EMA/596333/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMEA/H/C/005735/R/0046

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.

Steps taken for the assessment	
Description	**Date**
Start of procedure:	19 Jul 2021
CHMP and PRAC Rapporteurs Joint Assessment Report	17 Aug 2021
CHMP and PRAC members comments	23 Aug 2021
Updated CHMP and PRAC Rapporteurs Joint Assessment Report	N/A
PRAC endorsed relevant sections of the assessment report	02 Sep 2021
Request for supplementary information	16 Sep 2021
MAH responses to (RfSI) received on	21 Sep 2021
CHMP and PRAC Rapporteurs' joint assessment report	28 Sep 2021
PRAC endorsed relevant sections of the assessment report	30 Sep 2021
CHMP and PRAC members comments	N/A
Updated CHMP and PRAC Rapporteurs joint assessment report	N/A
Opinion	14 Oct 2021

Procedure resources	
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PRAC Rapporteur:	Menno van der Elst

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1. Background information on the annual renewal

The European Commission issued on 21 December 2020, a conditional marketing authorisation (MA) for Comirnaty. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH BioNTech Manufacturing GmbH, submitted to the Agency on 18 June 2021 an application for renewal of the conditional marketing authorisation for Comirnaty. The expiry date of the MA is 21 December 2021.

The period covered by this annual renewal is 21 December 2020 to 29 April 2021.

2. Specific Obligations

2.1. Specific Obligations adopted by the CHMP at time of initial marketing authorisation

Number	Description	Due date
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
SOB 003	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

2.2. Outstanding Specific Obligations – Status report for period covered

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
Specific Obligation 1 (SO1)	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021	02/08/2021		Not Fulfilled
SO1 (a)	Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into Assessment report EMA/707383/2020 Page 37/140 truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated.	July 2021	02/08/2021		Ongoing
SO1 (b)	The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail.	July 2021	02/08/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO1 (c)	Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the in vitro expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated	July 2021	02/08/2021		Ongoing
Specific Obligation 2 (SO2)	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021	02/08/2021		Not Fulfilled
SO2 (a)	The active substance and finished product specifications acceptance limits should be reassessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials.	July 2021	02/08/2021		Ongoing
SO2 (b)	Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed, and appropriate acceptance criteria should be set.	July 2021	02/08/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO2 (c)	The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes.	July 2021	02/08/2021		Ongoing
SO2 (d)	Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability.	July 2021	02/08/2021		Ongoing
SO2 (e)	Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly.	July 2021	02/08/2021		Ongoing
SO2 (f)	Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021.	July 2021	26/07/2021		Ongoing
Specific Obligation 3 (SO3)	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021	29/03/2021	20/05/2021	Fulfilled
SO3 (a)	Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities.	March 2021	29/03/2021	20/05/2021	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO3 (b)	The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment.	March 2021	29/03/2021	20/05/2021	Fulfilled
Specific Obligation 4 (SO4)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021	06/01/2021 26/07/2021		Not Fulfilled
SO4 (a)	A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO4 (b)	Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed by July 2021.	July 2021	26/07/2021		Ongoing
SO4 (c)	Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided.	July 2021	26/07/2021		Ongoing
SO4 (d)	Information and justification on critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021		Ongoing
SO4 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies.	July 2021	26/07/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO4 (f)	The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate.	July 2021	26/07/2021		Ongoing
SO4 (g)	The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product.	July 2021	26/07/2021		Ongoing
SO4 (h)	Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided.	July 2021	26/07/2021		Ongoing
SO4 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021		Ongoing
Specific Obligation 5 (SO5)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021	06/01/2021 26/07/2021		Not Fulfilled
SO5 (a)	A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO5 (b)	Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG.	July 2021	26/07/2021		Ongoing
SO5 (c)	Information and justification of critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO5 (d)	The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product.	July 2021	26/07/2021		Ongoing
SO5 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies.	July 2021	26/07/2021		Ongoing
SO5 (f)	The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate.	July 2021	26/07/2021		Ongoing
SO5 (g)	Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO5 (h)	Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided.	July 2021	26/07/2021		Ongoing
SO5 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021		Ongoing
Specific Obligation 6 (SO6)	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023			Pending

SOB 1: Quality: Characterisation

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0056/G is under assessment. An interim report was submitted within a PAM-ANX procedure in March 2021 and monthly status reports submitted in January, February and May 2021.

SOB 2: Quality: Control strategy

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0056/G is under assessment. An interim report was submitted within a PAM-ANX procedure in March 2021 and monthly status reports submitted in January, February and May 2021.

SOB 4: Quality: Process and control strategy for the excipient ALC-0315

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0054/G is under assessment. Interim reports were submitted in January and April 2021.

SOB 5: Quality: Process and control strategy for the excipient ALC-0159

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0054/G is under assessment. Interim reports were submitted in January and April 2021.

SOB 6: Clinical

In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.

Interim results from study C4591001 were included in the initial Marketing Authorisation Application for Comirnaty, and the study design and results were extensively assessed during the approval procedure. The study is still ongoing according to plan, and final results are expected in December 2023.

CHMP comment:

Specific Obligations 1,2, 4, 5 and 6 are ongoing and progressing according to plan.

The CHMP issued an opinion on the 20th of May 2021 concluding that Specific Obligation 003 had been fulfilled, and therefore deleted from the Annex II.

2.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, several aspects for all quality SOBs have been addressed.

SOB 004 and SOB 005 relating to the novel excipients are partially fulfilled. The data to fulfil the remaining parts of these SOBs have been submitted in variation EMEA/H/C/005735/II/0054/G and are currently under assessment by the CHMP. A Request for Further Information has been adopted on 14

October 2021.

Similarly, data to fulfil SOB 001 (characterisation) and SOB 002 (control strategy & specifications) have been submitted in variation EMEA/H/C/005735/II/0056/G and are currently under assessment by the CHMP. A Request for Further Information has been adopted on 14 October 2021.

Therefore, overall SOB 001, SOB 002, SOB 004 and SOB 005 are not fulfilled at the time point of the present assessment report; nevertheless, the MAH has been compliant in providing the data in response to these SOBs in line with the imposed deadlines, and therefore, the overall status of compliance is satisfactory.

Regarding SOB003*: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data,* the due date for this SOB was March 2021 and the SOB was fulfilled with the variation EMEA/H/C/005735/II/0023/G (approved on 20 May 2021).

During the period covered by this annual renewal interim data on the clinical SOB 006 have been submitted that overall are compliant in terms of adherence to deadlines and in terms of acceptability of data submitted. The available clinical evidence includes a tolerable safety profile and high vaccine efficacy against COVID-19 in individuals ≥12 years of age.

3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

3.1. Quality

For several of the remaining Quality SOBs the due date was July 2021 and variations EMEA/H/C/005735/II/0054/G and EMEA/H/C/005735/II/0056/G are currently under assessment.

3.2. Clinical efficacy

Since approval of Comirnaty the MAH has submitted efficacy and safety data for children 12-15 years of age, and approval of an indication in this age group was obtained on May 31, 2021. (EMEA/H/C/005735/II/0030). For further details on the efficacy of Comirnaty, please see the initial marketing authorisation approval.

3.3. Clinical safety

The MAH submitted the Addendum to the Clinical Overview (ACO), covering the period from 21 December 2020 until 29 April 2021.

Worldwide Marketing Authorisation Status

BNT162b2 received a first temporary authorisation for emergency supply under regulation 174 in the UK on 1 December 2020 and in EEA countries on 21 December 2021. Up to the DLP (29 April 2021), it is currently conditionally approved in 42 countries (including EEA).

