediates are the same as currently approved for the manufacture of tozinameran, riltozinameran and famtozinameran.

3.2.2.5. Process validation and/or evaluation (CTD section: S.2.5)

For process validation of the Omicron (XBB.1.5) variant the MAH refers to data on the original version of the active substance. This can be accepted since the manufacturing process is identical to that used for the original variant.

3.2.2.6. Manufacturing process development (CTD section: S.2.6)

Section 3.2.S.2.6 has been updated with a document describing manufacturing process history for the Omicron (XBB.1.5) variant.

The MAH states that since the manufacturing process is identical to that used for the original variant and the constructs are similar, the cause and effect and the FMEA risk assessment apply to both constructs. This is agreed to.

Critical process parameters (CPPs) have been defined and in-process test for monitoring (IPT-M) and for control (IPT-C) are presented for the Omicron (XBB.1.5) active substance manufacturing process. The CPPs, IPT-Cs and IPT-Ms are the same as those defined for the approved variants and the acceptance criteria are in almost all cases the same as for the approved variants. This is found acceptable.

The MAH refers to that the Omicron (XBB.1.5) active substance leverages the platform manufacturing process and control strategy established for BNT162b2, assuring comparable variant drug substance across manufacturing sites. This is found acceptable.

3.2.3. Characterisation (CTD module 3.2.S.3)

The MAH has provided characterisation data for the Omicron (XBB.1.5) variant active substance. The package includes confirmation of primary structure, poly(A)tail, 5'-Cap structure, higher order structure and biological activity. Essentially, the same methods as those used for characterisation of the original variant, Omicron (B.1.1.529) and Omicron (BA.4/BA.5) have been applied. As compared to the characterisation of Omicron (B.1.1.529) and Omicron (BA.4/BA.5), an orthogonal test to characterise primary structure and an orthogonal test to confirm the presence and determine the length of the poly(A) tail is added. Both methods have, however, been used for characterisation of the original variants. The results for primary structure, 5'-Cap structure, poly(A)tail, and higher order structure are found acceptable, sufficiently supporting the expected characteristics of the Omicron (BA.4/BA.5) variant.

Biological activity is confirmed by cell-free in vitro translation and western blot analysis. A band corresponding to the expected protein size was identified. The expressed aglycosylated protein size was confirmed and since the WB result of the original variant is comparable, the biological characterisation is found acceptable.

3.2.4. Control of active substance (CTD module 3.2.S.4)

The active substance specification for Raxtozinameran / Omicron (XBB.1.5) contains tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (ddPCR, RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Poly(A) Tail Length (IP-RP-HPLC), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for Omicron (XBB.1.5) variant active substance is based on the available data and follows the specification established and approved for the original variant and therefore is considered adequate. The acceptance criteria are applicable from batch release to end of shelf-life.

Analytical procedures for (XBB.1.5) Omicron variant active substance release and stability testing are listed and briefly described in the dossier. Most of the analytical procedures are identical to the corresponding commercial BNT162b2 original vaccine procedures, apart from identity testing, for which Omicron XBB.1.5 variant-specific reagents are utilized. Considering that the active substance concentration, formulation process and process control remain unchanged as compared to BNT162b2 original active substance and only a change in nucleotide sequence is differentiating the Omicron (XBB.1.5) variant, the approach is endorsed. The method is sufficiently described, and additional validation exercises have been performed.

The Poly A Tail Length procedure based on IP-RP-HPLC has been slightly revised as compared to the procedure applied for the original variant. This difference is considered minor and the revised procedure is found acceptable.

Batch results presented met the specification acceptance criteria in place at the time of release. The specification and limits for Omicron (XBB.1.5) variant active substance is based on the BNT162b2 original active substance. Although limited data is provided for the Omicron XBB.1.5 variant to support these limits, the strategy is found acceptable considering that only a change in the nucleotide sequence is driving the present variation.

3.2.5. Reference standards of materials (CTD module 3.2.S.5)

The reference standards are the same as currently approved for tozinameran, riltozinameran and famtozinameran.

