



# RECOMMENDATION FOR AN EMERGENCY USE LISTING OF TOZINAMERAN (COVID-19 mRNA VACCINE (NUCLEOSIDE MODIFIED)) SUBMITTED BY BioNTech Manufacturing GmbH

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## Abstract

*Tozinameran,<sup>1</sup> Novel COVID-19 mRNA vaccine (Nucleoside Modified) - Comirnaty®, was submitted to the World Health Organization (WHO) for evaluation under the Emergency Use Listing (EUL) procedure by BioNTech Manufacturing GmbH.*

*Tozinameran is a vaccine for preventing coronavirus disease 2019 (COVID-19) in individuals aged 16 years and older. Tozinameran contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2, the virus that causes COVID-19. Tozinameran does not contain the virus itself and cannot cause COVID-19.*

*The use of Tozinameran under an emergency situation has been also endorsed by the European Medicines Agency (EMA), the Food and Drug Administration (FDA) of the United States of America and Health Canada and other regulatory authorities (including Bahrain, Israel, Kuwait, Mexico, Oman, Qatar, Saudi Arabia, Singapore and the United Kingdom).*

*This report was prepared by the product evaluation group (PEG) and discussed by the technical advisory group for EUL (TAG-EUL).*

## 1 Introduction

### 1.1 Background

The current COVID-19 pandemic is unprecedented in the 21<sup>st</sup> century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020<sup>2</sup> to assess what is known about the new severe acute respiratory coronavirus -

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<sup>1</sup> Tozinameran is the International nonproprietary name of Novel COVID-19 mRNA vaccine (Nucleoside Modified) - Comirnaty® <https://www.who.int/teams/health-product-and-policy-standards/inn>

<sup>2</sup> <https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research>

2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint<sup>3</sup> aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

## **1.2 COVID-19 vaccines**

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The COVID-19 vaccine pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

The information available on COVID-19 candidate vaccines<sup>4</sup> and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g. MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials.

Vaccines that could exert protective immunity after a single dose are preferred, however most of the current candidate vaccines for COVID-19 require two doses.

## **1.3 Emergency Use Listing**

The Emergency Use Listing (EUL) is a time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the manufacturer

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<sup>3</sup> <https://apps.who.int/blueprint-brochure/>

<sup>4</sup> <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for its use following a thorough scientific risk benefit assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under EUL within their country.

## **2 Assessment process**

The COVID-19 vaccine manufactured by BioNTech Manufacturing GmbH was assessed under the WHO EUL procedure based on rolling submissions. The quality, safety, efficacy, risk management plan (RMP) and programmatic data were assessed by WHO Vaccine Prequalification experts and evaluators from National Regulatory Authorities (NRAs) from different regions.

Emphasis was placed on the RMP because of the need to consider the perspectives and concerns of regulators from different regions, that might otherwise not be considered by the NRA of reference for WHO – whose assessment is expected to be focused on issues related to its own jurisdiction.

The NRA of reference for WHO for this submission is the European Medicines Agency (EMA). The rolling submission data packages following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) were sent to WHO in parallel with the submissions to the EMA.

## **3 Scientific Review**

### **3.1 Nonclinical overview**

Tozinameran was immunogenic in mice, rats, and non-human primates (NHPs). In mice and NHPs, a rapid antibody response with measurable SARS-CoV-2 neutralizing titers after a single dose of BNT162b2 was observed. In NHPs given two doses of 30 µg or 100 µg BNT162b2, an increase in neutralizing antibody titers was shown after a second dose that exceeded titers observed in COVID-19 convalescent patient sera. Th-1 biased immune responses were observed in mice and NHPs. The vaccine provided complete lung protection in NHPs challenged with SARS-CoV-2, without evidence of vaccine-associated enhanced respiratory disease (VAERD). However, there was reduced but detectable virus in the nose and throat in vaccinated animals compared to controls.

Pharmacokinetic studies evaluated the biodistribution of an LNP-formulated modified RNA encoding luciferase in place of BNT162b2 and the metabolism and excretion of the two novel lipid excipients, ALC-0159 and ALC-0315, that are part of the BNT162b2 LNP formulation. The findings of a biodistribution study in mice suggested predominant biodistribution of BNT162b2 to the site of injection and the liver. According to the findings of the metabolism studies, ALC-0159 and ALC-0315 are slowly metabolized by hydrolysis. ALC-0159, in the unchanged form, was shown to be extensively excreted via the faecal route, and not by the urinary route, whereas excretion of ALC-0315 in the unchanged form was minimal by both the faecal and urinary routes.