Actions Taken for Safety Reasons During the Period Covered Since the Initial Marketing Authorisation

Issue	Country	Action Taken	Date
Compared to the global supply of BNT162b2, an increased complaints rate for leakages was observed by the MAH in Hong Kong, with 19 vials with leakages reported from 3 different vaccination sites in the country; overall 26 vials with leakages and/or loose caps were reported. All vials were from 1 batch, the only batch in use for vaccination in Hong Kong and Macau. During the investigation, it became apparent that the root cause of the reported product quality complaints is a combination of the container closure process (crimping) at 1 single CMO and of the specific transport conditions on dry ice that are required for BNT162b2. Vaccination in Hong Kong and Macau was stopped as soon as the issue became apparent (24 March 2021). A total of 2 batches have been affected (including the one being used and another one already shipped to Hong Kong, but still in storage) and were quarantined. The root cause of the reported product quality complaints was clearly identified through analysis of the data generated and collected as of 31 March 2021. According to the data, the crimping process used for batches at the CMO fill and finish site requires optimization to ensure the container integrity during storage and shipment with dry ice. Under the ultra-cold conditions created by storing and shipping on dry ice, the stopper loses flexibility and, if not optimally crimped, allows the ingress of ambient gas into the vial. During thawing the flexibility of the stopper is regained and the stopper reseals the vial. This can result in increased pressure in the vial and presence of elevated CO2 levels. Due to the identified root cause the MAH could exclude any influence on batches that are on the market anywhere outside of Hong Kong and Macau. The CMO in question has not manufactured any batch that was released for any market other than Hong Kong and Macau. Vaccinations in Hong Kong and Macau were resumed with a vaccine batch from a different CMO on 3 April 2021; discussions to address the issue and resume supplies with the previous CMO are ongoing, no batches from this CMO are currently distributed.	Hong Kong and Macau	Vaccination in Hong Kong and Macau was stopped on 24 March 2021 and was resumed with a vaccine batch from a different CMO on 3 April 2021	24 March 2021
On 5 February 2021 Health Canada requested to issue a joint Pfizer-Health Canada Health Product Risk Communication to communicate revisions to Product Monograph (addition of 6-dose vial information and text on anaphylaxis). Final HPRC was approved on 8 February 2021.	Canada	Health Product Risk Communication to inform about the revisions to Product	8 February 2021

Issue	Country	Action Taken	Date
		Monograph (addition of 6-dose vial information and text on anaphylaxis).	
On 15 January 2021, following fatal events involving elderly patients vaccinated with BNT162b2 in Norway, the Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.	Norway	Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.	15 January 2021

Significant Changes to the Reference Safety Information

The Reference Safety Information (RSI) for this ACO is the BNT162b2 CDS (Company Data Sheet) Version 3.0, dated 20 April 2021, in effect at the end of the reporting period.

The previous CDS version 2.0 (dated 2 March 2021) and CDS version 1.0 (dated 12 February 2021) were also in effect during the reporting period. The safety related changes made in CDSs is as follows:

CDS version 3.0 (dated 20 April 2021)		
Section Number	Revision Type	Revision
4.8	Addition	A summary of the safety profile in the adolescents 12 through 15 years of age was added in Section 4.8 Undesirable effects, based on the planned data analysis from the ongoing multi-country clinical trial, C4591001, on adolescent study participants 12 through 15 years of age.
CDS version 2.0 (dated 2 March 2021)		
4.8	Addition	Diarrhoea, Pain in extremity (arm) and Vomiting were added as adverse reactions from post-authorisation experience in Section 4.8 Undesirable effects

The MAH also reported that **after the DLP of this ACO**, the CDS has been further updated (CDS ver. 4.0 dated 19 May 2021) with the following:

- a warning on stress-related responses associated with the process of vaccination was added in section 4.4 Special warnings and precautions for use
- data from studies in section 4.8 Undesirable effects was updated to add available data in 12 to 15-year-old subjects and in stable HIV-infected subjects
- Decreased appetite, Lethargy, Hyperhidrosis, Night sweating and Asthenia were added as Adverse Drug Reactions in section 4.8 Undesirable effects.

Respectively on 5 May 2021, on 10 May 2021 and on 28 May 2021, BNT162b2 was authorized for use in individuals 12 years of age and older in Canada, in US and in Japan.

Variation 0030 (EMEA/H/C/005735/II/0030) was also submitted to EMA on 30 April 2021 to seek expansion of the indication to subjects 12 to 15 years of age; on 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 years and the European Commission adopted a decision accordingly on 31 May 2021.

PRAC comment:

The SmPC is in line with the core data sheet (CDS).

Furthermore, the CHMP adopted an Opinion on the 16th September 2021 to add asthenia, lethargy, decreased appetite, hyperhidrosis, and night sweats as side effects to the product information. In addition, following the PRAC meeting in July, myocarditis and pericarditis were added to sections 4.4. and 4.8 of the SmPC, and the package leaflet was updated accordingly.

Patient exposure

Clinical studies

Cumulatively up to 21 April 2021, the MAH estimated that 49,315 subjects have participated in the Pfizer-managed studies of the COVID-19 vaccine clinical development program: 195 subjects received BNT162b1 (modRNA which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain); 41,368 subjects received BNT162b2 (modRNA which encodes a membrane-anchored SARS-CoV-2 full-length spike) of which, 20,291 subjects, who had received Placebo, were offered BNT162b2 post-unblinding and 758 subjects received BNT162b2 and the Blinded boost; 329 received BNT162S017, 6,370 subjects received blinded-therapy; and 1,053 subjects received placebo.

Additionally, 1,691 subjects have participated in 2 studies managed by BioNTech (BNT162-01 and BNT162-04) and in 2 studies (BNT162-03 and BNT162-06) managed by Shanghai Fosun Pharmaceutical in China.

PRAC comment:

The MAH was requested to explain what "BNT162S017" is, compared to BNT162b1 and BNT162b2. (**Request for Supplementary Information**)

Post-marketing experience worldwide

This estimation is based on the proportion of doses administered out of those shipped upon review of data currently available for the EU countries and the US.

The MAH estimated that approximately 415,922,715 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 1 December 2020 through 29 April 2021, corresponding to 332,738,172 estimated administered doses.

The estimated cumulative number of shipped and administered doses of BNT162b2 by region based on data provided in the shipment tracker (Order Book), from the receipt of the first temporary authorisation for emergency supply on 1 December 2020 through 29 April 2021, are summarized in Table 1 below.

Table 1. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	**37.1%**	**154,251,240**	**123,400,992**
European Union[a] (27)	28.9%	120,356,925	96,285,540
Commonwealth of Independent States[d]	**0.0%**	**170,820**	**136,656**
North America[e]	**41.8%**	**173,708,925**	**138,967,140**
Central and South America[f]	**5.1%**	**21,330,270**	**17,064,216**
Asia	**15.3%**	**63,627,720**	**50,902,176**
Oceania	**0.6%**	**2,377,440**	**1,901,952**
Africa[h]	**0.2%**	**627,120**	**501,696**
Total	**100.0%**	**415,922,715**	**332,738,172**

a. In this Region BNT162b2 was conditionally approved;
b. Includes Georgia, Moldova and Ukraine; in these countries BNT162b2 was shipped for COVAX;
c. In this Region BNT162b2 received authorization for emergency supply;
d. Includes Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru and Uruguay where BNT162b2 received authorisation for emergency supply (some doses in Colombia and Peru were also shipped for COVAX), Brazil where BNT162b2 was conditionally approved, and Bolivia and El Salvador where BNT162b2 was shipped for COVAX;
e. Includes Cape Verde, Rwanda and Tunisia where BNT162b2 was shipped for COVAX and South Africa where BNT162b2 received authorization for emergency supply.

Post-marketing exposure data in the EU

The MAH estimated that approximately 121,880,460 doses of BNT162b2 were shipped in the EU-EEA countries from the receipt of the first conditional marketing authorisation approval on 21 December 2020 through 29 April 2021, corresponding to 97,504,368 estimated administered doses.

Table 2 provide the cumulative estimated number of persons who received 1 dose or 2 doses of BNT162b2, in total, and by age group where available, in the EU-EEA countries.

