Rapporteur Rolling Review critical assessment report

Assessment report on the claim of new active substance (NAS) status of 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein contained in COVID-19 mRNA Vaccine BioNTech

International non-proprietary name: Not yet assigned

Procedure no.: EMEA/H/C/005735/RR

Applicant: BioNTech Manufacturing GmbH

Rapporteur:	**Filip Josephson, Sweden**
Co-rapporteur:	**Jean-Michel Race, France**
EMA PL:	**Vanessa Seguin**
Start of the procedure:	**RR1 2020-10-06** **RR2 2020-11-07**
Date of this report:	**2020-11-19**
Deadline for comments:	**2020-11-23**
Date of the revised report	
Date of final report	

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Administrative information

Name of the medicinal product:	**COVID-19 mRNA Vaccine BioNTech**
Applicant:	BioNTech Manufacturing GmbH
Active substance:	5'capped mRNA encoding full length SRAS-CoV-2 Spike protein
International Nonproprietary Name/Common Name:	Not yet assigned
Pharmaco-therapeutic group (ATC Code):	J07BX
Therapeutic indication(s):	TBD
Rapporteur's contact person:	**Elin Blom** +46(0) 18 17 15 60 elin.blom@lakemedelsverket.se
Names of the Rapporteur assessors (internal and external):	**Anna Karin Rehnström** anna-karin.rehnstrom@lakemedelsverket.se

Declarations

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

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

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

1. Executive summary

1.1. Scope of the rolling review submission

This second rolling review cycle (RR2) included quality data only.

1.2. Problem statement

The applicant requested the active substance BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein contained in the above medicinal product to be considered a new active substance in itself.

2. Scientific evaluation

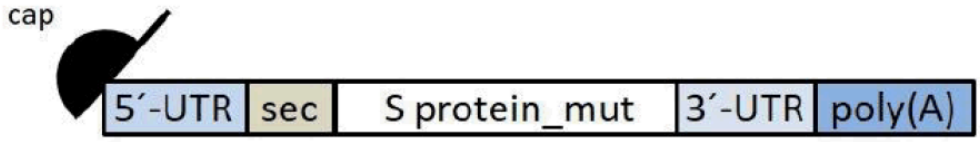
2.1. Quality aspects

Discussion on quality aspects

The active ingredient (BNT162b2, CAS Registry number 2417899-77-3, INN not yet assigned) of the COVID-19 mRNA Vaccine is a modified messenger ribonucleic acid (mRNA) encoding for a mutated full-length variant of the SARS-CoV-2 S protein, as described in Module 3.2.S.1.2 Structure. The RNA is encapsulated into lipid nanoparticles, which protect the RNA from degradation and enable transfection of the RNA into host cells after intramuscular injection for vaccination. The mode of action relies on intracellular translation of the mRNA to generate the target protein. The antigen is incorporated into the cellular membrane or secreted into the extracellular environment to induce an adaptive immune response. The primary read-out are antibody titers for the SARS-CoV-2 S protein that are expressed on the viral membrane. The expressed SARS-CoV-2 S protein is expected to mediate an immune response to the virus in several ways:

- The SARS-CoV-2 S protein is the antigen that recognizes and drives infection of the host cells. Therefore, the induction of neutralizing antibodies is crucial for the mode of action.
- As the SARS-CoV-2 S protein is fragmented and the resulting peptides are presented at the cell surface, the specific immune response against the virus is also based on T cell activation.

Figure 1 depicts the general structure of the COVID-19 mRNA. The mRNA structure is determined by the respective nucleotide sequence of the linear DNA used as template for in vitro RNA transcription and the 5'-cap analog. Of note, BNT162b2 uses N1- methylpseudouridine instead of uridine. In addition to the codon-optimized sequence encoding the target protein, the RNA displays common structural elements (described below in Table 1), which have been optimized for maximal efficacy (5'-cap, 5'-UTR, sec, 3'-UTR, poly(A)-tail).



Schematic illustration of the general structure of the RNA vaccine with 5'-cap, 5'- and 3'-untranslated regions, coding sequences with signal peptide, and poly(A)-tail. Please note that the individual elements are not drawn exactly true to scale compared to their respective sequence lengths.
UTR = Untranslated region; sec = signal peptide; S protein_mut = S protein sequence containing the two mutations K986P and V987P. These two mutations ensure that the S protein remains in an antigenically optimal prefusion conformation.

Figure 1 Structural schematic

The modified mRNA in the COVID-19 mRNA Vaccine is a chemical active substance that has not been previously authorised in medicinal products in the European Union. From a chemical structure point of view, the modified mRNA is not related to any other authorised substances. It is not structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance in the European Union.

The modified mRNA is not an active metabolite of any active substance(s) approved in the European Union. The modified mRNA is not a pro-drug for any existing agent. The administration of the applied active substance does not expose patients to the same therapeutic moiety as already authorised active substance(s) in the European Union.

A justification for these claims is provided in accordance with the "Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances" (EMA/CHMP/QWP/104223/2015), COVID-19 mRNA Vaccine is therefore classified as a New Active Substance and considered to be new in itself.

Conclusions on quality aspects

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the Rapporteur considers that BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein is to be qualified as a new active substance.

2.2. Non-clinical aspects

NA

2.3. Clinical aspects

NA

3. Overall conclusions

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the Rapporteur considers that BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein is to be qualified as a new active substance.

4. List of questions

Not applicable.