3.2.6. Container closure system (CTD module 3.2.S.6)

The container closure system is the same as currently approved for tozinameran, riltozinameran and famtozinameran.

3.2.7. Stability (CTD module 3.2.S.7)

The proposed shelf-life for the Omicron (XBB.1.5) active substance is 6 months when stored at the - intended storage condition of $-20 \pm 5^{\circ}\text{C}$ in EVA bags. Thus, the proposed shelf-life and storage conditions are identical to those for the original variant, Omicron (B.1.1.529) and Omicron (BA.4/BA.5). The shelf-life claim is based on primary stability studies conducted on the commercial active substance batches of the original variant and Omicron (BA.4/BA.5) variant.

Stability studies for two Omicron XBB.1.5 batches are on-going. In response to a question raised, the MAH submitted long-term stability data and stability data from accelerated storage conditions for both

batches. All results met the specification acceptance criteria. The MAH commits to update section 3.2.S.7 with updated real-time stability data by the end of Q1 2024. This is found acceptable.

3.3. Finished product (CTD module 3.2.P)

3.3.1. Description and composition of the drug product (CTD module 3.2.P.1)

The BNT162b2 Omicron (XBB.1.5) Variant finished product (herein referred to as Variant), is supplied as a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration.

There are 6 presentations for the Variant finished product providing doses of either 30, 10 or 3 µg of Raxtozinameran per dose in multi-dose vial (MDV) and single-dose vial (SDV) presentations.

Each presentation is formulated in Tris buffer, sucrose, pH 7.4. The presentations differ in RNA concentration (0.1 mg/mL and 0.033 mg/mL), fill volume, and requirement for dilution prior to administration and are summarized in Table P.1-1.

Table P.1-1. Drug Product Presentations

Drug Product Presentation ^a	Drug Product RNA Concentration (mg/mL)	Fill volume (mL)	Dilution with 0.9% sodium chloride (mL)	Injection Volume	Doses per vial
30 µg MDV	0.1	2.25	N/A	0.3	6
30 µg SDV	0.1	0.48	N/A	0.3	1
10 µg MDV	0.033	2.25	N/A	0.3	6
10 µg SDV	0.033	0.48	N/A	0.3	1
10 µg MDV (dilution required)	0.1	1.3	1.3	0.2	10
3 µg MDV (dilution required, 10 dose vial)	0.1	0.4	2.2	0.2	10

a. Dilution with 0.9% sodium chloride is only required for presentations described as "dilution required"
Abbreviations: MDV= multi-dose vial, SDV= single dose vial; N/A = not applicable

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl elastomeric stopper and an aluminium seal with a flip-off plastic cap.

The composition of the finished product, including quality standard, function, concentration and amount per dose for the finished product presentations were provided. The list of excipients are stated in section 3.1 of this report and in SmPC Section 6.1.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply to Ph. Eur. grade. The functional lipids, the structural lipids as well as the Tris buffer and sucrose are all used in the currently approved Tris/sucrose vaccine finished products of Comirnaty.

The container closure system is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl rubber stopper and is the same container closure system as for the already approved Tris/sucrose vaccine drug product of Comirnaty.

The processing aids and active substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered as excipients in the finished product.

3.3.2. Pharmaceutical development (CTD module 3.2.P.2)

The Omicron XBB.1.5 vaccine finished product is a preservative-free, sterile dispersion of lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular administration. The finished product is formulated at 0.1 mg/mL or 0.033 mg/mL total RNA in Tris buffer, sucrose, pH 7.4. There are 6 presentations for the Variant finished product providing doses of either 30, 10 or 3 µg RNA. The ratio of RNA to lipid components is also constant across the presentations.

The variant vaccine finished product is formulated and manufactured in a highly similar way as the original finished product in the Tris/Sucrose formulation. As the overall length of the omicron XBB.1.5 RNA is essentially the same as that of the original vaccine RNA, it is argued by the MAH, that no change in physicochemical properties, processability, or stability is expected for the Omicron XBB.1.5 active substance as compared to the original active substance. Therefore, no change in physicochemical properties, processability, or stability of the finished product is expected for the omicron XBB.1.5 variant vaccine as compared to the original vaccine. This is agreed to.