Table 2. Cumulative Administered 1&2 doses of BNT162b2 by Age Group in EU-EEA Countries[a]

Countries	18-24 years		25-49 years		50-59 years		60-69 years		70-79 years		≥80 years		Age Unknown		All	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Austria	32601	18144	239207	130993	219059	90021	318379	75014	326639	140700	335807	293603	4546	2246	1476238	750721
Belgium	52593	35800	293119	213871	244493	116179	509734	90760	521985	95815	379603	200561	2596	2161	2004123	755147
Bulgaria	6159	2994	91073	53735	62270	40928	68639	39715	45433	21092	13544	6110	230	114	287348	164688
Croatia	4569	1560	66321	29122	57981	20840	104365	27281	95611	32417	54000	28683	82	34	382929	139937
Cyprus	67	132	24777	1459	17825	1449	7243	5255	112	877	19812	7812	58343	47244	128179	64228
Czech Rep	24298	14744	300516	182307	186681	102898	411983	75205	462712	285166	233366	213979	1024	415	1620580	874714
Denmark	12172	11349	100433	95272	70155	64869	215219	79996	489102	148799	234027	216113	807	0	1121915	616398
Estonia	3900	1995	35929	15436	29141	9623	39210	10497	51796	18286	38854	24687	96	25	198926	80549
Finland	20009	5211	164266	52763	163750	27400	211291	16390	432259	13109	249309	50709	0	0	1240884	165582
France													10678144	5870393	10678144	5870393
Germany													16302110	6165751	16302110	6165751
Greece	8657	5508	178846	131191	123573	76311	174906	40155	478077	215987	463446	402532	3193	77	1430698	871761
Hungary	68071	19492	532097	164815	234138	84751	323113	159588	287650	208967	197264	170584	4142	928	1646475	809125
Iceland	1510	515	12660	4461	8658	1911	12582	4204	8571	8268	12357	12290	131	63	56469	31712
Ireland	14443	9893	121182	83267	73386	35093	48177	20871	297164	119213	163486	151163	2070	610	719908	420110
Italy	152389	107855	1179042	1023120	914562	659910	1258996	558357	1603504	535098	3295757	2773399	515532	2289	8919782	5660028
Latvia	1701	831	12069	2349	7009	1394	8473	1285	3894	1714	1595	776	15986	13069	50727	21418
Liechtenstein													4617	2152	4617	2152
Lithuania	17322	6725	86710	42364	72027	36875	109972	60902	89537	66043	52024	37840	752	292	428344	251041
Luxembourg	999	647	8506	5009	23442	2410	28819	1773	12309	11142	18133	17509	5221	4796	97429	43286
Malta	3715	2544	34966	18553	16833	9036	17636	10225	35820	32940	21394	19093	500	1	130864	92392
Netherlands													2867626	1059516	2867626	1059516
Norway													666707	77265	666707	77265
Poland	85825	60529	987763	418915	926701	235199	1332294	267273	1748066	896698	899037	738724	5781	3406	5985467	2620744
Portugal	19908	10838	248888	132357	143630	61761	248335	49080	400468	76875	557181	498668	365	232	1618775	829811
Romania													2626409	1655770	2626409	1655770
Slovakia													610591	451720	610591	451720
Slovenia	1710	1419	21019	18350	16002	11063	69804	30038	85139	70616	61059	56730	227	132	254960	188348
Spain	74690	66594	780878	720572	437097	401459	411832	270351	3037645	697953	2640774	2434770	1744	1209	7384660	4592908
Sweden	22699	12657	154168	96111	158728	61720	498361	63157	526616	125817	418347	323265	0	8	1778919	682735
Total	**630007**	**397976**	**5674435**	**3636392**	**4207141**	**2153100**	**6429363**	**1957372**	**11040109**	**3823592**	**10360176**	**8679600**	**34379572**	**15361918**	**72720803**	**36009950**

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6, cumulative period as of week 17, 02 May 2021).

PRAC comment:

Up to 29 April 2021, it is estimated that over 332 Mio doses of BNT162b2 were administered worldwide.

During the reporting period of this renewal, it is estimated that over 97 Mio doses of Comirnaty were administered in the EU and EEA countries.

Data in Summary Tabulations

Cumulatively, there have been 882 clinical trial cases (1072 SAEs) reported.

Cumulatively[1] up to 29 April 2021, there have been 109,692 post-marketing cases (414,594 unique PTs) reported. During the reporting interval, there have been 108,980 post-marketing cases (412,318 unique PTs) reported.

Significant Findings from Clinical Trials and Non-Interventional Studies

Completed Clinical Trials

No clinical trials were completed up to 21 April 2021.

Ongoing[2] Clinical Trials

There were 10 ongoing clinical trials up to 21 April 2021 (sponsored by BioNTech SE), out of which 2 studies (BNT162-03 and BNT162-04) for study vaccines BNT162b1 and BNT162b3.

Six studies were conducted by Pfizer: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020.

Four studies were conducted by BioNTech, including 2 studies in China managed by Shanghai Fosun Pharmaceutical Development (BNT162-03 and BNT162-06).

Clinically important emerging efficacy and/or safety findings were identified for Study C4591001/BNT162-02[3] and C4591005 and are summarized below.

- **Study C4591001/BNT162-02**

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
Countries: Argentina, Brazil, Germany, South Africa, Turkey, US

This study is a Specific Obligation in the context of BNT162b2's conditional marketing authorisation and it is being conducted in order to confirm the efficacy and safety of the vaccine; the MAH should submit the final Clinical Study Report, including a 2-year follow up of the studied population.

Study C4591001/BNT162-02 is an ongoing, randomized, placebo-controlled, observer-blind, dose-finding Phase 1/2/3 registration study evaluating the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.
Study C4591001/BNT162-02 was started as a Phase 1/2 study in adults in the US and was then amended to expand the study to a global Phase 2/3 study to accrue sufficient COVID-19 cases to conduct an efficacy assessment. The protocol was initiated in adults 18 years of age and older and subsequently amended to include adolescents as young as 12 years of age. The study has

[1] Collected since 01 December 2021, the date of the first temporary authorisation for emergency supply under regulation 174 in the UK.
[2] Includes ongoing studies as well as studies in which patient enrolment and follow-up have been completed, but the analysis and CSR are in-progress.
[3] Pfizer-conducted clinical trial C4591001/BNT162-02 has an interim study report that is available upon request.

enrolled approximately 46,000 participants, including 2,260 young adolescents 12 to 15 years of age. Data from the Phase 1 part of the study was the basis for selection of the vaccine candidate and dose level for Phase 2/3. The Phase 2/3 part of the study evaluated the safety, immunogenicity, and efficacy of the selected vaccine candidate, BNT162b2, and is intended to support licensure globally.

The available clinical evidence for BNT162b2 includes a tolerable safety profile and high VE against COVID-19 in individuals ≥12 years of age.

The potential risks are based on the observed safety profile to date, which shows mostly mild to moderate reactogenicity, an acceptable incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19, as defined by the FDA Guidance for Industry (June 2020)[4], in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of vaccine-associated enhanced disease.

Vaccine efficacy was ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those irrespective of prior infections. Observed VE was >93% when data were stratified by age, sex, race/ethnicity, and country with the exception of the "all others" race group (89.3% VE) and Brazil (87.7% VE).

Severe cases evaluated for efficacy were confined predominantly to the placebo group; only 1 severe case was reported in the BNT162b2 group in the final analysis. The efficacy data suggest high efficacy against COVID-19 in a broad population of individuals.

- **Study C4591005**

Title: A Phase 1/2, Placebo-Controlled, Randomized, and Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate Against Covid-19 In Healthy Japanese Adults
Country: Japan

Study C4591005 is a Phase 1/2, randomized, placebo-controlled, and observer-blind study in healthy Japanese adults. The study will evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 mRNA vaccine candidate (BNT162b2) against COVID-19 administered as two 30-µg doses, 21 days apart, in Japanese adults 20 to 85 years of age.