In a repeat-dose toxicity study in which rats were administered three once-weekly doses of 30 µg/animal of BNT162b2 by intramuscular injection, vaccine administration was associated with increased cellularity in draining and inguinal lymph nodes, spleen, and bone marrow, along with increased body temperature, increased white blood cell (WBC) counts, and decreased reticulocyte counts coupled with decreased red blood cell mass. An acute phase response was suggested by observed clinical chemistry changes like increased acute phase protein levels. Inflammation and oedema at the site of injection was also observed on histopathological examination. These findings were expected and are consistent with an immunostimulatory response and acute phase response following the administration of a vaccine by the intramuscular route. Periportal hepatocellular vacuolation was observed, a finding that is consistent, with hepatic distribution of lipids that are part of the LNP formulation without evidence of altered liver function. After a 3-week follow-up these findings had totally or partially resolved.

### **3.2 Quality overview**

The dossier submitted by the BioNTech Manufacturing GmbH consisted of information related to the development, production and control of drug substance (DS) and drug product (DP).

The following summarizes the information contained in the different packages (20NOV20 / 09DEC20 / 11DEC20 / 24DEC20) submitted as part of the rolling submission.

With regards to the drug substance (immunogenic mRNA) of the vaccine, this includes the following:

- Control of source and starting materials of biological origin, including the cell banking system and its characterization;
- The manufacturing process, controls and process validation;
- Characterization, specifications and control of the drug substance, and selection of reference materials;
- The container-closure system and stability of the drug substance.

As for the drug product (LNP-mRNA vaccine) the assessed information included:

- Pharmaceutical development and description of the composition of Tozinameran;
- Development and description of the manufacturing process, process control and critical steps and control. Batch formula;
- Process validation or evaluation;
- Specifications, justification of the specifications and quality control of the vaccine, including description and validation of analytical methods;
- Reference materials;
- Vaccine batch analysis;
- Characterization of impurities and justification of specifications;
- The vaccine container-closure system;
- Stability and stability commitments;
- Information facilities and key equipment used in the manufacturing of the vaccine.

Tozinameran is currently manufactured targeting at a vaccine batch size of at least 300,000 vials. Smaller scale lots but comparable in terms of quality, safety and efficacy attributes, were used in the development of nonclinical and clinical lots.

Vaccine lots manufactured at the emergency lots scale are put on the stability studies to accumulate more data to support the claim of 6 months of shelf life when stored at -90 °C to -60 °C, and ultimately extend it to a desirable 12 months.

The manufacturing process of Tozinameran is complex but very controlled. It depends on important quality attributes of the RNA and the lipid nanoparticles that protect it and make it viable to deliver the desire antigenic payload in the human body. Critical is also the cold chain requirements to maintain the stability of the vaccine. These are critical aspect of this new generation of vaccines.

The company is committed to continue working to review and reassess the whole manufacturing process and critical parameters, as more batches are produced, and more data becomes available. This will also support the current information on consistency, not only by the availability of more data but also through a comparability exercise that will be carried out across lots, including the process qualification lots. Emergency vaccine lots as well as process qualification batches are part of the on-going stability programme. Therefore, more stability data will be available in the coming months.

### **3.3 Clinical overview**

The evidence to support Tozinameran comes from interim results of a phase 1/2 study (study BNT 162-01), a dose-escalation study conducted in healthy adults 18 to 55 years of age, in order to evaluate the safety and immunogenicity of several candidate vaccines at different dose levels, and a phase 1/2/3 pivotal clinical trial (study C4591001). Both studies are still ongoing. Study C4591001 is a randomized, placebo-controlled, observer blind, dose-finding, efficacy clinical trial conducted in the United States, Turkey, Germany, Brazil, Argentina and South Africa, with over 40,000 participants aged 12 to 85 years of age, to be followed up for two years. The first part of this study (phase 1/2) aimed at choosing the vaccine candidate based on safety and immunogenicity findings, whereas the second part (phase 3) aimed at assessing efficacy against symptomatic COVID-19 disease.

#### **3.3.1 Vaccine efficacy**

Vaccine efficacy was assessed from the phase 3 portion of study C4591001, which involved 43,651 participants (21,823 in the vaccine arm, who received 2 vaccine doses separated by 21 days, and 21,828 in the placebo arm). More than 20% of the participants (~8,000) were older than 65 years of age, whereas 88 participants, aged 12 to 15 years, were included in the study but not in the analysis. Immunocompromised individuals and those with previous clinical or microbiological diagnosis of COVID-19 were excluded from the trial, however people with pre-existing stable disease or infection (including those with human immunodeficiency virus (HIV), hepatitis C virus and hepatitis B virus) were not.

Symptomatic COVID-19 confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was the primary efficacy outcome of the study, determined in participants who did not have evidence of prior infection with SARS-CoV-2, occurring at least 7 days after the second dose of the vaccine or placebo.

Vaccine efficacy was estimated by comparing the incidences of symptomatic COVID-19 per 1000 person-years of follow-up in the vaccine and placebo study arms.

The final primary efficacy analysis included 36,523 participants 16 years of age and older followed up for a median 2 months. There were 8 confirmed symptomatic COVID-19 cases in the vaccine arm, and 162 cases in the placebo arm. Vaccine efficacy (determined at least 7 days after the second dose) was 95.0% (95% credible interval [CI] of 90.3% to 97.6%), whereas in participants 65 years of age and older this was 94.7% (95% CI of 66.7% to 99.9%).