A new QTPP has been developed and provided for the Omicron XBB.1.5 containing vaccine finished product as a basis for the development and reflects the evolution of the Tris/Sucrose vaccine to address new virus variants. The QTPP was provided and reflects the evolution of the Tris/Sucrose vaccine to address new virus variants.

A development history has been provided. It gives a comparison of the finished product manufacturing processes and release criteria for the original, bivalent (original, omicron BA.4/BA.5) and the omicron XBB.1.5 variant vaccine. The omicron XBB.1.5 variant vaccine finished product will be administered at the same dose as the already approved original and/or bivalent vaccine presentations of Comirnaty. It has been shown that the manufacturing processes for the large scale lots are highly similar between the Tris/Sucrose original vaccine, the bivalent finished product and the XBB.1.5 variant finished product.

Comparability has previously been acceptably demonstrated between clinical and commercial scale original drug product, between various manufacturing sites and between the PBS/sucrose finished product and Tris/sucrose finished product via comprehensive studies including both release testing and extended characterization testing. Comparability has also been established and sufficiently demonstrated between the bivalent vaccine finished products (original and omicron BA.1, original and omicron BA.4/BA.5 strains) to the original finished product based on an evaluation of release testing results against the acceptance criteria in the finished product specification as well as via extended characterization testing.

For the omicron XBB.1.5 variant vaccine, batch analysis data are provided for the batches manufactured to date. All these batches met the acceptance criteria in the respective specifications documents for each presentation and comparability has been established based on an evaluation of these release testing results. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original vaccine finished product and the bivalent vaccine finished products, extensive prior experience is leveraged, and the comparability demonstration found sufficient and agreed to. This is found acceptable.

In conclusion, the information provided in section 3.2.P.2 on Pharmaceutical development for the omicron XBB.1.5 variant vaccine finished product is found sufficient and acceptable.

3.3.3. Manufacture (CTD module 3.2.P.3)

The monovalent XBB.1.5 vaccine is manufactured at some of the existing and approved manufacturing sites used for the original and bivalent Comirnaty Tris/Sucrose vaccine formulations using the same platform process. The GMP compliance of these sites has been previously confirmed.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk drug product formation, sterile filtration and aseptic filling. The manufacturing process is the same as for the current approved vaccines (monovalent Original, bivalent Original/Omicron B.1 and bivalent Original/Omicron BA.4/BA.5) . The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

No process validation is performed for the monovalent XBB.1.5 vaccine. Confirmatory batches are manufactured at the approved manufacturing sites used the validated manufacturing process.

3.3.4. Control of excipients (CTD module 3.2.P.4)

The monovalent XBB.1.5 vaccine contains the same excipients as the currently approved Comirnaty vaccines (Tris/Sucrose formulations).

The lipid nanoparticle (LNP) consists of two functional lipids; a cationic lipid (ALC-0315) and a PEGylated lipid (ALC-0159) and two structural lipids; DSPC and cholesterol. Other excipients are sucrose, tromethamine (Tris base), Tris HCl and water. Processing aids used during manufacturing are ethanol, citric acid monohydrate, sodium hydroxide, HEPES and EDTA. All excipients are sufficiently controlled in accordance with in-house specifications and/or Ph. Eur. monographs.

3.3.5. Control of finished product (CTD module 3.2.P.5)

The finished product specifications for BNT162b2 monovalent vaccine (0.1 mg/mL) and for BNT162b2 monovalent (0.033 mg/mL) vaccine include tests for tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD, HPLC-ELSD), ALC-0159 content (HPLC-CAD, HPLC-ELSD), DSPC content (HPLC-CAD, HPLC-ELSD), Cholesterol content (HPLC-CAD, HPLC-ELSD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD, HPLC-ELSD), Identity of encoded RNA sequence (ddPCR or RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion).

