SPF SANTE PUBLIQUE, SECURITE
DE LA CHAINE ALIMENTAIRE ET
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FOD VOLKSGEZONDHEID,
VEILIGHEID VAN DE
VOEDSELKETEN EN LEEFMILIEU

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Advisory board COVID-19 vaccins

Avis portant sur Advanced Purchase Agreement with Pfizer/BioNTech

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Advies Advanced Purchase Agreement with Pfizer/BioNTech

Réunion
18 novembre 2020

Vergadering
18 november 2020

Avis portant sur Advanced Purchase Agreement with Pfizer/BioNTech

I. Dossier

Lors de sa réunion du 16.11.2020 l' Advisory Board vaccins COVID-19 s'est penché sur le dossier d'achat anticipé (APA) portant sur le candidat vaccin COVID-19 de Pfizer/BioNTech, négocié par la Commission Européenne.

En ce qui concerne cet APA, le comité formule l'avis suivant :

"Compte tenu des évidences favorables fournies par les études non cliniques et cliniques ; l'avancement rapide de l'étude Ph3 et l'autorisation de mise sur le marché attendue par l'EMA en [redacted] *l'absence d'immunité préexistante des vecteurs ;* [redacted]*;*

Compte tenu également de l'incertitude générale relative aux vaccins de la plate-forme à ARNm (aucun vaccin à ARNm n'est actuellement approuvé, et [redacted]*, de l'absence de données sur la durée de la protection et sur la réponse cellulaire chez les personnes âgées, des conditions complexes de stockage et de distribution à très basse température,* [redacted]

L' Advisory Board *considère que dans le contexte actuel, sur la base des données disponibles, il n'y a*

I. Dossier

De Advisory Board COVID-19 vaccins heeft op 16.11.2020 het Advance Purchase Agreements (APA's) mbt het kandidaat COVID-19 vaccin van Pfizer/BioNTech besproken waarover de Europese Commissie heeft onderhandeld.

Met betrekking tot deze Advanced Purchase Agreement geeft de Board volgend advies:

"Gezien de beloftevolle resultaten van de niet-klinische en klinische studies; de snelle vooruitgang van de Faze 3-studie en de verwachte vergunning door het EMA in [redacted]*; de afwezigheid van reeds bestaande vectorimmuniteit;* [redacted]

Rekening houdend met de algemene onzekerheid over het mRNA-vaccinplatform (momenteel geen mRNA-vaccin goedgekeurd, [redacted]*, het ontbreken van gegevens over de duur van de bescherming en over de cellulaire respons bij ouderen, de complexe opslag- en distributieconditie bij ultra lage temperatuur,* [redacted]

is het Advisory Board *COVID 19 vaccins van mening dat er in de huidige context, op basis van de beschikbare*

pas de raisons significatives nécessitant de ne pas poursuivre ce contrat.

L' Advisory Board *recommande d'acheter le nombre de doses allouées au prorata de la population belge (~ 5,1 millions de doses).*

Le rapport complet de l' Advisory Board est ci-joint.

gegevens, geen belangrijke redenen zijn om dit contract niet te aanvaarden.

Het Advisory Board *beveelt aan om de toegewezen doseringen pro rata voor de Belgische bevolking aan te schaffen (~ 5,1 miljoen doseringen).*

Het integrale rapport van de Advisory Board is toegevoegd als bijlage.

II. Décision de la CIM

La CIM suit l'avis de l' Advisory Board sur l'APA avec Pfizer/BioNTech. La CIM donne son accord pour que le Ministre des Affaires Sociales et de la Santé informe la Commission Européenne de la position de la Belgique sur le contrat Pfizer/BioNTech-contract.

II. Beslissing van de IMC

De IMC volgt het advies van de Advisory Board mbt het Advanched Purchase Agreement with Pfizer/BioNTech. De IMC gaat akkoord dat de federale Minister van Sociale Zaken en Volksgezondheid de Europese Commissie op de hoogte brengt van het standpunt van België over het Pfizer/BioNTech-contract.

ANNEXES

Advisory board review 13 November 2020
Advanced Purchase Agreement with Pfizer BioNTech Vaccines
Pre-meeting Fiche

1. Administrative data

- Vaccine: **BNT162b2 (BioNTech/Pfizer)**
- Type: mRNA vaccin
- Administration: 0,3 ml , 2-dose schedule, separated by 21 days. The selected dose level is 30 µg RNA
- Route of administration: The vaccine is administered intramuscularly (IM).
- Clinical development phase: Phase III ongoing
- Marketing Authorization: Expected approval date [redacted]).