No meaningful differences in vaccine efficacy were observed in subgroup analyses of participants based on age, sex, race/ethnicity, and country. Vaccine efficacy before the second dose administration was 52.4%. (95% CI of 29.5% - 68.4%).

### **3.3.2 Vaccine safety**

Vaccine safety took into consideration data from the two clinical trials, involving 37,706 participants monitored for solicited local/systemic reactions, unsolicited adverse events (AEs) and serious adverse events (SAEs). A subset of 8,183 participants 18 years of age and older, who received the vaccine or placebo were monitored for reactogenicity. The most frequent adverse events in vaccinated subjects were injection site pain (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%) and fever (14.2%), usually considered mild or moderate in intensity and that resolved within a few days.

Lymphadenopathy (0.3%), with an average duration of 10 days, was the unsolicited AE observed in the study participants. Four cases of Bell's palsy (facial paralysis) were reported in the vaccine arm, whereas none were observed in the placebo group. The applicant claims that the observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and that therefore there is no clear basis to support a causal relationship. Ten severe cases of COVID-19 were observed, 9 of them occurring in the placebo arm and one in the vaccine group, a finding that suggests that there is no evidence of the occurrence of VAERD. The AEs were in general milder and less frequent in the older participants ( $\geq 56$  years of age). No life-threatening AE or death was observed in this safety dataset.

There were no vaccine-related cases of anaphylaxis observed in the phase 2/3 clinical trial. After the vaccine's approval for emergency use in the United Kingdom and the United States and the start of its deployment for priority groups in these countries around mid-December 2020, though, there have been reports of anaphylactic/anaphylactoid reactions (as of 19 December, the Centers for Disease Control, in the United States, had seen six cases of anaphylaxis following the vaccination of 272,001 people).

Therefore, anaphylactic reaction reports have been very closely monitored and are continuously reviewed to ensure that labelling recommendations are appropriate and commensurate with the safety profile of the vaccine.

The current labeling provides patients and health care providers with appropriate guidance based on the currently known safety profile of the vaccine, including instructions on administration of the vaccine in

an appropriate setting with appropriately trained personnel, and contraindicating individuals with hypersensitivity to the vaccine or any of the listed components.

### **3.3.3 Immunogenicity**

In pivotal study C4591001 immunogenicity was studied in phase 1 and phase 2. Based on outcomes of the phase 1 study choice was made for the BNT162b2 30µg dose level vaccine candidate. In phase 2 this formulation was tested in 360 participants randomised to active group or placebo, stratified by age category 18-55 or 56-85 years. All 360 participants received both doses of study vaccine, except for 1 participant in the younger age group. Immunogenicity was measured with neutralisation assay and S1-binding IgG assay. In all analyses strong immune responses were observed compared to baseline and placebo.

Immune responsiveness also seems to be clearly age dependent. Both in the neutralisation assay and IgG titres, post dose 2 responses in the older adults (56-85 years) are significantly lower compared to the younger age category but responses were similar or higher than those measured in human convalescent sera. The same holds for the geometric mean fold rise. Pre-vaccination SARS-CoV-2 exposure had a strong influence on both neutralisation titers and IgG levels, which is similar to what is seen after re-infections. There is no indication of negative impact of prior exposure to wild virus on vaccine immune responsiveness.

The immunogenicity data generated in the phase 1 and phase 2 studies suggest that the vaccine is capable of inducing a strong immune response, in both the neutralisation assays as well as the S1-binding IgG assay. Data are available until 21 days post dose 2. It is important that long term follow up data are generated to better appreciate the persistence and possible need for booster vaccination. The cellular immune responses provide an indication that memory immunity is generated, which needs to be confirmed. The Th1- skewing in the CD4+ T cells is reassuring that the occurrence of disease enhancement will be less likely. Whether this will be the same in the population with prior SARS-CoV-2 exposure is presently unknown.

### **3.3.4 Special populations**

Regarding special populations, as already mentioned above, efficacy in individuals over 65 years of age was 94.7%, of similar magnitude to that observed in younger adults, whereas AEs were generally milder and less frequent in participants 56 years and older. Efficacy was not assessed in adults over 85 years of age, which includes the most frail individuals. The current evidence is that the efficacy and safety of the BioNTech Manufacturing GmbH COVID-19 vaccine is comparable in the elderly (older than 65 years of age) and other adults. A total of 23 pregnancies were observed in the study participants, 9 of whom withdrew from the study. No follow-up data about the outcome of these pregnancies was known at the time of the application. The use of the Tozinameran during pregnancy and for lactating women should only be considered when the potential benefits outweigh any potential risk for the mother and foetus or baby. The final result of the developmental and reproductive toxicity (DART) study was not available by the time of the review. There are currently limited data on the safety and effectiveness of this vaccine in immunocompromised individuals and the available data may not be generalizable to populations in low and middle-income (LMIC) countries who have profiles that can impact on the efficacy profile of the vaccine (for example, ethnicity, concomitant infections and malnutrition).