The finished product specifications for the Omicron XBB.1.5 variant vaccine includes a comprehensive set of relevant tests with corresponding acceptance criteria and are based on those established for the original finished product and the bivalent vaccine finished products for the majority of the test attributes. The acceptance criteria for release and stability testing of the Omicron XBB.1.5 variant vaccine finished products (0.1 mg/mL and 0.033 mg/mL) are the same as for the original vaccine finished product and bivalent vaccine drug product for all quality attributes, with the exception of appearance, RNA content and Lipid content which were updated for the 0.033 mg/mL finished product (approved in procedure EMEA/H/C/005735/X/180) and are related to the lower RNA concentration for this presentation.

Since the acceptance criteria for the Omicron XBB.1.5 variant vaccine finished products are based on the currently approved original vaccine finished product (and bivalent vaccine finished product) for the

majority of test attributes, these acceptance criteria for test attributes are considered as clinically qualified to ensure quality, efficacy and safety.

The test methods used for the original Tris/Sucrose finished product are identical to those used for the omicron XBB.1.5 variant vaccine finished products, except for the identity methods, which differ solely in the variant-specific PCR primers used in the assay. The ddPCR method has been added allowing for identity to be tested by either ddPCR or RT-PCR. It can be noted that the Identity test by ddPCR was first introduced for the bivalent vaccine finished product.

Finished product method verifications/validations performed for the original vaccine are considered applicable to the omicron XBB.1.5 vaccine drug product since the operating parameters of the methods are unchanged and this is agreed to. Due to the variant specific reagents (primers), supplemental validation of RT-PCR and ddPCR methods for identity were performed and the reports are provided. Furthermore, as there were no changes to the IVE assay when compared to the method previously approved, a supplemental validation of the IVE method specific to omicron XBB.1.5 was performed and the report provided. This is found acceptable.

For the omicron XBB.1.5 variant vaccine, batch analysis data are provided for the batches manufactured to date, . All these batches met the acceptance criteria in respective specifications documents for each presentation and comparability has been established based on an evaluation of these release testing results. This is found acceptable.

Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original vaccine finished product and the bivalent vaccine finished products, extensive prior experience is leveraged, and the comparability demonstration is found sufficient and agreed to. This is found acceptable.

In addition, stability studies have been initiated for the omicron XBB.1.5 vaccine finished product.

The information provided on control of finished product is found sufficient and acceptable.

3.3.6. Reference standards or materials (CTD module 3.2.P.6)

The reference standards are the same as currently approved for the currently approved Comirnaty vaccine (Tris/Sucrose formulation).

3.3.7. Container closure system (CTD module 3.2.P.7)

The container closure system is the same as for the currently approved Comirnaty vaccine (Tris/Sucrose formulation). No new information is provided. The monovalent XBB.1.5 vaccine is filled in type 1 borosilicate glass or aluminosilicate glass vials with bromobutyl rubber stoppers and aluminium vial seal.

3.3.8. Stability (CTD module 3.2.P.8)

The proposed shelf-life for the Omicron XBB.1.5 variant vaccine finished product at 0.1 mg/mL is 18 months when stored at the recommended storage temperature of -90 to -60 °C, including a short-term storage at 5 ± 3°C for up to 10 weeks (within the 18-month shelf-life). Furthermore, the proposed shelf-life for the Omicron XBB.1.5 variant drug product formulated at 0.033 mg/mL is 12 months at the recommended storage temperature of -90 to -60 °C including a short-term storage at 5 ± 3°C for up to 10 weeks (within the 12-month shelf-life).

The proposed shelf-lives for both omicron XBB.1.5 variant vaccine finished products (0.1 mg/mL and 0.033 mg/mL) are based on the shelf-life for the original Tris/sucrose finished product at 0.1 mg/mL as well as for the approved shelf-life for the 0.033 mg/mL bivalent (original and omicron BA.4/BA.5 variant) vaccine finished product (approved via procedure EMEA/H/C/005735/X/180). Release data are available for the commercial scale XBB.1.5 vaccine finished product stored at the intended storage condition (-90 to -60 °C) as well as at the accelerated storage conditions (5 ± 3°C). These stability studies are currently on-going and data from these studies will be used to confirm the shelf shelf-life of the Omicron XBB.1.5 variant vaccine finished product. The original Tris/sucrose studies as well as the bivalent studies (original and omicron BA.4/BA.5 variant) are also on-going and will be used to extend the shelf life based on the acceptability of these data.