2. Scientific evaluation

This report is mainly based on limited published data and on the IB available via the EU scientific committee (v5).

CLINICAL DEVELOPMENT

Pfizer/BioNTech is [redacted]. The BNT162b2 candidate, encoding the full-length Spike protein, is currently evaluated in a Phase 3 efficacy trial. The vaccine will be administered in a 2-dose schedule, separated by 21 days, at a dose level of 30 µg RNA in both young and old adults. The BNT162b2 vaccine was the first of any COVID19 vaccine for which efficacy results were announced (press release).

IMMUNOGENICITY AND CHALLENGE STUDIES

Pharmacology studies performed by BioNTech demonstrate that a single immunization with BNT162b2 induces dose-dependent antigen-binding IgG and neutralizing antibody responses. T cell responses were assessed for the highest dose of 5µg. Both CD4+ and CD8+ cellular responses were induced, with a cytokine secretion indicative of a TH1-dominant profile. Humoral responses were confirmed in rats.

The NHP study, with a 2-dose regimen, confirms induction of both humoral and cellular immune response. A single dose induced binding and neutralizing antibodies, with substantial increases following the second immunization. [redacted]

Upon challenge 55 days after the second immunization, monkeys from the high dose group had lower levels of viral RNA in BAL compared to controls. [redacted]

However there is currently no identified NC major concern [redacted]

CLINICAL IMMUNOGENICITY AND EFFICACY

The first immunogenicity results indicate that binding and neutralizing antibodies are induced following two doses of BNT162b2 at a dose levels of 20 and 30 µg, in both young (18-55 yoa) and old (65-85 yoa) adults (n=12/group). Whereas the nAb GMTs induced by 2 vaccine doses of either 20 or 30 µg were similar in the younger adults, 2 vaccine doses of 30 µg induced higher nAb GMT when compared to the dose of 20 µg in the older adults. Similar trend was observed for S1-binging Ab. In contrast to the younger adults, GMT still increase through Day 35 in the older adults vaccinated with the dose of 30 µg. No data are available over a longer duration. [redacted] Based on these results, together with the reactogenicity data, the dose of 30 µg was selected to proceed in efficacy trial.

Pfizer Inc. and BioNTech announced in a press release of 09/11/2020 that their mRNA-based vaccine candidate, BNT162b2 against SARS-CoV-2 has demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis. The vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants, starting 28 days after the initiation of the vaccination (i.e. 7 days pot-dose 2). The clinical trial continues through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoints. It is not clear yet what the final vaccine efficacy will be, over a longer follow period. There is currently no published efficacy data available for this vaccine candidate, as for any of the COVID-19 vaccine candidates.

All the vaccine candidates reaching Phase 3 in Europe or the US can be assumed 'sufficiently promising' in terms of the limited data suggesting benefit, as they should have demonstrated sufficiently robust immune responses (at least nAb and Th1 responses) and an acceptable safety profile on a limited safety database in the earlier development phases. However, in this particular case of COVID-19, the absence of a correlate of protection makes early development not predictive of the efficacy.

NON-CLINCAL SAFETY

No nonclinical issues were identified [redacted]

CLINICAL SAFETY

Preliminary data for the vaccine candidate BNT162b2 indicate an acceptable reactogenicity profile at dose levels up to 30 µg, in both the younger and older individuals. Reactogenicity was slightly lower in the older group compared to younger individuals. Reactogenicity was higher with the second dose compared to the first. Based on limited data through 1 month after the receipt of the second dose, no safety issue was observed.

Safety data are very limited for mRNA-based vaccines in general.

Reactogenicity was observed to increase with vaccine dose levels for mRNA vaccines.
Subtle differences exists in the design and applied synthesis/manufacturing processes of the different mRNA candidates. Each Company has its own approach, and it is currently not possible to predict which approach is able to achieve the best balance between reactogenicity and immunogenicity.
Vaccine induced enhanced disease (VED) is considered as a theoretical risk with SARS-COV-2 vaccines based on data generated with inactivated SARS-COV-1 and other coronaviruses vaccines in animals.
The occurrence of autoimmune disease is a theoretical risk associated with mRNA vaccines, as with many other types of vaccines (such as adjuvanted vaccines).
mRNA is a non-infectious, non-integrating platform. Hence, there is no potential risk of infection (as compared to potential risk for live-attenuated vaccines or vaccines based on replication active vectors)