### 3.4 Risk Management Plan

The RMP submitted for EUL review is clearly focused on Europe and in the United States. The applicant's RMP includes one important identified risk - anaphylaxis , one important potential risk - vaccine-associated enhanced disease (VAED) including VAERD - and includes as missing information:

- Use in pregnancy and while breast feeding;
- Use in immunocompromised patients;
- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders);
- Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines;
- Interaction with other vaccines;
- Long term safety data.

The proposed routine and additional pharmacovigilance activities: studies, including 3 interventional and 5 noninterventional, for the above safety concerns, are considered acceptable but not sufficient for LMIC settings. Additional activities related to these specific conditions are discussed in Section 3.4.4 (pharmacovigilance plan).

The reviewers conducted the following analysis and provided recommendations.

#### 3.4.1 Product description

Acceptable in general.

#### 3.4.2 Nonclinical information

Experts considered that the nonclinical update including results from the DART study in Wistar Han rats should be submitted as soon as they are available (expected to be complete on Q1 2021).

In the repeat dose toxicity study in rats, after vaccine injection there was increased cellularity in the draining iliac lymph nodes, bone marrow and spleen and hepatocyte vacuolation in the liver.

Vacuolation of hepatocytes was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (liver functional enzymes were not elevated) and this is believed to be associated with hepatocyte uptake of the LNP lipids.

Injection site reactions: it is possible that the injection will generate site reactions like oedema and erythema in humans.

Inflammation and immune activation: There were changes secondary to inflammation including slight and transient reduction in body weights and transient reduction in reticulocytes, platelets and RBC mass parameters. In humans they could lead to increased body temperature and higher acute phase proteins.

Conclusion: An update of the ongoing DART study is required, however at this moment there is no need for additional information.



### 3.4.3 Clinical information

Important identified risks:

Risk	BioNTech	WHO Reviewers
None	√	
Anaphylaxis		√ The clinical information is not complete because the clinical trial is still ongoing. Two cases reported after emergency use approval in the United Kingdom and the United States.
Reactogenicity		√ The clinical information is not complete because the clinical trial is still ongoing. Reactions may be more severe after the second dose. Severe reactions could compromise the completion of the vaccination schedule.

Important potential risks:

Potential risk	BioNTech	WHO Reviewers
Vaccine-associated enhanced disease (VAED), including VAERD	√	√
Programmatic error		√

Missing information:

Missing information	BioNTech	WHO Reviewers
Use in pregnancy and lactation	√	√
Vaccine effectiveness	√	√
Long-term safety		√ (Limited safety data and follow-up to date)
Use in immunocompromised patients and patients with chronic or debilitating conditions		√ These populations were not included in the clinical trial program.
Interaction with other vaccines		√

## **Pharmacovigilance plan**

The tools for spontaneous reporting should be harmonized among countries. Ideally the Vigibase platform should be used.

Signal detection is another proposed approach to analyse the safety information. The proposal for Traceability and Cold Chain Traceability is very important, the sponsor should provide a “Vaccination Reminder Card” to the recipient or their caregiver (in all WHO regions) with the date of vaccination, the date when the recipient needs to return, the name of the recipient, the name of the vaccine, and a telephone number where to report side effects. It is important to ask the sponsor about their plans to implement the routine pharmacovigilance plan in all WHO regions.

The sponsor should be requested to provide a summary of interim and final studies in the Periodic Benefit-Risk Evaluation Reports (PBRERs) to be submitted to the WHO.

Pharmacovigilance plan and risk minimization activities should be provided for the required safety issues (See first table).

There is a general concern about the collection of adverse events (AEs) in regions such as Africa and Latin America that lack adequate pharmacovigilance structures. Some regions may lack data on background rates of specific diseases of interest and structures that require the manufacturer to monitor safety of their products in-country.

The manufacturer should clarify how the AE data obtained in-country through the web-based AE reporting portal will be made available to NRAs in the LMIC to enable country decisions on safety of the vaccine especially in countries where the pharmacovigilance system is in an early stage of implementation.

The manufacturer should clarify how the use of Data Capture Aids will be implemented and at which level of the healthcare delivery system, to capture accurately the clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine.

Additional pharmacovigilance activities: BioNTech Manufacturing GmbH should share the draft of the protocols of the observational studies, that were sent to other agencies. Also, the draft terms and conditions related to the RMP noted that BioNTech Manufacturing GmbH agrees to provide information to patients and healthcare professionals. In a global context important to know is not only which countries will participate in those activities, but also know about how information will be collected from different regions and how the analyses will identify differences between regions if any.

In support of EUL:

- Non-interventional studies (for primary data collection in healthcare workers) on AESI-based safety events should be proposed in some of the countries outside of EU and US (that is Rest of the World (RoW) countries), preferably, in a few countries spread across the WHO Regions with priority consideration for the countries that participated in the studies. The WHO-protocol (to be available mid-January) or an equivalent should be considered for these studies. The study design should be shared with WHO/PQ.