This approach to extrapolate the shelf-life from the already authorized original vaccine to the Omicron XBB.1.5 variant vaccine finished product is found acceptable since comparability has previously been acceptably demonstrated for a number of various comparisons of Comirnaty finished product such as between clinical and commercial scale original finished product, between various manufacturing sites, between the PBS/sucrose finished product and the Tris/sucrose finished product and between the monovalent and bivalent vaccine finished product. Comparability has been demonstrated via comprehensive studies including both release testing and extended characterization testing. Due to the application of the same formulation, manufacturing process, and the use of the same manufacturing sites as the original drug product, extensive prior experience is leveraged for the Omicron XBB.1.5 variant vaccine finished product and comparability previously convincingly proven and concluded.

Therefore, it is agreed to the proposed shelf-life for the Omicron XBB.1.5 variant vaccine finished product at 0.1 mg/mL of 18 months when stored at the recommended storage temperature of -90 to -60 °C, including a short-term storage at 5 ± 3°C for up to 10 weeks (within the 18-month shelf-life). In addition, it is also agreed to the proposed shelf-life for the Omicron XBB.1.5 variant finished product at 0.033 mg/mL of 12 months at the recommended storage temperature of -90 to -60 °C including a short-term storage at 5 ± 3°C for up to 10 weeks (within the 12-month shelf-life). This is in-line with the wording in section 6.3 in the SmPC and is found acceptable.

3.3.9. Appendices (CTD module 3.2.A)

Not applicable.

3.4. Discussion on chemical, and pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, one question was raised on active substance stability data. In response the MAH submitted stability data from two batches and committed to update the dossier with real-time stability data by the end of Q1 2024. This was considered acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.6. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

For this application concerning a monovalent Omicron XBB.1.5 variant vaccine, novel non-clinical data on immunogenicity in mice have been provided. In addition, a study report on distribution and protein expression in mice after injection of a Green Fluorescent Protein (GFP) modRNA lipid nanoparticle (LNP) was submitted.

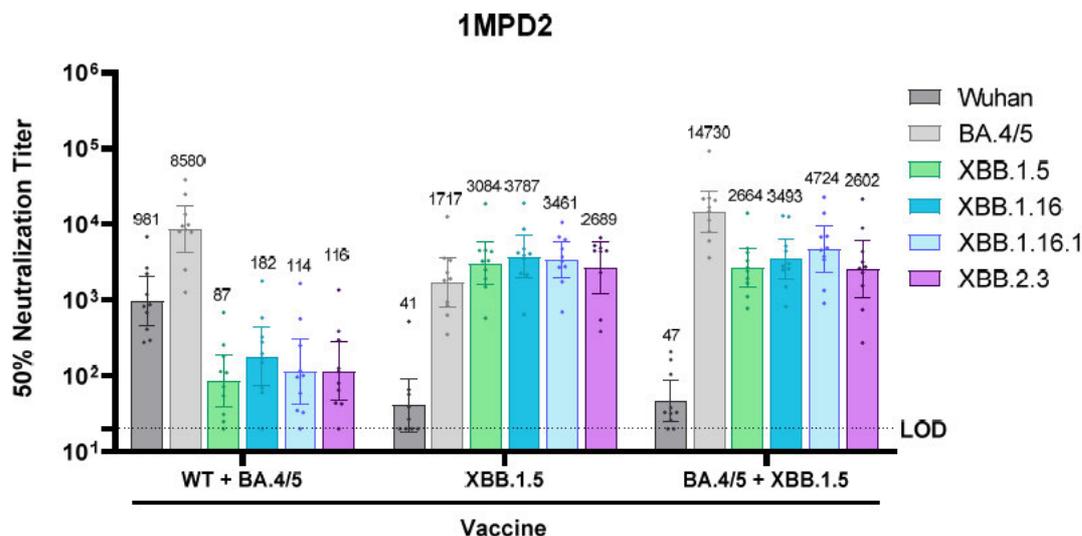
All aspects on non-clinical safety are considered covered by studies supporting the initial Comirnaty MAA.

