SCIENTIFIC COMMITTEE ON COVID-19 VACCINES

BioNTech/Pfizer mRNA VACCINE RECOMMENDATIONS

Paris, August 3, 2020

This note was transmitted to the Ministry of Higher Education, Research and Innovation (MESRI), the Ministry of Solidarity and Health and the Vaccine Task Force of the Ministry of Economy and Finance on 3 August 2020.

PARTICIPANTS

Scientific Committee: 5.1.2e

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BioNTech/Pfizer : 5.1.2e

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INTRODUCTION

According to the WHO, some 20 teams around the world are now working on the development of COVID-19 vaccines based on the mRNA platform. This platform, developed over the last two decades, allows for rapid development and has certain advantages in terms of production. This does not mean that the price set by producers will be low. On the other hand, the efficacy of these vaccines has yet to be demonstrated in humans. To date, no mRNA vaccine has been registered for use in humans.

The Committee had a first meeting with representatives from BioNTech/Pfizer on June 26, and provided the French government on July 5 with a comparative recommendation on three mRNA vaccines in clinical development, based on the available evidence, following hearings with representatives of three pharmaceutical companies (MODERNA, BioNTech and CureVac).

BioNTech/Pfizer has initially developed in parallel four mRNA candidates: two of them are based on an mRNA with nucleoside modifications (modRNA), the third does not contain modified nucleotides (uRNA), the last one is a self-amplifying mRNA (saRNA). The mRNAs are transported into cells using lipid nanoparticles.

At the June 26, 2020 hearing, BioNTech/Pfizer representatives chose to present only their – at that time - most advanced candidate vaccine BNT162b1, which contains an mRNA with modified nucleosides encoding only the Spike *Receptor* Binding *Domain* (RBD). Based on the data submitted, the Committee

expressed a reserved opinion on this vaccine. The Committee concluded that the candidate vaccine BNT162b1 showed a very high degree of reactogenicity in man and appeared to induce modest levels of neutralizing antibodies, which were of course directed exclusively against RBD. The Committee reasoned that this could limit efficacy of the vaccine and increase the risk of virus escape if mutations in the RBD coding sequence occur. Moreover, strong CD4 and CD8 responses have been demonstrated against RBD and the rest of the Spike protein, which argues against concentrating only on RBD.

BioNTech/Pfizer finally selected the BNT162b2 (modRNA) vaccine candidate, which encodes a complete stabilized Spike protein in pre-fusion conformation, for their Phase 2/3 study. This choice was based on their analysis of non-clinical data (faster viral clearance in the upper respiratory tract in rhesus monkeys after infectious challenge with SARS-CoV-2), clinical (lower reactogenicity than the BNT162b1 candidate) and immunological (increased CD8 responses), which further supported dose reduction from 100 to 30ug. The Phase 2/3 clinical trial began on July 27, 2020.

Following this decision, BioNTech/Pfizer proposed to the Committee on July 28, 2020 to organize a second meeting to present the preclinical and clinical data obtained for the BNT162b2 vaccine candidate.

All Committee members and the MESRI representative have signed individual confidentiality agreements with BioNTech/Pfizer.

PRESENTATION OF THE VACCINE CANDIDATE BNT162b2

- Description of the vaccine:
  Complete spike with modified nucleosides (modRNA) stabilized in pre-fusion form (variant described by Barney Graham).
  Optimization of capping and translation in dendritic cells to stimulate CD4 and CD8 responses.
  Lipid content : 12 lipid units/1 mRNA units.

- Preclinical Data:
  Vaccination and challenge with SARS-CoV-2 (dose 10^6 $TCID_{50}$ administered half by intratracheal and half by intranasal route). Transient viral load in bronchoalveolar fluid and nasal secretions in the 6 vaccinated animals.

- Clinical Development:

    - Phase 1/2 (NCT04380701): initiation 23 April 2020 - Germany. 200 participants; 18-55 years old. Doses used: 10, 30 or 100µg (booster at 28d except for the highest dose)
    - Phase 1/2 (NCT04368728): Initiation May 2020 - USA. 7,600 volunteers. Doses used: 10, 30 or 100µg (booster at 28 days except for the highest dose).
    - Phase 2/3 (continuation of NCT04368728): Initiation on July 27, 2020; Argentina, Brazil, Germany, Turkey and the United States. 30,000 participants, 18-85 years old. Proportion of subjects aged 65-85 targeted: 50%. Dose of 30µg with booster at 21d. Primary endpoint: prevention of COVID-19; secondary endpoint: prevention of severe COVID-19. Results expected in October 2020 or earlier (based on analysis after 120 cases, for an

expected vaccine efficacy of 70%). BioNTech/Pfizer is targeting a potential authorization to use the vaccine in Q4 2020.

- Production capacity, presentation and storage:
  Production capacity in expansion with Pfizer (Europe and United States): 1 billion doses in 2021.
  10-dose vials; product frozen and stored at -70°C; storage possible at least for 2-3 days at 4°C.

CONCLUSIONS

- The reactogenicity of BioNTech/Pfizer BNT162b2 vaccine appears to be less than that of BNT162b1 (mainly concerning fever and chills) after the booster dose in volunteers aged 18-55 and 55-85 years. BioNTech/Pfizer representatives suggested that this might be due to mutations (codon optimization) made on their mRNA. However, the decrease in mRNA dose from 100 to 30ug could also play a direct or indirect role (*via* the decrease in associated lipids). It should be noted that the Committee is not aware of the number of patients analysed and is therefore unable to definitively conclude on this lower reactogenicity.
- The BNT162b2 vaccine candidate does not protect rhesus monkeys against infection after a virulent challenge with 10^6 $TCID_{50}$ CoV-2-SARS by mixed intratracheal and intranasal routes. One positive point: the viral load appears to be very transient (for 1-3 days only) – as detected by PCR - in bronchoalveolar fluid and nasal secretions in vaccinated animals.
- Neutralization tests: 50% neutralization of the SARS-CoV-2 virus. Negligible neutralising response after the 1st dose and low titres after the 2nd dose: around 1/150-200e - compared to 1/650e for MODERNA in a more stringent $PRNT_{80}$ test (NEJM). A positive point is that neutralizing antibodies are also observed in subjects aged 65-85 years.
- Cellular responses (results published in Met. Archives) measured by IFNγ elispot. CD4 and CD8 responses similar to those obtained with candidate BNT162b1, with the additional demonstration of abundant T responses against the Spike region outside RBD. Response observed in all 5 volunteers tested.

COMMITTEE RECOMMENDATIONS

The Committee reviewed the data set provided by BioNTech/Pfizer for their BNT162b2 mRNA vaccine candidate. On the basis of the still very preliminary data at its disposal, the Committee made the following recommendation:

- The BNT162b2 vaccine candidate appears to be a more interesting candidate than the BNT162b1 vaccine candidate previously evaluated by the Committee.

These recommendations were endorsed by the COVID-19 Vaccine Scientific Committee during its meeting of August 3, 2020. None of the members of the committee were in a situation of deportation.

The members of the COVID-19 Vaccine Scientific Committee are available to the Government to provide additional information, if necessary.