Clinical laboratory tests were performed for the first 24 participants (12 participants 20 to 64 years of age and 12 participants 65 to 85 years of age) (clinical laboratory subset). Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain), and use of antipyretic medication were collected by all participants in an e-diary from Day 1 through Day 7 after each administration of study intervention. AEs were collected from the time the participant provided informed consent through 1 month after Dose 2. SAEs will be collected from the signing of the ICD to approximately 12 months after Dose 2.

In this study, 160 Japanese participants (including 130 participants 20 to 64 years of age [younger age group] and 30 participants 65 to 85 years of age [older age group]) were randomized in an approximate 3:1 ratio of BNT162b2 to placebo. Interim data show BNT162b2 was well tolerated, with local reactions and systemic events mostly mild or moderate in severity, and no immediate AEs within 30 minutes reported. An acceptable safety profile was observed in both younger and older Japanese adults with no SAEs reported through 1 month after Dose 2. Immune responses elicited by BNT162b2 were robust 1 month after Dose 2, consistent with data from the global program. These

[4] Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry June 2020.

encouraging results led to the marketing authorization of BNT162b2 in Japan. This study has since been converted to a post-marketing study.

PRAC comment:

This small study does not add to the current knowledge on the safety profile of Comirnaty.

Non-Interventional Studies

There were 3 ongoing non-interventional studies (C4591008, C4591012 and C4591006) up to 21 April 2021, which are presented below:

Study No.	Study Title and Country
C4591008 Voluntary PASS	**Study Title**: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers. **Country**: United States **Primary study objectives**: • Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization. **Secondary objectives:** • Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post vaccination. • Estimate the incidence rates of safety events of interest and other clinically significant events among sub cohorts of interest such as individuals who are pregnant, individuals who are immunocompromised, and stratified by age.
C4591012 Committed PASS (post-authorisation commitment)	**Study Title**: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine **Country**: United States **Primary study objectives:** • To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. • To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. **Secondary study objective**: • To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA, including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.
C4591006	**Study Title**: General Investigation of Comirnaty Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post- Approval Stage) **Country**: Japan **Study objective**: The healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of this product, information on serious adverse events and COVID-19

Study No.	Study Title and Country
	observed during the follow-up period will be collected, and the long-term safety of this product will be assessed (to be conducted as 11-month follow-up investigation after completion of Investigation of Health Status of Recipients Vaccinated First).

According to the MAH, there was no new safety information reported regarding these ongoing non-interventional studies.

PRAC comment:

Within the first interim report of the PASS study C4591012, which is listed in the RMP of Comirnaty, (procedure EMEA/H/C/005735/MEA/010), only demographic and clinical characteristics of the two cohorts (Pfizer-BioNTech COVID-19 vaccine recipients and seasonal influenza vaccines recipients) were provided. No safety information was provided in the first interim report of study C4591012. Studies C4591008 and C4591006 are not part of the EU RMP.

Medication Errors

During the reporting interval, there were no serious clinical trial cases contained in the Global safety database that reported medication errors.

From post-authorisation sources, 4,591 cases potentially indicative of medication errors were retrieved from the global safety database worldwide up to 29 April 2021. Upon review, 447 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- Off-label use or misuse rather than medication error was reported in 95 cases;
- Questions about the scheduling of the 2 doses of BNT162b2 and/or information that the second dose may be administered (but it was not administered yet at the time of reporting) or was scheduled outside the prescribed dosing window were reported in 169 cases;
- No error or intercepted/potential error with BNT162b2 were identified in 183 cases, including 55 cases where the callers asked for information other than the scheduling of the 2 doses of BNT162b2.

Among the 4,144 relevant medication error cases, the following scenarios, were described:

- Medication errors associated with harm [i.e., resulting in adverse reaction(s)] were reported in 154 cases (3.7% of relevant medication error cases);
- Medication errors without harm [i.e. not resulting in adverse reaction(s)] were reported in 3,814 cases (92.0% of relevant medication error cases), of which 2,043 cases involved co-reported AEs;
- Potential medication errors were reported in 172 cases (4.1% of relevant medication error cases).
- Intercepted medication errors were reported in 4 cases (0.1% of relevant medication error cases).

The analysis of the relevant cases indicative of medication error did not lead to any change in the RSI with regard to the instructions for preparation, administration or storage of BNT162b2.

PRAC comment:

No new safety signal was identified from the cases reporting medication errors.

Medication errors are also analysed in the MSSRs for Comirnaty. From the MSSR assessments covering the period from 21 December 2020 to 29 April 2021, no safety issues were identified that required mitigation activity.

The MAH stated that further analysis of cases indicative of medication errors will be provided in the PSUR with DLP of 18 June 2021. This is accepted.

Non-clinical Data

No new non-clinical safety findings were identified in the period from 21 December 2020 to 21 April 2021.

Literature

Nonclinical (Published)

According to the MAH, a search of the Medline and Embase databases did not identify non-clinical studies that presented important new safety findings for Comirnaty up to 21 April 2021.

Clinical (Published)

From a search of the Medline and Embase databases up to 21 April 2021, the MAH identified 4 clinical trials that presented important new safety/efficacy findings for Comirnaty when administered in at risk patients (i.e., patients on haemodialysis) or special population, including elderly and pregnant/lactating women. The abstracts are presented in table 3 below.

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	At Risk Patients
1.	***Grupper A, Sharon N, Finn T, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol. 2021. doi: 10.2215/CJN.03500321.*** **Background and objectives:** Coronavirus disease 2019 (COVID-19) is associated with higher morbidity and mortality in patients on maintenance hemodialysis. Patients on dialysis tend to have a reduced immune response to infection or vaccination. We aimed to assess, for the first time to the best of our knowledge, the humoral response following vaccination with the BNT162b2 vaccine in patients on maintenance hemodialysis and the factors associated with it. **Design, setting, participants, & measurements:** The study included 56 patients on maintenance hemodialysis (dialysis group) and a control group composed of 95 health care workers. All participants had received two doses of the BNT162b2 (Pfizer-BioNTech) vaccine. The serology testing was done using Quant II IgG anti-Spike severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) assay by Abbott a median of 30 days after receipt of the second dose of the vaccine. **Results:** All subjects in the control group developed an antibody response compared with 96% (54 of 56) positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; interquartile range, 1128–5651) were significantly lower than in the control group (median, 7401; interquartile range, 3687–15,471). A Mann–Whitney U test indicated that this difference was statistically significant (U=1238; P<0.001). There was a significant inverse correlation of age and IgG levels in both groups. The odds of being in the lower quartile were significantly higher for older individuals (odds ratio, 1.11 per year of age; 95% confidence interval, 1.08 to 1.20; P=0.004) and for the dialysis group compared with the control group (odds ratio, 2.7; 95% confidence interval, 1.13 to 7.51; P=0.05). Within the dialysis group, older age and lower lymphocyte count were associated with antibody response in the lower quartile (odds ratio, 1.22 per 1-year older; 95%