COMPARISON TO OTHER VACCINE CANDIDATES
- Compared to other platforms such as adenovirus vectored vaccines, or technologies such as recombinant adjuvanted vaccines, the mRNA concept is associated with a higher level of uncertainties as this is a more novel concept. There is very limited clinical safety and immunogenicity data for the mRNA platform. There is no published efficacy data for a mRNA-based vaccine against infectious diseases. The BNT vaccine was the first of any COVID19 vaccine for which efficacy results were announced (press release).
- The BioNTech/Pfizer vaccine is one of the most advanced COVID-19 vaccine candidates in terms of the Phase 3 trial together with the Moderna. Astra Zeneca and Janssen vaccines also are in Phase 3, but recruitment is less advanced.
- mRNA constructs can intrinsically trigger the innate immune responses needed to initiate generation of antigen-specific responses. Hence, theoretically, there is no need for additional adjuvants as compared to protein-based subunit vaccines or inactivated vaccines.
- Beside induction of humoral and CD4+ T cell responses (also typically induced by protein-based subunit vaccines or inactivated vaccines), mRNA-based vaccines can potentially also induce strong CD8+ T cell responses. This is a common characteristic of mRNA, plasmid DNA, viral-vectored or live-attenuated vaccines.
- Anti-vector immunity is in principle not induced, in contrast to the human viral-vector based vaccines, and this implies that the mRNA platform can potentially be used to target different diseases or for prime/boost immunization schemes for a same targeted pathogen.
-Immunogenicity data observed in humans cannot be compared across vaccine candidates, due to the absence of a correlate of protection, and the lack of standardisation of assays.
- Comparison the 3 mRNA vaccine candidates :
Levels of induced innate responses, and therefore impact the antigen-specific adaptive immunity induced, can be modulated by the rational design of the mRNA construct and by the production process applied/used. Each Company has its own approach, and it is currently not possible to predict which approach is able to achieve the best balance.
All three vaccines require a two-dose schedule (3 or 4 weeks apart).

BioNTech/Pfizer and Moderna vaccines are currently evaluated in efficacy trials, which is not the case of the CureVac vaccine. BioNTech published data from their Phase 1. Not data are yet published for Curevac.

CONCLUSION

Overall, based on the data we had available at the time of assessment, we consider BNT162b2 as a promising vaccine candidate. We did not identify concerns that would render this candidate a lesser choice from scientific point of view. There are currently no data available that could justify the selection of one mRNA-based vaccine over the other.

3. Manufacturing considerations

Number of doses to be purchased: Pfizer/BioNTech plans to deliver 200 million regimens in 4 phases (interim delivery schedule):

[redacted]

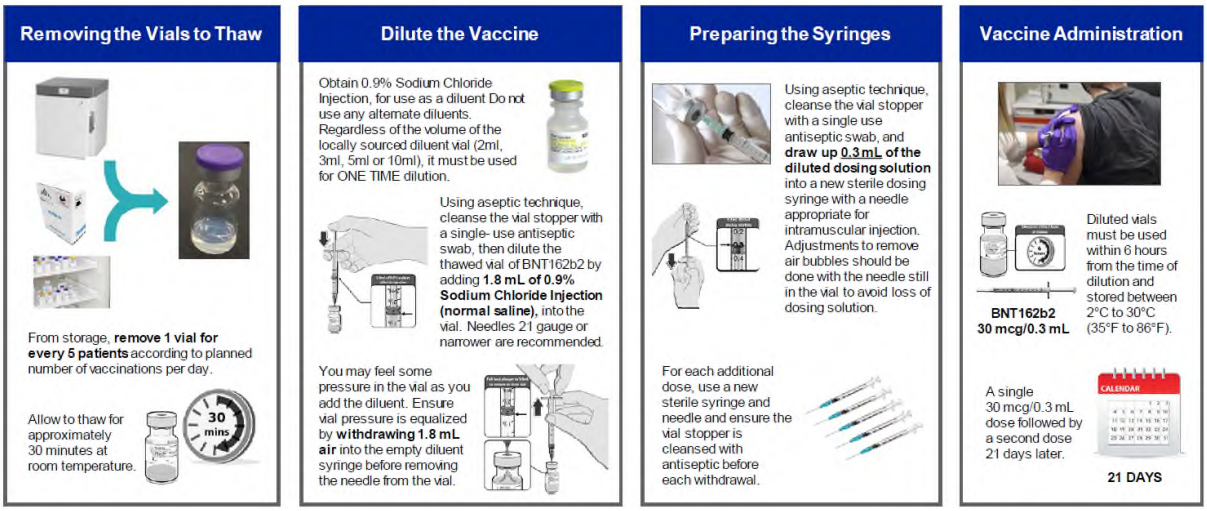
Possibility to purchase an additional volume of 100 million regimens.