4.2. Pharmacology

Immunogenicity of COVID-19 Monovalent and Bivalent Omicron XBB.1.5 Sublineage-Modified Vaccines in Naïve Mice as a Primary Series

XBB.1.5 sublineage-modified monovalent and bivalent vaccines as a primary 2-dose series induced robust neutralizing antibody responses against the matched and antigenically related strains. Compared to the bivalent BNT162b2 (WT+BA.4-5), XBB.1.5 modified monovalent and bivalent (BA.4-5+XBB.1.5) vaccines produced 19-to-42-fold higher neutralizing antibody response against XBB.1.5, XBB.1.16, XBB.1.16.1 and XBB.2.3. The strongest responses were observed in the monovalent BNT162b2 XBB.1.5 group. None of the XBB sublineages tested showed evidence of immune escape. Monovalent and bivalent vaccines containing XBB.1.5 induced a CD4+ and CD8+ T-cell response.

Figure 1. 1M Post Dose 2 Neutralizing Geometric Mean Titers (GMT) with XBB.1.5 Monovalent and Bivalent Vaccines as a Primary Series

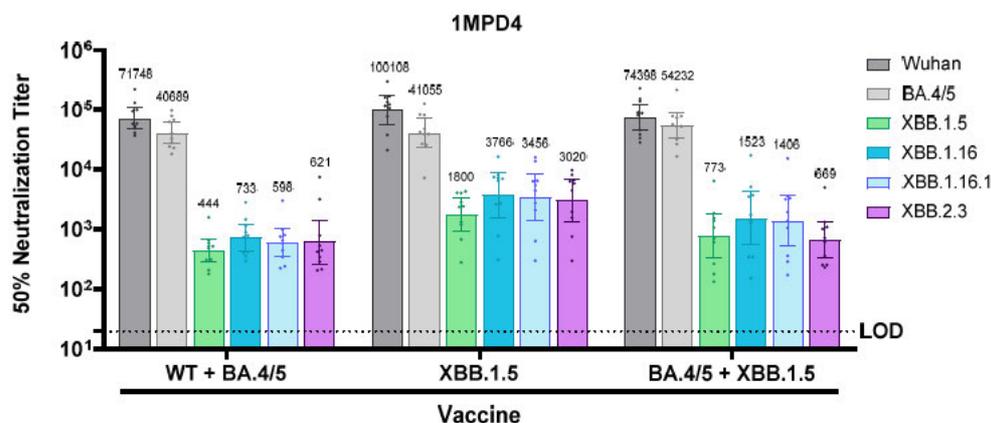


10 BALB/c mice per group were immunized IM on Days 0 and 21 with a 0.5 µg of monovalent BNT162b2 XBB.1.5, bivalent BNT162b2 (WT + BA.4/5, or BA.4/5 + XBB.1.5, 0.25 ug each) and sera were collected at day 49 (1 month post 2nd dose). Neutralizing antibody responses against the Wuhan reference strain (dark grey) and Omicron BA.4/5 (light grey), XBB.1.5 (green), XBB.1.16 (blue), XBB.1.16.1 (light blue), and XBB.2.3 (purple) variants of concern were measured by pseudovirus neutralization assay. The numbers on top of each bar are GMT.

Immunogenicity of COVID-19 Monovalent and Bivalent Omicron XBB.1.5 Sublineage-Modified Vaccines in BNT162b2 Experienced Mice as a Fourth Dose Booster

In BNT162b2 experienced mice, XBB.1.5 variant-modified vaccines induced robust neutralizing antibody responses against the Wuhan reference strain and Omicron sublineages (BA.4-5, XBB.1.5, XBB.1.16, XBB.1.16.1 and XBB.2.3) as a fourth dose booster. Monovalent BNT162b2 XBB.1.5 induced four-to-six-fold higher neutralizing responses against Omicron sublineages XBB.1.5, XBB.1.16, XBB.1.16.1 and XBB.2.3 compared to benchmark bivalent BNT162b2 (WT + BA.4-5). None of the XBB sublineages tested showed evidence of immune escape. Monovalent and bivalent vaccines containing XBB.1.5 formulations induced robust T cell responses. Together these data suggest that XBB.1.5 sublineage-modified monovalent or bivalent vaccines improve immune responses against more currently dominant circulating XBB sublineages.

