EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMNCHMP/822048/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMEA/H/C/005735/II/0148/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: 0419

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	10 Oct 2022	10 Oct 2022
☐	CHMP Rapporteur Assessment Report	14 Nov 2022	14 Nov 2022
☐	CHMP members comments	28 Nov 2022	28 Nov 2022
☐	Updated CHMP Rapporteur Assessment Report	01 Dec 2022	01 Dec 2022
☐	Start of written procedure	06 Dec 2022	06 Dec 2022
☒	Opinion	08 Dec 2022	08 Dec 2022

Procedure resources	
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Declarations

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

DYes ~ 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 29 September 2022 an application for a group of variations.

The following changes were proposed:

Variations requested		Type	Annexes affected
B.I.b.1.g	B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat.jintermediates, which may have a significant effect on the quality of the AS and/or the FP	Type II	None
B.I.b.2.c	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	Type IB	None
B.I.b.1.z	B.Lb.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	Type IB	None
B.La.2.a	B.La.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	Type IB	None
B.I.z	B.Lz - Quality change - Active substance - Other variation	Type IB	None

Type II (B.Lb.1.g) To widen the specification limits for DNase I and Pyrophosphatase Activity used in the manufacturing process of the active substance [redacted] at Wyeth BioPharma Division of Wyeth Pharmaceuticals, 1 Burtt Road, Andover.

Type IB (B.Lb.1.z) To add the specification limit for activity test method in the manufacturing process of the active substance at BioNTech Manufacturing GmbH, An der Goldgrube 12, 55131 Mainz, Germany, BioNTech Manufacturing Marburg GmbH, Emil-von-Behring-StraBe 76, 35041 Marburg, Germany and Pfizer Ireland Pharmaceuticals Grange Castle Business Park, Clondalkin, Dublin 22, Ireland as a fulfilment of REC#3.

Type IB (B.Lz) To remove from section 3.2.5.2.3 the reference to Ph. Eur. for the reagent ammonium sulfate for the active substance manufacturing sites at BioNTech Manufacturing GmbH, An der Goldgrube 12, 55131 Mainz, Germany and BioNTech Manufacturing Marburg GmbH, Emil-von-Behring-StraBe 76, 35041 Marburg, Germany.

Type IB (B.Lb.2.c) To add descriptions of the test methods for the enzymes DNase I, Proteinase K, Pyrophosphatase, T7 polymerase and RNase inhibitor used in the manufacturing of the active substance

in section 3.2.5.2.3 as a fulfilment of REC#3.

Type IB (B.La.2.a) Minor change in the manufacturing process of the active substance to add the maximum number of cycles of.runs that the UFDF membra ned can be reused based on validation and data collected at commercial scale.

In addition, data is provided to fulfil REC#7 (The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step).

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

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

In the current grouped variation, the MAH proposes introduction of acceptance criteria for activity testing of the enzymes (DNase I, Proteinase K, Pyrophosphatase, T7 polymerase, and RNase inhibitor) that are utilized as raw materials in the drug substance manufacturing process at the BioNTech manufacturing sites (Marburg and Mainz) to fulfil REC#3 (reference the Assessment Report for EMEAjH/Cj005735/IB/0106jG). Furthermore, as new results for Activity testing are available, the Marketing Authorization Holder (MAH) is proposing updates to the DNase I and Pyrophosphatase acceptance criteria at the Pfizer, Andover site and apply those to the BioNTech sites (Marburg and Mainz) and to Pfizer, Grange Castle in Ireland. Sufficient justification for the updated acceptance criteria has been provided and data included in the variation demonstrate that the implemented process enhancements (within the proven acceptable ranges) have resulted in decreased levels of residual DNA, ensuring manufacturing process consistency and quality of the drug substance.

In addition, a reference to a PhEur monograph has been removed and the maximum number of runs for the ultrafiltration diafiltration (UFDF) membrane re-use has been updated based on relevant validation studies.

Based on the submitted data and justifications, the grouped variation is considered approvable and therefore REC3 and REC7 are now considered to be fulfilled.