## 4 Outcome of review

### 4.1 Quality

As a result of the assessment conducted by WHO, the possibility of interacting with the EUL applicant, having participated in EMA meetings and discussions, as well as having access to responses the applicant provided to EMA to relevant questions, outstanding issues have been resolved. In addition to this, the applicant is committed to provide more information and data as soon as this is generated and re-assessed across the qualification lots, the emergency use lots and the clinical lots. Much more supporting information will be gathered in the months ahead, not only for the vaccine as a finished product but also from the formulation process.

Few issues with no impact on the quality of the product remain. The manufacturer has yet to submit part of the answers to the list of questions, however the outstanding answers should be provided as part of the post EUL recommendation.

Considering the above, there is sufficient information to support the listing of Tozinameran for emergency use.

### 4.2 Clinical

This clinical assessment raised a series of queries on different aspects of the nonclinical and clinical submitted evidence, and on issues related to the RMP. As of 22 December 2020, a list of comments and questions sent to BioNTech Manufacturing GmbH on 18 December was not yet replied to, and the CHMP approval document (conditional marketing authorization was recommended on 21 December) is not yet available for review.

From the clinical point of review both the PEG and TAG-EUL recommended that an EUL may be granted by WHO to BioNTech Manufacturing GmbH Tozinameran, provided that BioNTech Manufacturing GmbH commits to providing the following requested information post-EUL as soon as such information becomes available:

- The applicant should submit the final clinical study report of the study BNT 162-01, once the study is completed;
- The applicant should submit the final clinical study report (including safety, efficacy and immunogenicity data up to 2 years after Dose 2) for the randomized, placebo-controlled, observer blind study C4591001. That study report should be available by December 2023;
- The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing phase 3 study-C4591001 as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine;
- The outcome of the pregnancies observed in the clinical studies should be reported;
- The Risk Management Plan should include/address the following:
  - Safety specifications:  
Identified risks: include *Anaphylactic reactions (including history of anaphylaxis), reactogenicity*

- Potential risks: Include medication error
- Missing information: include *long term safety data, use in immunocompromised patients and patients with chronic or debilitating conditions, use in paediatric population <16 years of age, interaction with other vaccines and use in immunocompromised patients and other co-morbidities*
  - Pharmacovigilance plan:  
As part of the routine activities, “Traceability and vaccination reminder cards” should consider differences between regions or countries and the company should submit the tools and process to implement this.  
The manufacturer should clarify how adverse events / safety information is going to be collected as this may vary depending on the differences of health and pharmacovigilance systems; the clarification must address how the quality of the information will be guaranteed. The protocols of the observational studies should be included in the pharmacovigilance plan – they were not sent to WHO for review.
  - Risk minimization activities:  
The applicant should present regional annexes that advise the correct implementation of risk minimization activities in consideration with the differences between regions or countries. They should include:
    - Guidance that the vaccine should only be administered in appropriately equipped facilities that have professionals trained to attend cases of anaphylactic shock;
    - A proposal for the educational materials for healthcare professionals to administer the vaccine;
    - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.

## 5 Technical considerations

### 5.1 Vaccine characteristics

Comirnaty® Novel COVID-19 mRNA vaccine (nucleoside modified), is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) for injection.

The vaccine is presented in a multidose vial and must be diluted before use.

The vaccine is presented in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminium seal with flip-off plastic cap. It is a preservative-free multiple dose vial that contains 6 doses of 0.3 mL after dilution with 0.9 % sodium chloride. The undiluted vaccine vial requires a storage at -60 °C to -90 °C and comes with instructions to dispose of within 6 hours of opening to comply with the WHO Multi-Dose Vial Policy. Each vaccine vial must be diluted with 1.8 ml of 0.9 % sodium chloride to produce 6 doses of 0.3 mL each.

1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles or LNP).

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

The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

The composition of Novel COVID-19 mRNA vaccine is given in the table below.

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
BNT162b2 DS	In-house	Active ingredient	0.5	225 µg	30 µg
ALC-0315	In-house	Functional lipid	7.17	3.23 mg	0.43 mg
ALC-0159	In-house	Functional lipid	0.89	0.4 mg	0.05 mg
DSPC	In-house	Structural lipid	1.56	0.7 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	3.1	1.4 mg	0.2 mg
Sucrose	Ph. Eur.	Cryoprotectant	103	46 mg	6 mg
Sodium chloride	Ph. Eur.	Buffer component	6	2.7 mg	0.36 mg
Potassium chloride	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate	Ph. Eur.	Buffer component	1.08	0.49 mg	0.07 mg
Monobasic potassium phosphate	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Water for Injection	Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.

The diluent (sodium chloride 9 mg/mL (0.9%) solution for injection) contributes an additional 2.16 mg sodium chloride per dose.