Figure 2. 1M Post Fourth Dose Booster Neutralizing Geometric Mean Titers (GMT) with XBB.1.5 Monovalent and Bivalent Vaccines



Groups of 10 female BALB/c mice were immunized intramuscularly (IM) on Days 0 and 21 with 0.5 µg of BNT162b2 and on Day 105 with 0.5 µg of bivalent BNT162b2 (WT 0.25 µg + BA.4/5 0.25 µg); one month following dose 3, mice were boosted with an additional dose of bivalent vaccine BNT162b2 (WT+ BA.4/5, 0.25 µg of each), monovalent BNT162b2 XBB.1.5 (0.5 µg), or bivalent vaccine BNT162b2 (BA.4/5 + XBB.1.5, 0.25 µg of each). Neutralizing antibody responses against the Wuhan reference strain (dark grey), BA.4/5 (light grey), XBB.1.5 (green), XBB.1.16 (blue), XBB.1.16.1 (light blue) and XBB.2.3 (purple) variants of concern were measured by pseudovirus neutralization assay at 1 month post fourth dose. The numbers on top of each bar are GMT.

4.3. Pharmacokinetics

8-Day (1-Dose) Intramuscular Investigative Study of Green Fluorescent Protein (GFP) ModRNA LNP in CD-1 Male Mice

Intramuscular administration of GFP modRNA LNP as a single dose of 2 µg to CD-1 male mice was tolerated through 168 hours post dose (HPD) and did not induce a strong innate immune response. IFN-α, CXCL1 (KC), IL-6, CCL2 (MCP-1), and CXCL10 (IP-10) levels peaked at 6 HPD. GFP levels in serum peaked at 6 HPD and gradually declined through 168 HPD. GFP distribution by in situ hybridization (ISH) and immunohistochemistry (IHC) was most frequent at the injection site as well as in the draining and inguinal lymph nodes and spleen, with rare observations in the liver.

GFP+ signal by IHC and/or ISH was consistently detected in multiple cell types at the injection sites from GFP modRNA LNP-administered mice: adipocytes, endothelium and perivascular connective tissue from thin-walled vessels (presumptive venules, capillaries, lymphatics), dermal fibroblasts, muscle connective tissues (epimysium, perimysium, and endomysium), rare myocytes, and mononuclear cells, as well as presumptive leukocytes in lymph nodes and spleen, and hepatocytes in liver (only by ISH at 6 HPD). Frequency of positive signal in muscle compartments in the injection site was generally greatest at 6 and 24 HPD except in myocytes where the highest incidence occurred at 168 HPD. GFP+ staining was not observed in heart by either method. IHC and ISH staining generally overlapped in the cell types labelled across timepoints with a few noteworthy exceptions: in spleen and liver wherein GFP+ expression was only detectable by ISH and in inguinal LN where ISH+ labelling was present in multiple animals across timepoints but IHC+ labelling was only observed in 2 animals. Electron microscopy was conducted on spleen, draining LN, and injection site muscle from a subset of animals at 6, 24, and 72 HPD. Structures consistent with LNPs were detected in spleen samples at 24 and 72 HPD, but not at 6 HPD nor in the draining LN or injection site muscle samples.

4.4. Discussion

To support the approval of the Omicron XBB.1.5 variant vaccine, the MAH has provided mouse immunogenicity data comparing the response to the XBB.1.5 vaccine with that of the bivalent Original/Omicron BA.4-5 vaccine as well as an investigational bivalent Omicron BA.4-5/Omicron XBB.1.5 vaccine. Comparisons were made both for a primary series and for a fourth dose booster in mice that previously received the Original vaccine in a primary series and the bivalent Original/Omicron BA.4-5 vaccine as a booster.