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	confidence interval, 1.13 to 1.68; P=0.03 and odds ratio, 0.83 per 10-e3/µl-higher lymphocyte count; 95% confidence interval, 0.58 to 0.97; P=0.05). **Conclusions**: Although most patients on maintenance hemodialysis developed a substantial humoral response following the BNT162b2 vaccine, it was significantly lower than controls. Age was an important factor in the humoral response, regardless of chronic medical conditions.
	Special Patient Population(s)
2.	***Abu Jabal K, Ben-Amram H, Beiruti K, et al. Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: Real-world evidence from healthcare workers, Israel, December 2020 to January 2021. Euro Surveill. 2021; 26(6):2100096. doi: 10.2807/1560-7917.ES.2021.26.6.2100096*** The BNT162b2 mRNA COVID-19 vaccine showed high efficacy in clinical trials but observational data from populations not included in trials are needed. We describe immunogenicity 21 days post-dose 1 among 514 Israeli healthcare workers by age, ethnicity, sex and prior COVID-19 infection. Immunogenicity was similar by ethnicity and sex but decreased with age. Those with prior infection had antibody titres one magnitude order higher than naïve individuals regardless of the presence of detectable IgG antibodies pre-vaccination.
3.	***Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Efficient maternofetal transplacental transfer of anti- SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis. 2021: ciab266. doi: 10.1093/cid/ciab266. (Accepted manuscript).*** Maternal and cord blood sera were collected from 20 parturients who received the BNT162b2 vaccine. All women and infants were positive for anti S- and anti-RBD-specific IgG. Cord blood antibody concentrations were correlated to maternal levels and to time since vaccination. Antenatal SARS-CoV-2 vaccination may provide maternal and neonatal protection.
4.	***Kelly JC, Carter EB, Raghuraman N, et al. Anti-SARS-CoV-2 antibodies induced in breast milk after Pfizer-BioNTech/BNT162b2 vaccination: SARS-CoV-2 antibodies in breast milk after vaccination. Am J Obstet Gynecol. 2021: S0002-9378(21)00211-8. doi: 10.1016/j.ajog.2021.03.031.*** **Objective:** In December 2020, 2 lipid nanoparticle-formulated, nucleoside-modified messenger RNA–based vaccines received emergency use authorization by the US Food and Drug Administration, after their trials demonstrated 94% to 95% efficacy in preventing coronavirus disease 2019 (COVID-19). Although no lactating people were included in the vaccine trials, national organizations support vaccination of this population, suggesting potential infant protection by passive transfer of maternal antibodies. The authors sought to characterize breast milk levels of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in lactating people undergoing COVID-19 vaccination. **Study Design:** Participants were prospectively recruited during phase IA rollout of the COVID-19 vaccine at a tertiary care center, after institutional review board approval. Inclusion criteria included lactation and planned vaccination with the Pfizer-BioNTech BNT162b2 vaccine. After obtaining informed consent, participants provided frozen breast milk samples at the following time points of vaccination: before, within the first 24 hours, and the following week. Samples were assessed for SARS-CoV-2 RNA by quantitative real-time polymerase chain reaction and antispike immunoglobulin (Ig) G and IgA by an enzyme-linked immunosorbent assay. **Results:** A total of 5 subjects and 29 human milk samples were included in the analysis. All prevaccine milk samples tested negative for SARS-CoV-2 RNA, as defined by the cycle threshold value of >40 for the N1 target. Antispike IgG and IgA levels were significantly elevated relative to the prevaccine baseline at all time points. Antispike protein IgG remained sustained at a significant elevation beginning at 20 days after the first dose compared with the prevaccine baseline (P=.0061), through the final milk sample (day 30–39 P=.0095, >40 days P=.0040. Levels of antispike protein IgA were significantly elevated from baseline, starting 2 weeks after the first dose (P=.0286) through to the final sample (day 20–29 P=.0121, day 30–39 P=.0095, >40 days P=.0040); however, individual level data suggest a possible gradual decline in antispike IgA in human milk over time after the second dose.

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Conclusion. The Authors characterized longitudinal breast milk levels of antispike IgG/A following Pfizer-BioNTech BNT162b2 vaccination, demonstrating sustained elevation of IgG/IgA levels. This response is similar to previous studies on maternal vaccination, which have shown high levels of breast milk IgA/G production for up to 6 months after vaccination for influenza and pertussis. A concurrent decrease in infant respiratory illness rates suggest that maternal vaccination confers protection against infection in breastfed infants. Thus, the Pfizer-BioNTech/BNT162b2 vaccination may also confer protection against COVID-19 to breastfed infants as well. Our study is limited by a small number of participants, but we report data that suggest a potential immune benefit to infants of lactating people up to 80 days after COVID-19 vaccination. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination.

PRAC comment:

It is agreed with the authors that further investigation regarding vaccination with BNT162b2 in subjects at higher risk of COVID-19 (e.g., patients on hemodialysis) or special populations, including elderly and pregnant/lactating women, is needed. From the literature provided by the MAH, no new safety issues were identified. No changes to the product information are considered warranted at this moment.

Overview of Signals: New, Ongoing, or Closed

Tabular Summary of Safety Signals Evaluated During the Reporting Period (21 December 2020 – 29 April 2021)

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Open Signals							
Myocarditis and Pericarditis	15 Feb 2021 Re-opened 19 April 2021 and closed as no risk on 05 May 2021. Re-opened 24 May 2021	Ongoing	-	Ongoing discussions with a health authority (Israel MoH) Requests from health authorities	To determine if myocarditis or pericarditis is a risk.	Clinical study and post-authorization safety database review	The available data has not supported a causal association with BNT162b2. The signal remains open as further data accrues, and independent health authority evaluations are in progress.
Dizziness	Initially opened on 18 Jan 2021 and closed on 31 March 2021 as risk not important) Re-opened after DLP of ACO (10 May 2021)	Ongoing	-	Post-authorization spontaneous reports and inquiry from a competent authority Re-opened due to inquiry from a competent authority	Dizziness is a frequently reported AE; EMA PRAC request for safety evaluation.	Clinical study and safety database case series review	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021). Dizziness was re-opened for evaluation after the DLP of this ACO.
Signal determined to be Important identified risk							
Anaphylaxis	08 Dec 2020	Closed	30 Dec 2020	Post-authorization reports of anaphylaxis; EMA request to include as an Important identified	Post-authorization reports of anaphylaxis	Review of unblinded clinical study data; review of post-authorization data	Anaphylaxis was included in the EU-RMP and US-PVP as an Important Identified Risk and was included as an adverse reaction in

				risk in EU-RMP and as an adverse reaction in EU SmPC at time of conditional approval; FDA request to include it as an Important Identified Risk in the US PVP			the Section 4.8 of the CDS and EU SmPC.
Signals Determined to be Risks							
Hypersensitivity reactions (other than anaphylaxis)	19 Dec 2020	Closed	13 Jan 2021	EMA request to include "Hypersensitivity" as an adverse reaction in EU SmPC at time of conditional approval	Potential hypersensitivity events (other than anaphylaxis) were assessed to determine if product labeling information needed to be updated for completeness.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Hypersensitivity was added as an adverse reaction (not important) to Section 4.8 of the EU SmPC per EMA request. Core Position: "Hypersensitivity (e.g. rash, pruritus, urticaria, angioedema)" was added to the CDS as an adverse reaction.
Pain in extremity	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether pain in extremity is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, pain in extremity was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Pain in extremity has been added to the CDS as an adverse reaction.
Paraesthesia	29 Dec 2020	Closed	31 Mar 2021	Post authorization spontaneous reports and inquiry from a competent authority	Inquiries from Israel MOH and PRAC request for review.	Post-authorization reports and clinical study cases were reviewed. Reported events	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).

						that were reviewed included dizziness, paraesthesias and tachycardia among others	
Vomiting	16 Nov 2020 (before starting period of this ACO, ie., 21 December 2020) Re-opened 18 Jan 2021 following receipt of the 1st SMSR PRAC assessment report	Closed	Initially closed on 07 December 2020 (before starting period of this ACO) After re-evaluation, closed on 10 Feb 2021	Initially reviewed as a potential reactogenicity event in using unblinded clinical study data (DLP 14 Nov 2020) Re-opened due to inquiry from a competent authority	In review of unblinded clinical study data (data lock date 14 Nov 2020), vomiting was not found to occur at an increased frequency in vaccine group compared to placebo group following vaccination.	Review of unblinded clinical study data Review of post-authorization safety data	Based on evaluation of the post-authorization data, Vomiting has been added to the CDS as adverse reaction.
Diarrhoea	16 Nov 2020 (before starting period of this ACO, ie., 21 December 2020) Re-opened 18 Jan 2021 following receipt of	Closed	Initially closed on 07 December 2020 (before starting period of this ACO) After re-evaluation, closed on 10 Feb 2021	Initially reviewed as a potential reactogenicity event in using unblinded clinical study data (DLP 14 Nov 2020) Re-opened due to inquiry from a competent authority	In review of unblinded clinical study data (data lock date 14 Nov 2020), diarrhoea was not found to occur at an increased frequency in vaccine group compared to placebo group following vaccination.	Review of unblinded clinical study data Review of post-authorization safety data	Based on evaluation of the post-authorization data, Diarrhea has been added to the CDS and local labels as an adverse reaction.