Delivery will be allocated based on population binding allocation key (around 2.5% for Belgium): this represent a total of **5,1 millions of doses for Belgium**.

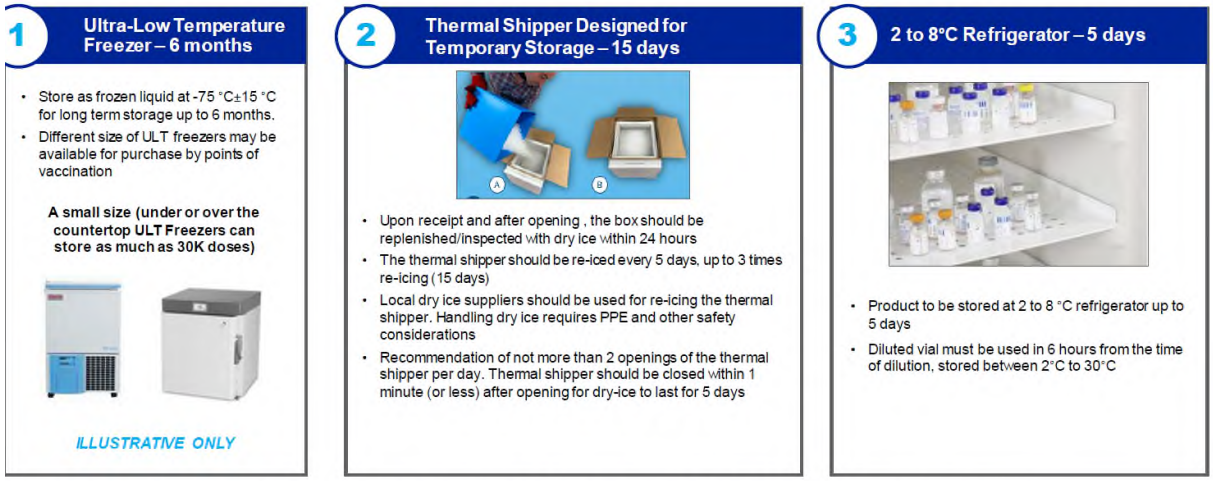
Vaccine presentation and storage condition: (see also annexe for detailed logistic of the vaccine)

- the Vaccine is expected to be a two dose regimen in a concentration liquid formulation that needs to be stored frozen at temperatures between -75 °C (+/- 15 °C). The Vaccine must be thawed on the day of administration and stored at 2-8 °C until administration.
- The concentrate will need to be diluted at point of use prior to dosing. **Vaccinators will need to obtain locally sourced 0.9% Sodium Chloride Injection (Normal Saline) for dilution**.
- The non-preserved multidose vial must be discarded after 6 hours of use.

Vaccine Preparation and Administration of BNT162b2



Vaccine Storage* Options At the Point of Vaccination



*Product temperature must always be monitored to ensure adherence to temperature requirements for different storage conditions are being met in alignment with site Standard Operating Procedures.

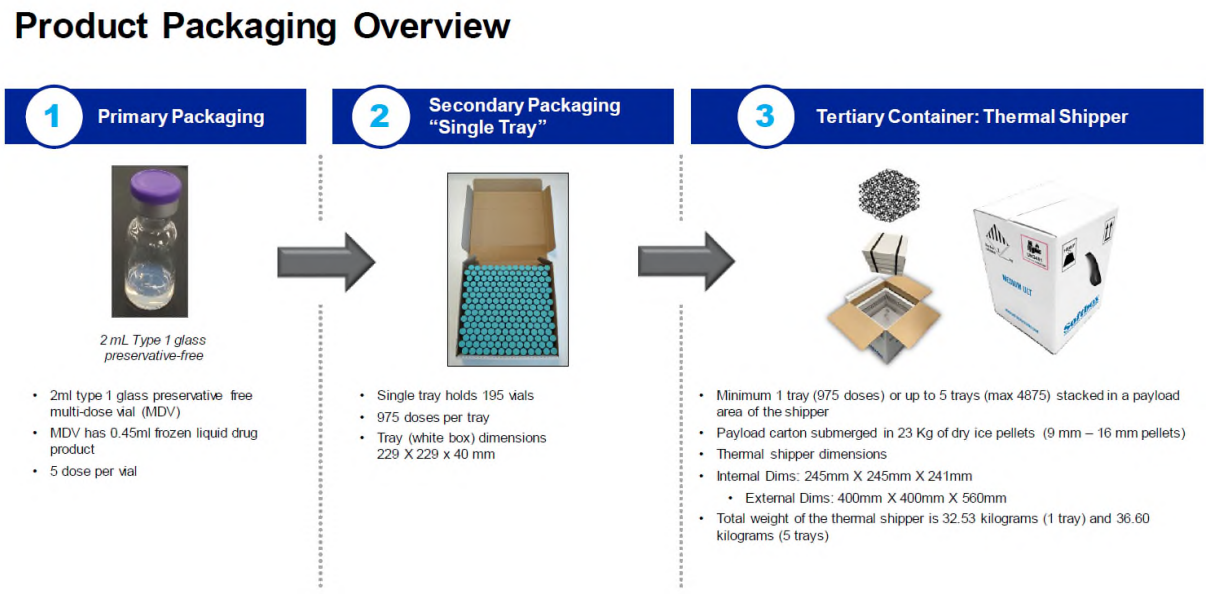
Please note that it is possible that the final preparation and logistical requirements may change in light of forthcoming data on dosing, stability, manufacturing and shipping requirements, but this deck reflects the Company's current understanding based on the totality of available data currently. Current as of September 8, 2020