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.Lb.1.g	B.Lb.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	Type II	None
B.Lb.2.c	B.Lb.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	Type IB	None

B.I.b.1.z	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	Type IB	None
B.I.a.2.a	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	Type IB	None
B.I.z	B.I.z - Quality change - Active substance - Other variation	Type IB	None

[8Jis 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 EPARwill 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 vaccine Comirnaty, COVID-19 mRNA Vaccine was developed by BioNTech (BNT) and Pfizer to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 infection. The vaccine is based on full-length SARS-CoV-2 spike (5) glycoprotein antigen encoded in nucleoside-modified messenger RNA and formulated in lipid nanoparticles (LNPs).

This grouping of variations below proposes introduction of acceptance criteria for activity testing of the enzymes (DNase I, Proteinase K, Pyrophosphatase, T7 polymerase, and RNase inhibitor) that are utilized as raw materials in the drug substance manufacturing process at the BioNTech manufacturing sites (ie, Marburg and Mainz) to fulfil REC#3 (reference the Assessment Report for EMENH/C/005735/IB/0106/G).

In addition, as new results for Activity testing are available, the Marketing Authorization Holder (MAH) is proposing updates to the DNase I and Pyrophosphatase acceptance criteria at the Pfizer, Andover site and apply those to the BioNTech sites (Marburg and Mainz) and to Pfizer, Grange Castle in Ireland.

This procedure includes a grouping of variations as follows:

- Type IB (B.I.b.1.z) Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance. Other change: addition of Activity test method acceptance criteria to addresses Recommendation 3 (REC#3) for BNT sites (Mainz and Marburg) and Pfizer, Grange Castle, Ireland.
- Type II (B.I.b.1.g) Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance. Widening of the approved acceptance criteria for DNase I and Pyrophosphatase Activity based on additional data with no impact on the in vitro transcription (IVT) manufacturing process for Pfizer, Andover only.
- Type IB (B.I.z) Editorial change in section 3.2.5.2.3 Control of Materials - Materials Used in Manufacture [BNT Marburg], to delete the reference to Ph. Eur. for the reagent ammonium sulfate for the drug substance manufacturing sites BioNTech Mainz and BioNTech Marburg only. Ammonium sulfate was initially referenced to comply with Ph. Eur. and USP/NF. There is no monograph for this substance in the European Pharmacopoeia and therefore the reference has been deleted in the dossier.
- Type IB (B.I.b.2.c) Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance (Conditions 3 and 6 unmet). To address the assessor's comments and fulfill REC#3, short descriptions of the methods are included in Section 3.2.5.2.3 Control of Materials-Materials Used in Manufacture, for the enzymes and RNase inhibitor. The methods did not change as a result of this variation.

The MAH is also taking the opportunity to update Section 3.2.5.2.5 Process Validation and/or Evaluation-Additional Process Evaluation [Andover] with the maximum number of cycles that the ultrafiltration diafiltration (UFDF) membrane can be reused based on the completion of the study and analysis of the data. There is no change in the qualitative and quantitative impurity profile or in the physico-chemical properties. The process and drug substance specification remain unchanged.

- Type IB (B.I.a.2.a) Changes in the manufacturing process of the active substance. Minor change in the manufacturing process of the active substance (Condition 5 unmet). The maximum number of cycles that-the UFDF membra ned can be reused is established at [redacted] runs based on validation and data collected at commercial scale.

To fulfil REC #7, and address the assessor's comments (reference EMENH/C/005735/IB/0106/G), Section 3.2.5.2.6 Manufacturing Process Development-Process Development and Characterization is updated with the following:

- Description of the process enhancements that improve robustness of the process with a consistent approach to control the residual DNA template levels across all drug substance manufacturing sites.
- Residual DNA template data comparing batches prior and post the process enhancements from the BioNTech (Mainz and Marburg) sites and Pfizer, Andover drug substance site.

The Pfizer, Grange Castle, Ireland site was submitted as a drug substance manufacturing site after the process enhancements were established. No comparative data for the residual DNA template values are provided. All batches produced from the site have included the enhancements.