	the 1st SMSR PRAC assessment report						
Tachycardia	28 Jan 2021	Closed	31 Mar 2021	Board of Health PV report	Noted as potential signal in PV Report from France (Marseille PV Regional Centre) for period 17 Dec 2020 to 15 Jan 2021.	Post-authorization reports and clinical study cases were reviewed. Reported events that were reviewed included dizziness, paraesthesias and tachycardia among others	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).
Vaccine stress-related responses	10 Feb 2021	Closed	31 Mar 2021	Post authorization reports	To determine if data is supportive of including the concept in the CDS and local labels.	Post-authorization reports and clinical study cases were reviewed. Reported events that were reviewed included dizziness, paraesthesias and tachycardia among other	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).
Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats	27 Apr 2021	Closed	27 Apr 2021	Clinical Trial Data	Based on review of unblinded clinical study C4591001 safety data (data lock date 13 Mar 2021), and supported by post-authorization AE reports, the following AEs were determined to be causally	Review of unblinded clinical study data; review of post-authorization data	Decreased appetite, Lethargy, Asthenia, Night sweats, and Hyperhidrosis has been added as ADRs to the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).

					associated adverse reactions for BNT162b2.		
Signals determined not to be a risk							
Facial nerve palsy	03 Dec 2020 (before starting period of this ACO, ie., 21 December 2020) opened as safety topic. 19 Dec 2020 reopened	Closed	10 March 2020	Clinical Trial Data Enquiry from competent authority Post-authorization reports	Initially opened and closed following review of unblinded clinical study data (C4591001) (DLP 14 Nov 2020). Re-opened due to EMA request to include as adverse reaction in EU SmPC at time of conditional approval. Signal closed on 10 March 2021.	Review of unblinded clinical study data; review of post-authorization and epidemiological safety data (Observed vs Expected analyses)	At the time of conditional approval by the EMA, facial paralysis was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core position: Based on the results of the evaluation to date, a causal association with BNT162b2 has not been established. However, causality assessment will be further informed by additional safety data from clinical study C4591001, and from non-interventional post-authorization safety studies which are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy after vaccination through formal comparative analyses. Facial nerve paralysis, an adverse reaction as presented in the SmPC, but not in the CDS, was re-reviewed and closed on 10 March 2021; there was not sufficient evidence to conclude a causal association to the vaccine. This signal will be re-opened for re-evaluation if appropriate when non-interventional study safety data is available.

Insomnia	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether insomnia is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Insomnia was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Insomnia is determined not to be a risk and no further action is warranted at this time.
Injection site pruritus	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether injection site pruritus is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Injection site pruritus was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Injection site pruritis is determined not to be a risk and no further action is warranted at this time.
Overdose	27 Dec 2020	Closed	20 Jan 2021	Post-authorization cases received of full-vial dosing per patient.	Review occurred to determine if there was further useful information with which to update Overdose section of labeling.	Post-authorization medication errors of full vial dosing and co-reported adverse events were reviewed	No significant new safety information was associated with these cases of overdose therefore it was determined that no updates to Overdose section of labeling was warranted.
Eye Pain & Eye Swelling	22 Jan 2021	Closed	03 Feb 2021	Inquiry from a competent authority	The 1st SMSR (with reporting period 01 December 2020 – 31 December 2020) PRAC	Review of post-marketing safety data	Based on review of post-authorization data, Eye pain and Eye swelling was determined not to be a risk for the vaccine.

					Assessment Report request prompted a review of the topic.		
Deaths including in elderly or frail individuals	18 Jan 2021	Closed	20 Jan 2021	Inquiry from a competent authority	Due to cluster of deaths in elderly and frail adults in Norway, as assessment of the cases was undertaken.	Review of post-authorization data and epidemiological safety data	Based on review of post-authorization data and epidemiology background data, death was determined not to be a risk for the vaccine.
Delayed Syncope	04 Feb 2021	Closed	24 Feb 2021	Competent authority (US-FDA) request for assessment	To determine if delayed syncope is a risk following the US-FDA request to provide an assessment of syncope occurring at least 1 day after vaccination.	Clinical study and safety database case review	Delayed syncope and loss of consciousness were evaluated, and it was determined that there is insufficient evidence to support a causal relationship to vaccine. The topic will continue to be monitored.
Hearing Loss and Tinnitus	08 Feb 2021	Closed	17 Feb 2021	Post-authorization reports and clinical safety data review. Note: Following internal review of hearing loss, the 2nd SMSR (with reporting period 01 January 2021 – 31 January 2021) EMA/PRAC final assessment requested review of hearing loss and tinnitus (Competent authority [EMA] request for assessment)	Cases of hearing loss were noted in clinical study C4591001 and in post-authorization reports.	Clinical study and safety database case series review Epidemiology observed vs expected analyses Note: Following receipt of the 2nd SMSR PRAC Final assessment report, Hearing loss was re-evaluated, and Tinnitus was evaluated	Following evaluation of reports and vaccine literature, it was determined that that the available data did not support a causal association with vaccine. The topic will continue to be monitored.

Immune Thrombocytopenia	21 Jan 2021 Re-opened 25 Feb 2021	Closed	Initially closed on 26 January 2021 After re-evaluation, closed on 08 Mar 2021	Inquiry from multiple competent authorities Signal re-opened following receipt of EMA/PRAC final assessment report of the 2nd SMSR (with reporting period 01 January 2021 – 31 January 2021) requesting a review of immune thrombocytopenia	To determine if thrombocytopenia is a risk of vaccination.	Review of clinical and non-clinical study data and review of post-authorization and epidemiological safety data	Following evaluation, it was determined that that the available data did not support a causal association with vaccine. The topic will continue to be closely monitored.
Seizure	01 Mar 2021	Ongoing at DLP of this ACO; closed on 06 May 2021	06 May 2021	Routine review of post-authorization neurological events Request from a health authority (Saudi Arabia)	To determine if seizure is a risk.	Clinical study and post-authorization safety database review	The available data do not support a causal association with the vaccine. The topic will continue to be monitored.
Reaction associated with dermal fillers[a]	02 Mar 2021	Closed	24 Mar 2021	Medical literature and enquiry from health authority (EMA/PRAC)	To determine if this use of BNT162b2 causes reactions in individuals who have had dermal fillers injected.	Literature, clinical study cases and post-authorization safety database case series review	The available data do not support a causal association with BNT162b2 at this time. This topic will continue to be monitored.
Delayed skin reactions	08 Mar 2021	Closed	24 Mar 2021	Medical literature and enquiry from health authority (UK MHRA)	To determine if delayed skin reactions are a risk of BNT162b2.	Literature and post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. This topic will continue to be monitored.
Thrombo-embolic events, including	12 Mar 2021	Closed	31 Mar 2021	Reports for other COVID-19 vaccines and request for	To determine if thromboembolic events, including those associated	Post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. The topic will continue to be closely monitored.

those associated with thrombocytopenia				evaluation from health authorities	with thrombocytopenia, are a risk of BNT162b2.		
Extensive swelling of vaccinated limb[a]	18 Mar 2021	Closed	06 Apr 2021	Request from health authority (The Netherlands, Lareb and EMA PRAC)	To determine if extensive limb swelling following vaccination is a risk of BNT162b2.	Post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. This topic will continue to be closely monitored.
Herpes Zoster, including Ophthalmic herpes zoster	05 Oct 2020 as safety topic. Reopened 21 Feb 2021 Re-opened 26 Apr 2021	Ongoing at DLP of this ACO; closed on 30 April 2021	30 Apr 2021	Reports of herpes zoster in clinical studies and post-authorization AE reports on non-statistical line listing review	Initially opened as safety topic and closed as no risk following review of clinical study data (C4591001). To determine if herpes zoster including ophthalmic herpes zoster is a risk.	05 Oct 2020: Review of clinical study data 21 Feb 2021: Review of post-authorization safety and O/E analyses 30 Apr 2021: Review of post-authorization, clinical study and O/E data	The available data do not support a causal association with BNT162b2. The topic will continue to be monitored. The re-evaluation of this signal in April 2021 confirmed the above assessment.