Manufacturing sites : Vaccine supply in Europe will primarily come from [redacted] manufacturing site in [redacted] and shall incorporate RNA produced at [redacted] controlled manufacturing sites including sites operated by sub-contractors [redacted].

Distribution and delivery :

Vaccines will be delivered [redacted]

The Vaccine will be supplied in a thermal shipping box ("Thermal Shipper") containing up to 5 trays of multidose 2ml vials. Each tray will contain 195 vials. Each vial contains multiple doses of formulated Vaccine.



[redacted]

Pfizer/BioNTech will deliver the doses ordered by each of the Participating Member States to one or more locations selected by the Participating Member State in accordance with the vaccine Order Form. [redacted] The Participating Member States shall bear all costs and expenses for operating these distribution hubs and for use of the Vaccine, including, but not limited to, those for storage and distribution of the Vaccine after delivery, local duties and local QA testing.

4. Legal considerations

Conclusion on the assessment of contract by Deloitte Legal/ IUS Famhp (see detailed assessement in annex)

Aansprakelijkheid ten aanzien van derden en schadevergoedingen [redacted]:

- Het beginsel is dat de producenten aansprakelijk zijn voor de gebreken in hun producten wordt gehandhaafd [redacted]
- [redacted]

5. Financial considerations

- Estimated Price per dose: [redacted] per dose (excluding VTA)
- European Commission contribution: [redacted] per dose per Vaccine (=> contribution per MS: [redacted] (TVA included) [redacted] per dose ([redacted] per regimen)
- [redacted]
- Each Participating Member State shall submit a Vaccine Order Form in respect of its Allocated portion of the Base Volume Commitment in writing to Contractor [redacted]. **Note: In order to have the first doses of the vaccine in national locations as soon as they become available from the [redacted] manufacturer, the commission is requesting to receive vaccine order form (with number of doses and the national locations for the delivery) at the same time as the communication of opt-out decision (ie by 18 Nov 2020)**
- Member States shall pay to Contractor the Price Balance for such Vaccine Volume [redacted]
- Additional consideration:
  - [redacted]
  - [redacted]

6. Advisory Board recommendation

Considering the favourable non-clinical and clinical supportive package ; the adjuvant effect of mRNA ; [redacted]; the rapid progress of Ph3 study and expected marketing authorization by EMA in [redacted]; the absence of vector immunity; [redacted]

Taking also into consideration the general uncertainty on mRNA vaccine platform (no mRNA vaccine currently approved, [redacted]), the absence of data on duration of protection and on cellular response in elderly , the complex storage and distribution condition at ultra-low temperature, [redacted]

The advisory board considers that in the current context, based on available data, there are no critical issues requiring not to proceed with contract. The advisory board recommends to purchase allocated pro-rata number of doses (~ 5,1 million doses).

The list of experts having participated to this advisory board is listed below:

Name	Expertise
Yves Van Laethem (per mail)	Infectiologue et président du groupe vaccination du CSS
Charlotte Martin	Infectiologue (ULB)
Steven Van Gucht	Viroloog (Sciensano) en directeur van het wetenschappelijk comité corona

Laura Piraprez	Représentant de la communauté germanophone
Geert Top	Agentschap Zorg en Gezondheid
Pierrette Melin	Representant de la communauté Wallone
Stéphanie Mali	Coordinateur centre d'excellence vaccins (Afmps)
Sarah Goossens	Responsable du département légal (Afmps)
Xavier De Cuyper	CEO AFMPS et membre du Steering Board vaccin
Greet Musch	Directeur Général, DG Pre (Afmps)

Annexe

Advance Purchase Agreement Pfizer_Cor