ALC-0315 (((4-Hydroxybutyl)azanediyl) component of the lipid mixture used in the vaccine to form lipid nanoparticles.

ALC-0159 is a PEG/lipid conjugate (i.e. PEGylated lipid). 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide. It is a component of the lipid mixture used in the vaccine to form lipid nanoparticles.

DSPC or distearoylphosphatidylcholine is a phosphatidylcholine, a kind of phospholipid. It is used to prepare liposomes.

The LNPs are composed of 2 functional and 2 structural lipid components, enabling encapsulation of the RNA payload, formation and colloidal stability of the resulting LNPs, and the transfection process. The LNP components provides stability and protection to the capped RNA.

## 5.2 Special precautions for storage and handling

**Unopened vaccine vials have a shelf life of 6 months at -90 °C to -60 °C**. Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use. Once thawed, the vaccine should not be re-frozen.

Closed-lid vial trays containing 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 5 minutes for transfer between ultra-low-temperature environments. After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

Diluted medicinal product - Chemical and physical in-use stability has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, all opened WHO-prequalified multi-dose vials of vaccines should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first.<sup>5</sup>

The vaccine should be stored in a freezer at -90 °C to -60 °C, in the original package in order to protect it from light. During storage, minimise exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

When you are ready to thaw or use the vaccine, open-lid vial trays, or trays with less than 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments. Once a vial is removed from the vial tray, it should be thawed for use. After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

The vial must be diluted with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection before use.

## 5.3 Indication, warnings and contraindications

### Therapeutic indications

Comirnaty® is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

### Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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<sup>5</sup> [https://apps.who.int/iris/bitstream/handle/10665/135972/WHO\\_IVB\\_14.07\\_eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/135972/WHO_IVB_14.07_eng.pdf?sequence=1&isAllowed=y)

## Special warnings and precautions for use

### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

### General recommendations

#### *Hypersensitivity and anaphylaxis*

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty®.

#### *Anxiety-related reactions*

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

#### *Concurrent illness*

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

#### *Thrombocytopenia and coagulation disorders*

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

#### *Immunocompromised individuals*

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty® may be lower in immunosuppressed individuals.

#### *Duration of protection*

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

#### *Limitations of vaccine effectiveness*

As with any vaccine, vaccination with Comirnaty® may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

#### *Excipients*

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

## 5.4 Posology and method of administration

### *Posology Individuals 16 years of age and older*

Comirnaty® is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart (see sections 4.4 and 5.1).

There are no data available on the interchangeability of Comirnaty® with other COVID-19 vaccines to complete the vaccination course. Individuals who have received 1 dose of Comirnaty® should receive a second dose of Comirnaty® to complete the vaccination course.

### *Paediatric population*

The safety and efficacy of Comirnaty® in children and adolescents aged less than 16 years of age have not yet been established. Limited data are available.

### *Elderly population*

No dosage adjustment is required in elderly individuals  $\geq 65$  years of age.

### *Method of administration*

Comirnaty® should be administered intramuscularly.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6

## 5.5 Safety profile

The safety of Comirnaty® was evaluated in participants 16 years of age and older in 2 clinical studies that included 21,744 participants that have received at least one dose of Comirnaty®.

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty® and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty®.

At the time of the analysis of Study 2, a total of 19,067 (9,531 Comirnaty® and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty®. This included a total of 10,727 (5,350 Comirnaty® and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty® and 4,159 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Tabulated list of adverse reactions from clinical studies



Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common ( $\geq 1/10$ ),

Common ( $\geq 1/100$  to  $< 1/10$ ),

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ),

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ),

Not known (cannot be estimated from the available data).

**Table 1: Adverse reactions from Comirnaty® clinical trials**

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Blood and lymphatic system disorders			Lymph-adenopathy		
Immune system Disorders					Anaphylaxis; hypersensitivity
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache			Acute peripheral facial paralysis‡	
Gastrointestinal disorders		Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia		Pain in extremity		
General disorders and administration site conditions	Injection site pain; fatigue; chills; pyrexia*; injection site swelling	Injection site redness	Malaise; injection site pruritus		

\*A higher frequency of pyrexia was observed after the 2nd dose.

‡Throughout the safety follow-up period to date, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

The safety profile in 545 subjects receiving Comirnaty®, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

## **6 Monitoring of performance of the vaccine in the field**

BioNTech Manufacturing GmbH proposes a series of activities for post-authorization safety monitoring, focused on Europe and North America. Some of the proposed studies will also address effectiveness and immunogenicity.

These post-authorization activities do not include consideration of populations and special groups that may be commonly found in LMICs supplied with WHO approved COVID-19 vaccines. Available clinical data may not fully represent all populations.