ACO= Addendum to the Clinical Overview; ADR= Adverse Drug Reaction; AE= Adverse Event; CDS= Core Data Sheet; DLP= Data Lock Point; EMA= European Medicine Agency; EU= European Union; FDA= Food and Drug Administration; MHRA= Medicines and Healthcare Products Regulatory Agency ; MOH= Minister of Health; O/E= Observed vs Expected; PRAC= Pharmacovigilance Risk Assessment Committee ; PV= Pharmacovigilance; PVP= Pharmacovigilance Plan; RMP= Risk Management Plan; SmPC= Summary of Product Characteristics; SMSR= Summary Monthly Safety Report; US= United States

a. Variation (EMEA/H/C/005735/II/0038/G) has been submitted after DLP (on 19 May 2021) to add "Vaccine stress-related responses" to section 4.4 (Special warnings and precautions for use) and to add "Extensive swelling of the vaccinated limb" and "Facial swelling" to the EU SmPC section 4.8 (Undesirable effects).

PRAC comment:

Regarding the **ongoing signals** '*Myocarditis and Pericarditis*' and '*Dizziness*':

After the DLP of the ACO, section 4.4 of the SmPC has been updated with a warning for myocarditis and pericarditis (procedure IAIN/0050). Dizziness was included as part of 'stress-related responses associated with the process of vaccination' in section 4.4 of the SmPC. Myocarditis and Pericarditis were also added as ADRs in section 4.8 of the SmPC.

With regards to the **closed signals** for which signal closed is **accepted**:

Anaphylaxis: included as ADR in section 4.8 of the SmPC and added as important identified risk in the RMP. Signal closed is accepted.

Hypersensitivity reactions (other than anaphylaxis): included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G).
Signal closed is accepted.

Pain in extremity: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Vomiting: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Diarrhoea: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Tachycardia: as part of a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. Signal closed is accepted.

Vaccine stress-related responses: a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. Signal closed is accepted.

Facial nerve palsy: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Insomnia: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Injection site pruritus: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Overdose: based on review of post-authorisation medication errors of full vial dosing and co-reported adverse event in the 2nd MSSR, no significant new safety information was identified and no updates to the Overdose section of labelling was warranted. Signal closed is accepted.

Eye pain & Eye swelling: review of the cases reporting eye pain and/or eye swelling in the 2nd MSSR did not suggest a causal association with the Comirnaty vaccine. No update of the included ADRs in the Comirnaty SmPC was considered needed regarding eye pain and eye swelling. Closure of the signal concerning "Eye pain" and "Eye swelling" is accepted.

Hearing loss and Tinnitus: In the 3rd MSSR AR (covering 1 February until 28 February 2021), based on a cumulative review of the cases reporting hearing loss and/or tinnitus it was concluded that a causal association with Comirnaty exposure was not suggested and the signal was closed.

Seizure: under close monitoring as part of Neurological AESIs in the MSSRs. At the moment no new safety signal of seizure identified. Signal closed is accepted.

Reaction associated with dermal fillers: after the DLP of the ACO, Facial swelling (in vaccine recipients with a history of injection of dermatological fillers) has been added to section 4.8 of the SmPC (EMEA/H/C/005735/II/0038/G). Signal closed is accepted.

Delayed skin reactions: based on a review by the MAH of literature and cases reporting delayed skin reactions, a causal association was not supported. Signal closed is accepted.

Delayed syncope: following US-FDA request, delayed syncope and loss of consciousness were evaluated by the MAH. It was concluded that there is insufficient evidence to support a causal relationship to the vaccine. Signal closed is accepted.

Extensive swelling of vaccinated limb: after the DLP of the ACO, Extensive swelling of the vaccinated limb has been added to section 4.8 of the SmPC (EMEA/H/C/005735/II/0038/G). Signal closed is accepted.

The closed signals for which however further evaluation is **ongoing or requested in MSSR/PSUR** and therefore **cannot be considered closed** are the following:

Paraesthesia: as part of a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. This signal is closed, however, for the 8th MSSR (covering 1 July-31 July 2021) the MAH has been requested to provide an analysis of hypoaesthesia and paraesthesia and to discuss whether paraesthesia and hypoaesthesia are sufficiently covered in the product information in the context of stress-related reactions or these should be included in the product information as separate ADRs.

As an outcome of the review provided by the MAH in the 9th MSSR, PRAC did not agree that hypoesthesia/paraesthesia is sufficiently covered in the product information by the currently included text regarding stress-related reactions and requested the MAH to add hypoesthesia and paraesthesia to the product information (SmPC section 4.8 and PIL section 4) and to propose a frequency, via an appropriate variation procedure.

Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats: the CHMP adopted an Opinion on the 16th September 2021 to add as side effects to the product information of Comirnaty.

Deaths including elderly or frail individuals: no new safety information was identified based on review of the fatal cases (EMEA/H/C/005735/LEG/019). Death/fatal cases are reviewed in the MSSRs as a Special Situation.

Immune thrombocytopenia: a re-review of this signal is provided in the PSUR submitted in August 2021.

Thromboembolic events, including those associated with thrombocytopenia: at the moment, there is insufficient evidence to support a causal association. However, TTS (Thrombosis with Thrombocytopenia Syndrome) is an ongoing signal of the MSSR for Comirnaty. In addition, thromboembolic events are reviewed in the MSSRs as AESIs.

Herpes zoster, including ophthalmic herpes zoster: it should be noted that following assessment of the 7th MSSR, the MAH was requested to provide an analysis of herpes zoster and discuss possible mechanisms that could underpin herpes zoster reactivation following vaccination, in the PSUR submitted in August 2021.

Risk Evaluation

Summary of Safety Concerns

Safety Concerns at the beginning of the reporting period

Important Identified Risk	Anaphylaxis[a]
Important Potential Risk	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)[a,b]
Missing Information	Use in Pregnancy and While Breast Feeding[a,b]
	Use in Immunocompromised Patients[a]
	Use in Frail Patients With Co-Morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular disorders)[a]
	Use in Patients With Autoimmune or Inflammatory Disorders[a]
	Interaction With Other Vaccines[a]
	Long-Term Safety Data[a]
	Use in Paediatric Individuals <16 Years of Age[b]
	Vaccine Effectiveness[b]

a. As per EU RMP ver. 1.0 (dated 21 December 2020).
b. As per the EUA PVP ver. 0.2 (dated 05 December 2021).

During the reporting period, the EU RMP has been updated as follows:

- EU RMP version 1.0 (dated 21 December 2021, when the initial marketing authorization was granted) was updated during the reporting period (EU RMP version 1.1, dated 17 March 2021 and approved on 15 April 2021), to revise the post-authorization vaccine effectiveness study C4591014 included in the RMP (Category 3) as a commitment and to add 2 vaccine effectiveness epidemiology studies (WI235284 and WI255886) not sponsored by Pfizer.
- After DLP of this ACO, on 4 May 2021 and on 14 May 2021, EU RMP version 2.0 (dated 29 April 2021) and version 2.1 (dated 14 May 2021) were submitted.

  EU RMP version 2.0 was submitted on 30 April 2021 with Variation 0030 to seek for extension of the indication to individuals aged 12-15 years of age; on 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 years and the European Commission adopted a decision accordingly on 31 May 2021.

  EU RMP version 2.1 has been submitted in the context of Variation 0036.

No changes to the list of the safety concerns were implemented in the above stated EU RMPs during and after the reporting period of this ACO.

PRAC comment:

Based on the data submitted with the renewal application, no changes are warranted for the RMP.

At the end of the interval period, the missing information "*Use in pediatric individuals <16 years of age*" was re-worded to "*Use in paediatric individuals <12 years of age",* which is only applicable for the EUA US PVP.

