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Advisory board COVID-19 vaccins

Avis portant sur Advanced Purchase Agreement with Moderna

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Advies Advanced Purchase Agreement with Moderna

Réunion
30 novembre 2020

Vergadering
30 november 2020

Avis portant sur Advanced Purchase Agreement with Moderna

I. Dossier

Lors de sa réunion du 30.11.2020 l' Advisory Board vaccins COVID-19 s'est penché sur le dossier d'achat anticipé (APA) portant sur le candidat vaccin COVID-19 de Moderna, négocié par la Commission Européenne.

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

Considérant les evidences cliniques et non cliniques favorables ; considérant qu'une réponse immunitaire similaire a été observée chez les participants jeunes et âgés dans les études de phase 1 ; la progression rapide de l'étude Ph3 et l'autorisation de mise sur le marché attendue par l'EMA [redacted] *; un profil de réactogénicité relativement élevé mais acceptable ;* [redacted] *; la simplicité opérationnelle avec un vaccin prêt à l'emploi ; les conditions de stockage à -20 °C et pendant 1 mois entre 2-8 °C ;* [redacted]

L' Advisory Board *considère que dans le contexte actuel, sur la base des données disponibles, il n'y a pas de raisons significatives nécessitant de ne pas poursuivre ce contrat.*

L' Advisory Board *recommande d'acheter le nombre de doses initiales allouées au prorata de la population belge (~ 2 millions de doses). L'Advisory board recommande de postposer la décision*

I. Dossier

De Advisory Board COVID-19 vaccins heeft op 30.11.2020 het Advance Purchase Agreements (APA's) mbt het kandidaat COVID-19 vaccin van Moderna besproken waarover de Europese Commissie heeft onderhandeld.

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

Gezien het gunstige niet-klinische en klinische ondersteunende data; gezien het feit dat een vergelijkbare immuunrespons werd waargenomen bij jonge en oude vrijwilligers aan fase 1-onderzoeken; de snelle voortgang van de Ph3-studie en de verwachte vergunning voor het in de handel brengen door EMA [redacted] *; een relatief hoog maar acceptabel reactogeniteitsprofiel;* [redacted] *; de operationele haalbaarheid met een ' ready -to -use' vaccin; de stockage bij -20 ° C en de bewaarcondities gedurende 1 maand tussen 2-8 ° C;* [redacted]

De adviesraad is van mening dat er in de huidige context, op basis van de beschikbare gegevens, geen kritieke kwesties zijn die vereisen dat het contract niet wordt voortgezet.

De adviesraad raadt aan om toegewezen initiële aantal doses te kopen (~ 2 miljoen doses). De adviesraad raadt aan om [redacted] *te wachten om de Belgische interesse in optionele doses te bevestigen.*

d'acheter des doses optionelles (2 million supplémentaire) [redacted].

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

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 Moderna. 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 Moderna.

II. Beslissing van de IMC

De IMC volgt het advies van de Advisory Board mbt het APA with Moderna. 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 Moderna contract.

Advisory board review 30 November 2020
Advanced Purchase Agreement with Moderna
Post meeting Fiche

1. Administrative data

- Vaccine: mRNA-1273 (ModernaTX, Inc.)
- Type: mRNA-based CVnCoV COVID-19
- Administration: The selected dose level of mRNA-1273 is 100 µg to be administered in a 2-dose schedule with at least a 28-day interval between doses.
- Presentation: suspension of 5 ml; multi-dose vial with up to 10 doses per vial
- Route of administration: The vaccine is administered intramuscularly (IM).
- Clinical development phase: Moderna started a FIH in March 2020 (NCT04283461). The study completion date is estimated for November 2021. Safety and immunogenicity results informed the choice of mRNA-1273 vaccine dose levels to be tested in the Phase 2 trial. The Phase 2a study started in May 2020 (NCT04405076) and intended to confirm the dose level to be tested in the Phase 3 trial. The study completion date is estimated for August 2021. The Company initiated a Phase 3 end of July 2020 (NCT04470427). Enrolment is completed. The study completion date is estimated for October 2022.
- Marketing Authorization: Expected approval date [redacted] but because of the evidence of efficacy (announced 16/11/2020), the application might be submitted earlier. The rolling review has started.

2. Scientific evaluation

This report is mainly based on limited published data and on the IB available via the EU scientific committee (v4).