In both cases, the XBB.1.5 containing vaccines provided a superior response to XBB.1.5 and other related variants. The monovalent XBB.1.5 vaccine showed a higher response than the bivalent variant vaccine.

These data support the assumption that the XBB.1.5 monovalent vaccine is expected to provide better protection to XBB.1.5 and other related variants than previously approved variant vaccines.

With this submission the MAH has also provided data from a distribution study in mice with lipid nanoparticles containing modRNA for green fluorescent protein (GFP). This data showed presence of modRNA and expression of GFP predominantly at the injection site, draining lymph nodes and spleen with rare observations in the liver. These data are in line with information submitted with the original MAA where modRNA expressing luciferase was used.

4.5. Conclusions on non-clinical aspects

The CHMP is of the opinion that the non-clinical immunogenicity data are supporting the assumption that the Omicron XBB.1.5 monovalent vaccine is expected to provide better protection to XBB.1.5 and other related variants than previously approved variant vaccines.

5. Changes to the Product Information

As a result of this variation, relevant sections of the SmPC, PL and Labelling are being updated to adequately reflect the addition of a new strain (Omicron XBB.1.5, raxtozinameran).

5.1.1. Quick Response (QR) code

The updates of the QR code/URL to include further references to Comirnaty Omicron XBB.1.5, as well as the necessary layout changes on the website shall be submitted and assessed via an Article 61.3 notification (post-authorisation).

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

With this type II variation, the MAH sought the introduction of a monovalent vaccine targeting SARS-CoV-2 Omicron strain XBB.1.5 to assist in the continued management of COVID-19. This is in line with [EMA/ECDC statement](#), where it was recommended that *“the inclusion of a strain belonging to the XBB family of Omicron subvariants is adequate to ensure cross-reactivity against current dominant and emerging strains, and XBB.1.5 is considered as a reasonable choice to increase the breadth of immunity also against XBB descendent lineages”*.

The Omicron XBB.1.5 vaccine is manufactured at previously authorised/licensed Pfizer/BioNTech sites, formulated in Tris/Sucrose and presented as multi-dose vials (MDV) and single dose vials (SDV).

The MAH has submitted a full quality data package for Omicron XBB.1.5 active substance and monovalent finished product formulations. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, one question was raised on active substance stability data. In response the MAH submitted stability data from two batches and committed to update the dossier with real-time stability data by the end of Q1 2024. This was considered acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

As supportive, the MAH has also provided mouse immunogenicity data comparing the response of the Omicron XBB.1.5 vaccine with that of the bivalent Original/Omicron BA.4-5 and of the investigational bivalent Omicron BA.4-5/Omicron XBB.1.5 vaccine for both a primary series and booster. In both cases, the XBB.1.5 containing vaccines provided a superior response to XBB.1.5 strain. The monovalent XBB.1.5 vaccine showed a higher response than the bivalent. These data were acceptable.

The CHMP considers acceptable an approval based on quality and supportive non-clinical data. The absence of clinical data is considered satisfactory as this platform has shown predictability of clinical immunogenicity and reactogenicity following the variants updates to BA.1 and BA.4-5. This is in line with [EMA/ECDC statement](#). The benefit-risk balance of COMIRNATY, remains positive.

7. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type	Annexes affected
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A

Addition of a new strain (Omicron XBB.1.5, raxtozinameran) resulting in seven new monovalent presentations:

- Comirnaty Omicron XBB.1.5 (30 micrograms)/dose dispersion for injection (EU/1/20/1528/018-020)
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose concentrate for dispersion for injection (EU/1/20/1528/021)
- Comirnaty Omicron XBB.1.5 (10 micrograms)/dose dispersion for injection (EU/1/20/1528/022-023)
- Comirnaty Omicron XBB.1.5 (3 micrograms)/dose concentrate for dispersion for injection (EU/1/20/1528/024)

The Annex A, the SmPC, the Package Leaflet and Labelling are updated accordingly.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA, IIIB and A are recommended.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the addition of a new strain, the CHMP is of the opinion that the already existing entry in the EURD list needs to be amended as follows: tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5), raxtozinameran (COMIRNATY Omicron XBB.1.5).