### **6.1 Vaccine efficacy/effectiveness**

In addition to ongoing C4591001 clinical trial, that will determine vaccine efficacy up to two years after the second vaccine dose, BioNTech Manufacturing GmbH will sponsor other studies, mostly focused on safety, but some of them also aiming at studying vaccine effectiveness (study C4591014, in patients admitted to Emergency Department or hospital) or immunogenicity (studies C4591015, in pregnant women; C4591018, in rheumatoid arthritis assessed by Clinical Disease Activity Index; a phase 2 study in immunocompromised adults; and a study in immunocompromised individuals younger than 18 years).

### **6.2 Safety Monitoring**

In addition to the collection and monitoring of spontaneous reports by healthcare professionals and vaccinees:

Three post-authorization active surveillance epidemiologic safety studies, employing primary and secondary data collection methods, are planned to characterize the real-world incidence of safety events of interest. These include events indicative of severe or atypical COVID-19 disease in vaccinees. Three studies will identify cohorts of persons in the US receiving vaccine and estimate the incidence rate of AESIs over a 30-month period following vaccine availability under the EUA. These studies are designed to enable comparison with expected rates in unvaccinated population.

Two studies will include all patients documented as receiving vaccine within Department of Defence and Veteran's Healthcare Administration, which cover 10 million and 18 million lives, respectively.

The third aims to enrol 20,000 healthcare workers vaccinated with Tozinameran. These large studies conducted over a long period of time will allow for the study of rare outcomes in diverse populations including subgroups not yet studied in the clinical trial such as pregnant women, immune-compromised, and very elderly (>85 years of age) persons.

Four additional pharmacoepidemiology safety studies (two in the US, two in the EU) are planned to be implemented post-authorization. They will employ a variety of data sources and analytic methods that are intended to complement FDA/CDC active surveillance safety monitoring initiatives.

CDC will also implement a text messaging and web-based monitoring system called Vaccine Safety Assessment for Essential Workers (V-SAFE) designed as an active surveillance system to capture safety data among healthcare workers and other essential workers. The United States Vaccine Adverse Event Reporting System (VAERS) staff will follow up on reports of clinically important adverse events (AEs) to ensure a VAERS report is completed.

To ensure transparency, BioNTech Manufacturing GmbH results will be exchanged with a planned vaccine safety subcommittee that will enable communication between government agencies and manufacturers and the public.

### **6.3 Programmatic aspects**

The use of Tozinameran in the field in LMICs could be challenging. As mentioned, one of the critical issues to guarantee the stability and the quality of the vaccine are the cold chain requirements.

The conditions for the handling of vials, the withdrawal of the correct amount of diluent, and the way to dilute and homogenize the vaccine, would require dedicated training sessions and qualification.

The vaccine does not bear a vaccine vial monitor (VVM).

## **7 SAGE recommendations**

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, WHO has already issued two guidance documents in relation to COVID-19 vaccination, namely a Values Framework<sup>6</sup> and a Roadmap for prioritization of populations under situations of scarce supply<sup>7</sup>. Together, both documents provide orientation to countries on the ethical and values foundation of a vaccination programme against COVID-19, and a rationale for prioritizing populations under conditions of severely limited, limited and moderately limited supply and different epidemiological scenarios. The initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

On January 5, 2021, SAGE will review available data on Tozinameran with a specific view of addressing the above-mentioned use scenario. GRADing will be applied to clinical data on efficacy and safety for

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<sup>6</sup> <https://www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination>

<sup>7</sup> <https://www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply>

adult and older populations, and individuals with underlying conditions, and an evidence to recommendations framework will be used to consider additional criteria on values & preferences, resources requirements, equity, acceptability and feasibility of the intervention in a public health programme. A formal WHO position on the use of the vaccine will be communicated a few days after the SAGE meeting.

## **8 Regulatory oversight**

The National Regulatory Authority of record for Tozinameran is the EMA who granted a conditional Marketing Authorization to the vaccine. The WHO Vaccine Prequalification Team will continue to rely on the regulatory oversight of EMA and will continue fostering participation in EMAs decision making process, as possible and when possible.

## **9 Benefit/Risk Assessment**

According to WHO the COVID-19 pandemic has caused, as of 22 December, over 76 million cases of the disease and over 1.69 million deaths<sup>8</sup>. COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection proved to be incorrect because the large majority of the population remains seronegative, which is evidence that they are susceptible to the virus. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

Study C4591001 was conducted in six countries in the Americas, Europe and Africa, involving 43,651 participants, 21,823 of whom received two doses of Tozinameran separated by 21 days. This trial has provided convincing evidence of vaccine efficacy (95.0%) in participants 16 years of age and over including those 65 years of age and older (94.7%, almost identical point estimate). Similar efficacy was shown to be independent of age, sex, race/ethnicity and country. No evidence of VAERD was observed in this study; out of 10 cases of SAE, 9 belonged to the placebo study arm. Efficacy was measured in terms of prevention of symptomatic COVID-19. It is currently not known whether the vaccine protects against SARS-CoV-2 infection, therefore it is possible, in theory, that vaccinated individuals can be protected against the disease but be infected and transmit the virus to contacts.