CLINICAL DEVELOPMENT

The mRNA-1273 vaccine candidate, encoding the full-length Spike protein, is currently evaluated in a Phase 3 efficacy trial. The vaccine is administered in a 2-dose schedule, separated by 28 days, at a dose level of 100 µg RNA in both young and old adults. The mRNA-1273 vaccine was the second COVID-19 vaccine for which efficacy results were announced (press release). The CHMP has started the Rolling Review.

IMMUNOGENICITY AND CHALLENGE STUDIES

Nonclinical pharmacology studies in mice (including aged animals), Syrian Golden hamsters, and rhesus macaques (NHPs) were done to evaluate immunogenicity, protection and also to address the theoretical concern of enhanced respiratory disease (ERD). mRNA-1273 is immunogenic in all species assessed, showing a dose-dependent response in IgG binding antibody titers that correlates with neutralizing antibody activity. In addition, antigen-specific T-cell responses were observed in studies in mice and NHPs. Th1-directed CD4 (mice and NHP) and CD8 T cell responses (mice) were measured post boost in animals that were vaccinated with mRNA-1273.

Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of IgG2a/c/IgG1 antibody subclasses in mice, and the high levels of neutralizing antibody in all species lessens concerns regarding ERD associated with administration of mRNA-1273.

In addition, protection was addressed in challenge studies in all three species, [redacted] Those studies also include suboptimal doses, to address the potential for ERD. At higher doses, mice and NHPs were protected from viral replication in both upper and lower respiratory tract. At lower dose levels, animals either

remained protected in the lungs or had reduced viral load compared to control animals. There were no observations of increased viral load in vaccinated animals at any dose levels. In animals vaccinated with both optimal and suboptimal dose levels, histopathological evaluation of the lungs of mice and NHPs do not demonstrate signs of ERD. Immune response and protection from challenge were also demonstrated in aged mice. Preliminary data are indicative of protection in hamsters as well.
Although those results look promising the relevance to human is unknown.

CLINICAL IMMUNOGENICITY AND EFFICACY

The first immunogenicity results indicate that binding and neutralizing antibodies are induced following two doses of mRNA-1273 at a dose levels of 25 and 100 µg, in young adults (18-55 yoa, n=15/group) and both old adult age categories (56-70 years and ≥71 yoa, n=10/group). In all 3 age categories, binding IgG antibody GMTs to S-2P and RBD increased rapidly after the first vaccination and the responses to the first and second vaccination were dose-dependent. While nAb responses were in not elicited in more than half of the participant after the first dose, nAb were induced in all participants following the second dose at dose level of 100 µg. The responses were overall similar in all 3 age category. Preliminary results indicate that the vaccine elicited a CD4 cytokine response involving Th1 cells among participants in the 3 age categories who received the 100 µg dose. CD8 T cell responses to S-2P were detected at low levels after the second vaccination in the 100 µg dose group.
According to press release of 16/11/2020, the vaccine candidate of Moderna (at a dose level of 100 µg RNA) has demonstrated evidence of efficacy against COVID-19 in trial participants. The primary analysis of the Phase 3 COVE study (NCT04470427), that enrolled more than 30,000 participants in the US, is based on COVID-19 cases confirmed and adjudicated starting two weeks following the second dose of vaccine. The first interim analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% ($p < 0.0001$). A secondary analysis considered severe cases of COVID-19 and included 11 severe cases (as defined in the study protocol) in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group. The 95 COVID-19 cases included 15 older adults (aged 65+). It should be noted that efficacy was reported over a short period post-dose 2 (of a few weeks, specific period not provide in the press release). Therefore the level of efficacy that will be observed over a more standard period such as a year post last dose, is unknown. These efficacy data are derived from claims of the Company in the press and have not been evaluated by independent regulatory authorities. 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

The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102–containing LNP matrix encapsulating mRNA constructs that encode for various antigens have been evaluated in 6 GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats with a 2-week recovery period dosed IM with 9 to 150 µg/dose once every 2 weeks for up to 6 weeks. [redacted]
Those studies highlighted a transient inflammatory reaction as expected following vaccine administration.