6. Quality aspects

Table 2.3-1. O,-eniew of the Submission

Module 3 CTD Sections	Documents	Rationale
3.2.S.2.3	Control of Materials – Materials Used in Manufacture [Andover]	Updated Table 3.2.S.2.3-8 and Table 3.2.S.2.3-10 to reflect the change in acceptance criteria for Activity parameter for DNase I and pyrophosphatase. Method descriptions were added for the and the enzymes and RNase inhibitor.
3.2.S.2.3	Control of Material" -l\'lJ.teriai£ Used in ~'iIanufach_jre [BNT ?vIairu and Rentschler]	New tables added with the specification for all non-compendial starting materials (ie, NTPs, 5'cap solution) and enzymes. New Activity acceptance criteria for DNase I, Proteinase K, Pyrophosphatase, T7 polymerase, and RNase inhibitor are replaced with new acceptance criteria based on in-house methods. Method descriptions were added for the enzymes and RNase inhibitor.
3.2.S.2.3	Control of Materials – Materials Used in Manufacture [BNT Marburg]	New tables added with the specification for all non-compendial starting materials (ie, NTPs, 5'cap solution) and enzymes. New Activity acceptance criteria for DNase I, Proteinase K, Pyrophosphatase, T7 polymerase, and RNase inhibitor are replaced based on in-house methods. Method descriptions were added for the enzymes and RNase inhibitor.
3.2.S.2.3	Control of Materials – Materials Used in Manufacture [Pfizer, Grange Castle]	New tables added with the specification for all non-compendial starting materials (ie, NTPs, 5'cap solution) and enzymes. The Activity acceptance criteria for DNase I, Proteinase K, Pyrophosphatase, T7 polymerase enzymes and RNase inhibitor updated from report results to a numerical value based on new in-house methods. Method descriptions were added for the enzymes and RNase inhibitor. Removal of the reference to Ph. Eur. for ammonium sulfate.
3.2.S.2.5	Process Validation and/or Evaluation- Additional Process Evaluation [Andover]	Updated Table 3.2.S.2.5-1 with the maximum number of cycles (ie [redacted] that the ultrafiltration/ diafiltration membrane can be reused.
3.2.S.2.6	Manufacturing Process Development Process Development and Characterization	New section added describing commercial-scale process enhancements to control residual DNA template digestion including supporting data from BNT and Pfizer, Andover manufacturing sites to show residual DNA template results post the implementation of the process enhancements.

BNT = BioNTech; DS = drug substance; MAH = Marketing Authorization Holder; NTPs = nucleoside triphosphates

6.1 Discussion of the Change

- Control of Materials- Updates to Enzyme Acceptance Criteria

Enzyme activity test methods and acceptance criteria were implemented at the Pfizer, Andover site in the previous variation to address the REC#3 requirements (reference Procedure EMENHjCj005735jIBjOl06/G). In order to fulfill the requirements of REC#3, the MAH has agreed to apply the same activity methods and acceptance criteria to the BioNTech sites (Mainz and Marburg).

In addition, this variation is updating acceptance criteria for the DNase I and pyrophosphatase enzymes. These updated acceptance criteria for DNase I and pyrophosphatase enzymes along with the other enzyme activity criteria apply to all manufacturing sites including Pfizer, Grange Castle (approved April

2022; reference Procedure EMEA/H/C/005735/II/0116/G). Table 2.3-2 provides the previous and proposed acceptance criteria for enzyme activity for all drug substance manufacturing sites.

Table 2.3-2 Previous and Propose Activity Acceptance Criteria for Enzymes

Enzyme	[redacted]
DNase I	
Pyrophosphatase	
T7 Polymerase	
Proteinase K	
RNase Inhibitor	

Additional data for enzymes and RNase inhibitor were obtained from drug substance sites enabling reassessment of the acceptance criteria for in-house activity assays currently in place at the Pfizer, Andover site. The overall mean and pooled standard deviation (SD) for each enzyme was employed in the calculation of the lower and upper control limits.

For the control limits, the 3-SD intervals were constructed around the mean value for each enzyme. The acceptance criteria were calculated as follows:

Lower Control Limit = Enzyme mean - (3 * site pooled S.D)

Upper Control Limit = Enzyme mean + (3 * site pooled S.D)

Upon review of the calculated control limits versus the acceptance criteria initially implemented in Pfizer, Andover, updated acceptance criteria are necessary for DNase I and Pyrophosphatase. The remaining acceptance criteria are still acceptable.