Tozinameran was associated with frequent local (injection site pain) and systemic (fatigue, headache, myalgia, chills, arthralgia, and fever) adverse reactions, usually mild or moderate and self-limited within a few days of vaccination. Unsolicited adverse events (AEs) were restricted to cases of lymphadenopathy (0.3%) which resolved without sequelae. There were no life-threatening AEs and deaths related to the vaccine. The very recent reporting of cases of anaphylactic/anaphylactoid reactions after the vaccine was deployed in the United Kingdom and in the United States has provoked some concern and is being closely monitored.

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<sup>8</sup> <https://covid19.who.int/>

The most important limitation of the data is the lack of information on the long-term safety and efficacy of the vaccine. The identified limitations can be managed through labelling and the RMP. Study C4591001 is ongoing and will continue to collect information on the long-term safety and efficacy of the vaccine, although there are concerns that a large proportion of the placebo arm will opt to vaccinate as soon as possible. The national regulatory authorities, that have approved Tozinameran, have required post-authorization commitments from the applicant for monitoring the long-term safety and efficacy of the vaccine. The RMP submitted to WHO is focused on Europe and the United States and may not be fully satisfactory for low- and middle-income countries.

The PEG and TAG-EUL have considered that the benefits of Tozinameran outweigh the risks associated with its use.

## **10 Conclusion**

Considering the public health need to halt COVID-19 morbidity and mortality and start immunizing the world's population to the largest extent possible, the introduction of vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on the available evidence assessed, the PEG and TAG-EUL find that sufficient data is available on BioNTech Manufacturing GmbH Tozinameran for an EUL recommendation to, subject to the manufacturer's commitments as indicated in the below sections.

### **10.1 Quality (CMC) perspective**

The company must commit to provide additional data in order to complete the information of the dossier submitted as follows:

- Complete leachable studies that are being set up to support the labelled shelf life of the vaccine in its commercial container closure system out to 24 months;
- Completed reports on hold times of material during the LNP manufacturing ( $\leq 16$  hours for LNP formation) and drug product that will be confirmed based on hold time results of the cumulative process validation lots;
- Confirmatory data of stability studies to confirm the initial shelf life claimed for the vaccine and extend it as per the protocols.

Additionally, and in line with the conditional Marketing Authorization (cMA) granted by the European Medicines Agency, the company should provide the following:

- Additional supportive characterization studies of drug substance and drug product are still ongoing., The company should provide the relevant update of the ranges for process parameters;
- Completed validation/qualification (PPQ) of the manufacturing process;
- The results of the planned demonstration of comparability across clinical, emergency use and PPQ lots.

## 10.2 Clinical perspective

- Final data from the DART study should be submitted once available.
- The applicant should submit the final clinical study report of the study BNT 162-01, once the study is completed.
- The applicant should submit the final clinical study report (including safety, efficacy and immunogenicity data up to 2 years after Dose 2) for the randomized, placebo-controlled, observer blind study C4591001. That study report should be available by December 2023.
- The applicant should encourage participants to remain in the ongoing phase 3 Study-C4591001 as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine.
- A Periodic Benefit Risk Evaluation Report (PBRER) should be sent to WHO every 6 months in the first year post EUL, followed by reporting on an annual basis.
- The outcome of the cases of pregnancy observed in the clinical studies should be reported as part of the PBRER.
- The RMP should include/address the following:
  - Safety specifications

Identified risks: *anaphylaxis reactogenicity*.

Potential risks: include VAED including VAERD, programmatic error

Missing information: include *long term safety data, use in immunocompromised patients and patients with chronic or debilitating conditions, use in paediatric population <16 years of age, interaction with other vaccines (co-administration)*.

    - Additional data are needed on vaccine effectiveness and safety on population groups represented in LMIC including individuals with conditions such as malnutrition and populations with existing co-morbidities such as tuberculosis, human immunodeficiency virus (HIV) infection and other high prevalent infectious diseases.
    - Additional data are also needed for vaccine co-administration, particularly in the case of seasonal influenza vaccines that are administered in campaigns and are targeted to, among others, the elderly and people with chronic diseases, that overlap with the target population for Tozinameran.
  - Pharmacovigilance plan

As part of the routine activities, “Traceability and Vaccination Reminder cards” should consider differences between regions or countries and the applicant should submit the tools and process to implement this.

The manufacturer should clarify how adverse events / safety information will be collected as this may vary depending on different health and pharmacovigilance systems; the clarification must address how the quality of the information will be warranted wherever the vaccine is used.

The protocols of the observational studies should be included in the pharmacovigilance plan – they were not sent for WHO review.

○ Risk minimization activities

The applicant should present regional annexes that ensure the correct implementation of risk minimization activities given the differences between regions or countries

They should include:

- Guidance should be provided that the vaccine should only be administered in facilities equipped and with trained staff to attend cases of anaphylactic shock.
- A proposal for the educational materials for healthcare professionals to administer the vaccine.
- A minimum period of 15-minutes of observation of each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.