No nonclinical issues were identified.
CLINICAL SAFETY
Preliminary safety data in participants after the second injection revealed no serious adverse event (SAE) occurrences and no triggering of study pause rules.
Safety data are very limited for mRNA-based vaccines in general.
Preliminary early development data for the Moderna vaccine candidate suggest an acceptable reactogenicity profile at dose levels up to 100 µg, in both the younger and older individuals.
Reactogenicity was higher in severity and frequency with the second dose compared to the first.
Reactogenicity tended to be slightly lower in the older group compared to younger individuals.
Reactogenicity was observed to increase with vaccine dose levels, [redacted]
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 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), [redacted]
COMPARISON TO OTHER VACCINE CANDIDATES
- Initially, development of mRNA based vaccines against COVID-19 came with a higher degree of uncertainty in terms of potential benefit as compared to other vaccines in development against COVID-19 since there were limited clinical data. This uncertainty is now lower with the evidence of (high) and consistent efficacy for two COVID-19 vaccine candidates, the BioNTech and Moderna vaccine candidates. A higher level of uncertainty however remains with respect to safety given the limited clinical experience (in terms of size of the population exposed, and duration of follow up).
- The BioNTech/Pfizer and Moderna vaccines are among the most advanced COVID-19 vaccine candidates, both recently announced final (BioNTech) or interim (Moderna) efficacy results of ongoing phase 3 trials (press release). Astra Zeneca also announced evidence of efficacy (press release 23/11/2020). Janssen vaccines also is in Phase 3. CureVac is not yet in Phase 3.
- 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. [redacted]
- 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 and cannot be used to predict efficacy, 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 on 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. No data are yet published for CureVac.
CONCLUSION
Overall, based on the data we had available at the time of assessment, we consider mRNA-1273 as a promising vaccine candidate.

3. Manufacturing considerations

Number of doses to be purchased: Moderna plans to deliver 80 million doses "the initial doses" in 3 phases (interim delivery schedule):

- o [redacted]
- o [redacted]
- o [redacted]

Possibility for Commission to exercise [redacted] an option increase of 80 million doses "the option doses" with following delivery schedule:

- o [redacted]
- o [redacted]

The interim schedule is based on an expected marketing authorization received on [redacted].
If authorisation date is changed, the delivery schedule will be updated. Moderna will try to deliver the first delivery of Initial Doses within [redacted]

Delivery will be allocated based on population binding allocation key (around 2.5% for Belgium): this represent a total of **2.037.713 doses for Belgium** (initial doses). If Belgium is interested to exercise his option, an additional 2.037.713 doses could be purchased, meaning a total of ~ **4,1 millions of doses for Belgium**.
Vaccine presentation and storage condition:

- One vaccine vial is filled with the suspension (0.5ml), covering up to 10 doses per vial, packed by 10 vials in a secondary carton
- Primary and secondary labels in English
- Vaccine might be stored frozen 6 months at temperatures between -25 and 15°C and 30 days between 2 -8 °C.
- The Vaccine might be stored unopened 8 h at room temperature. at 2-8 °C until administration.
- The non-preserved multidose vial must be discarded after 6 hours of use.

Distribution and delivery :
Vaccines will [redacted]
Moderna will deliver the doses ordered by each of the Participating Member States [redacted] selected by the Participating Member State in accordance with the vaccine Order

Form. [redacted]

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]

- [redacted]
- [redacted]

5. Financial considerations

- Estimated Price per dose: [redacted] per dose (excluding VTA) : [redacted]
- For initial doses:
  - European Commission contribution : [redacted] per dose per Vaccine.
  - Contribution per MS: [redacted] (Excluding TVA) per dose : [redacted] (Excluding TVA)
  - Member States shall pay to Contractor the Price Balance for such Vaccine Volume [redacted]
- For optional doses [redacted]
- [redacted]
- Additional consideration:
  - [redacted]

6. Advisory board recommendation

Considering the favourable non-clinical and clinical supportive package ; considering that a similar immune response was observed in young and old participants in phase 1 studies ; the rapid progress of Ph3 study and expected marketing authorization by EMA [redacted]; a

relatively high but acceptable reactogenicity profile ; [redacted] ; the operational feasibility with a vaccine ready to use; the storage condition at -20 °C and during 1 month between 2-8 °C; [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 initial number of doses (~ 2 million doses). The advisory board recommend to wait [redacted] to confirm Belgium interest in optional 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
Pierre Louis Deudon	Representant de la Cocom
Stéphanie Mali	Coordinateur centre d'excellence vaccins (Afmps)
Steven Hippe	Responsable du département légal (Afmps)
Xavier De Cuyper	CEO AFMPS et membre du Steering Board vaccin
Greet Musch	Directeur Général, DG Pre (Afmps)

Annexe 1

Advance Purchase Agreement Moderna [redacted]