Furthermore, the CHMP adopted an Opinion on the 16th September 2021 for the EMEA/H/C/005735/II/0036 variation in which the RMP version 2.2 was approved.

3.4. Pharmacovigilance inspections

During the renewal period, the following inspection of MAH's pharmacovigilance system was conducted:

Inspecting Authority	Site Inspected	Inspection Start Date	Inspection End Date	Type of Inspection	Impact of findings on benefit/risk balance of BNT162b2
Swissmedic	Pfizer Switzerland Office (Virtual)	8 March 2021	9 March 2021	Routine Pharmacovigilance Inspection	None of the findings impacts the B/R of BNT162b2

PRAC comment:

The MAH was requested to provide the findings of the inspection performed by Swissmedic. (**Request for Supplementary Information**)

4. Risk management plan

The MAH has confirmed the current approved RMP remains unchanged and applicable.

Since the granting of the marketing authorisation, the following changes have been implemented in the RMP:

- Revision of the Pharmacovigilance Plan, including updates on milestones, objectives, study rationale and design;
- Revision of the post-authorization vaccine effectiveness study C4591014 and addition of 2 new vaccine effectiveness epidemiology studies;
- Update of the indication to include individuals aged 12-15 years, with supporting epidemiology and exposure data;
- Inclusion of myocarditis and pericarditis as important identified risks, with supporting data from clinical trials and safety databases and update of the information on planned/ongoing post-authorization safety studies with inclusion of 2 new studies, and the circulation of a DHPC;
- Inclusion of a new formulation and update on potential medication errors.

5. Changes to the Product Information

No changes to the Product Information (PI) are introduced with this renewal procedure.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Comirnaty (COVID-19 mRNA vaccine

(nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

The summary of product characteristics and the package leaflet therefore includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle

6. Request for Supplementary Information - RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI:

6.1. Other concerns

Clinical aspects

1. The MAH is requested to provide the findings of the inspection performed on 8-9 March 2021 by Swissmedic.
2. The MAH is requested to explain what "BNT162S017" is compared to BNT162b1 and BNT162b2.

7. Assessment of the MAH responses to the RfSI

7.1. Other concerns

Clinical aspects

Question 1

The MAH is requested to provide the findings of the inspection performed on 8-9 March 2021 by Swissmedic.

Summary of the MAH's response

The findings of the inspection performed on 8-9 March 2021 by Swissmedic can be found in the audit report herewith submitted as attachment to the cover letter. The audit report is a redacted copy of the final Pfizer response (redacted inspector names and Pfizer names for privacy), also you will notice there are track changes in the report as Swissmedic had asked for updated responses to be tracked in the final response as accepted by Swissmedic. Additionally, please note that this audit report contains information that is considered confidential by Pfizer..

Assessment of the MAH's response

As requested, the MAH provided the findings of the inspection performed by Swissmedic on 8-9 March 2021. It is acknowledged that the content of the audit report is confidential and therefore is not

presented in this assessment report. In the context of the MSSR assessment, several comments have been made regarding the handling and presentation of data. The inspection from Swissmedic did not raise additional issues relevant for the EU.

Conclusion

Issue is solved.

Question 2

The MAH is requested to explain what "BNT162S017" is compared to BNT162b1 and BNT162b2.

Summary of the MAH's response

The code BNT162S017 reported on page 12 of the Addendum to the Clinical Overview submitted in the renewal application results from a typo and should be read as BNT162b2s01.

The figure 7 at the end of the code refers to the footnote 7 where it is stated that BNT162S01 is also named BNT162SA. In the same footnote (footnote 7, Page 12) BNT162SA should read as BNT162b2SA.

Both these codes (BNT162b2s01 and BNT162b2SA, in the submitted ACO erroneously reported as BNT162S01 and BNT162SA) refer to the same clinical candidate, a new construct based on BNT162b2 and modified to address the B.1.351 lineage, first identified in South Africa. This clinical vaccine candidate has been introduced in study C4591001 / BNT162-02 as part of the global program to address emerging variants.

Assessment of the MAH's response

The code "BNT162S017" was a typo and should be BNT162b2s01, also named BNT162b2SA , which is explained as a new construct based on BNT162b2 and modified to address the B.1.351 lineage, first identified in South Africa. This is noted.

Conclusion

Issue is solved.

8. Overall conclusions and benefit-risk balance

8.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal, data on the Quality Specific Obligations (SOBs) have been submitted. Interim reports and monthly updates have been provided as requested.

Regarding the Quality SOB 003: *In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data,* on the 20th May 2021, following the assessment of additional validation data (provided in variation EMEA/H/C/005735/II/0023/G), the CHMP was of the opinion that the obligation had been fulfilled, and therefore recommended its deletion from the Annex II.

For the Quality SOB 001, SOB 002, SOB 004 and SOB 005 the due date was July 2021. On 27 July and 2 August 2021 respectively, the MAH submitted two variations (EMEA/H/C/005735/II/0054/G and EMEA/H/C/005735/II/0056/G) to provide the additional data requested to fulfil these SOBs. These variations are currently under assessment by CHMP and Requests for Further Information have been adopted on 14 October 2021.

During the period covered by this annual renewal interim data on the clinical SOB 006 have been submitted that overall are compliant in terms of adherence to deadlines and in terms of acceptability of data submitted. The available clinical evidence includes a tolerable safety profile and high vaccine efficacy against COVID-19 in individuals ≥12 years of age.

Updated list of specific obligations (SOBs)

In the framework of a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Number	Description	Due date
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

8.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the established benefit-risk balance of Comirnaty in the approved indication.

The data collected as part of the specific obligations for Comirnaty during the period covered by this annual renewal support its positive benefit-risk balance in the approved indication.

Favourable effects

The favourable effects were demonstrated in the initial marketing authorisation for persons 16 years of age and older and updated in a type II variation to also include adolescents 12-15 years of age. No additional efficacy data have been submitted during this renewal procedure. The most important favourable effects are briefly summarised below.

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

The efficacy of the vaccine (BNT162b2, 2 doses of 30 µg, separated by 21 days) to prevent COVID-19 in the adolescents aged 12- 15 years either without or with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 100.0% (CI95% 75.3, 100).

In addition, Comirnaty was shown to elicit non-inferior immune responses in subjects 12-15 years of age without previous Covid-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2.

Uncertainties and limitations about favourable effects

The uncertainties and limitations of favourable effects are similar to those at the time of the initial assessment and were updated in variation EMEA/H/C/005735/II/0030 (12-15-year-old subjects). The principal uncertainties remain on duration of protection and efficacy in risk groups, e.g. pregnant women and immunocompromised subjects. Since the initial approval, uncertainty regarding the vaccine efficacy against upcoming virus variants of concern has arisen with variants of concern (VOC) emergence.

Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty in the initial approval application. Overall, the safety profile of Comirnaty is considered acceptable. The product information has been updated since approval as new data has emerged. All data have been assessed in other procedures such as monthly safety updates, signal assessments and variations.

Uncertainties and limitations about unfavourable effects

The uncertainties and limitations of unfavourable effects have been discussed in other procedures. The principal uncertainties are related to long-term effects, and effects in specific risk groups.

Benefit-risk assessment and discussion

The benefits of Comirnaty in terms of protection against COVID-19 clearly outweigh the identified risks, and no new information has emerged during this renewal period that has changed the balance. The clinical SOBs are currently ongoing, according to plan. The quality related SOBs are also considered either fulfilled or ongoing according to plan.

Importance of favourable and unfavourable effects

Not Applicable.

Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk balance of Comirnaty remains positive.

9. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the marketing authorisation holder has complied with the specific obligations and the benefit-risk balance for Comirnaty in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable, and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

The renewal requires no amendments to the terms of the marketing authorisation.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific obligations to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

PSUR cycle

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.

10. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional marketing authorisation for Comirnaty, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

Please refer to Scientific Discussion 'Comirnaty/H/C/005735/R/0046'