The purpose of DNase I in the in vitro transcription (IVT) step is to digest the linear DNA template and thereby enable DNA removal by the ultrafiltration diafiltration (UFDF) operation downstream. For DNase I, a minimum activity is required for DNase I to perform its function.

Based on the review of the updated control limits and the purpose of DNase I, [redacted] from the acceptance criteria, and acceptance criteria for activity testing of DNase I will be changed to_for Pfizer, Andover.

Based on the review of the updated control limits for pyrophosphatase, the upper limit was extended for the acceptance criteria. Activity testing of the pyrophosphatase will be changed to [redacted] for Pfizer, Andover.

Section 3.2.5.2.3 Control of Materials- Materials Used in Manufacture [Andover] has been updated with the new acceptance criteria for DNase I and pyrophosphatase including descriptions of test methods for all enzymes and RNase inhibitor to fulfill REC#3 requirements.

Section 3.2.5.2.3 Control of Materials - Materials Used in Manufacture [Pfizer, Grange Castle]; Section 3.2.5.2.3 Control of Materials- Materials Used in Manufacture [BNT Marburg]; Materials Used in Manufacture- Materials Used in Manufacture [BNT Mainz and Rentschler] are updated to include the acceptance criteria for all enzymes and RNase inhibitor including descriptions of test methods to fulfill REC#3 requirements.

The MAH will continue to monitor the activity test results and the corresponding acceptance criteria may be adjusted accordingly as more data becomes available.

- Deletion of non-significant specification parameter for ammonium sulfate

Ammonium sulfate was initially referenced to comply with Ph. Eur. and U5P/NF. There is no monograph for this substance in the European Pharmacopoeia and therefore the reference has been deleted in the dossier. The quality control of this reagent is carried out as described in the related monograph of the National Formulary. This change is applicable to the BioNTech sites only.

- Ultrafiltration Diafiltration Membrane Re-use

The ultrafiltration diafiltration (UFDF) membrane re-use was monitored for membrane lifetime validation using the performance parameters with established acceptance criteria based on initial validation studies and early commercial production. Thus, Section 3.2.5.2.5 Process Validation and/or Evaluation- Additional Process Evaluation [Andover] is updated with the maximum number of runs for UFDF use.

- Description of Process Enhancements to Control Residual DNA Levels

The implemented process enhancements (within the proven acceptable ranges) have resulted in decreased levels of residual DNA, as shown in Figure 3.2.5.2.6-7 through Figure 3.2.5.2.6-10, ensuring manufacturing process consistency and quality of the drug substance. No new small-scale experiments are planned or considered to be needed to show correlation between DNase I activity and levels of residual DNA.

[redacted]

Section 3.2.5.2.6 Manufacturing Process Development-Process Development and Description has been updated with descriptions of the process enhancements implemented on the commercial scale. The section includes the addition of supporting data from the BioNTech and Pfizer, Andover sites to show the residual DNA template results post the implementation of the process enhancements. These updates address the Agency requests and fulfills requirements for REC#7.

Assessor's comments:

In the current grouped variation, the MAH proposes introduction of acceptance criteria for activity testing of the enzymes (DNase I, Proteinase K, Pyrophosphatase, T7 polymerase, and RNase inhibitor) that are utilized as raw materials in the drug substance manufacturing process at the BioNTech manufacturing sites (Marburg and Mainz) to fulfil REC#3 (reference the Assessment Report for EMENHjCj005735jIBj0106jG). Furthermore, as new results for Activity testing are available, the Marketing Authorization Holder (MAH) is proposing updates to the DNase I and Pyrophosphatase acceptance criteria at the Pfizer, Andover site and apply those to the BioNTech sites (Marburg and Mainz) and to Pfizer, Grange Castle in Ireland. Sufficient justification for the updated acceptance criteria has been provided and data included in the variation demonstrate that the implemented process enhancements (within the proven acceptable ranges) have resulted in decreased levels of residual DNA, ensuring manufacturing process consistency and quality of the drug substance.

In addition, a reference to a PhEur monograph has been removed and the maximum number of runs for the ultrafiltration diafiltration (UFDF) membrane re-use has been updated based on relevant validation studies.

Based on the submitted data and justifications, the grouped variation is considered approvable and therefore REC 3 and REC 7 are now considered to be fulfilled.

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