Steering Board Meeting with Experts from the Scientific Board of France, Spain and the Netherlands

27 July 2020

Subject: Scientific Considerations and Recommendations on COVID-19 vaccine candidates

Independent Experts:

1. [redacted]

2. [redacted]

3. [redacted]

General remarks and introduction:

Before concluding an Advance Purchase Agreement with the vaccine producers, the European Commission gathered the independent scientific advice of the above-mentioned experts. The members of the Joint Negotiation Team supported the European Commission's initiative and encouraged the independent experts to provide their prompt scientific advice for the benefit of the Steering Board and other national experts nominated by the Steering Board members.

The Co-Chair of the Steering Board (European Commission) welcomed participants and introduced the independent experts.

By way of introduction

Regarding the adenoviral vaccines, informed that there are teams world-wide working on these vaccines.

[1] Platforms are technologies used to express the viral antigens.

With respect to AZ, and the recent publication of their latest clinical trial results in *The Lancet* medical journal, [redacted] acknowledged that the vaccine can induce protection in rhesus macaques, however the animals continue to secrete the virus via the nasal tract and hence the vaccine would not effectively block transmission of the disease. The data in humans show neutralising antibodies of moderate titers, good T-cell immunity as AZ is relatively advanced [redacted] in their Phase III clinical trial. Whilst the advantage of this platform is the ease with which the vaccine could be produced, the immunogenicity in older adults is yet to be demonstrated/ observed. [redacted] issued the recommendation to continue monitoring this candidate's evolution [redacted].

With regards to Johnson & Johnson (J&J), a vaccine based on human Adenovirus 26 was expected to enter Phase I clinical trials on [redacted] July in Belgium and in US in people older than 55 years of age. The booster would follow the first administration at day 56. [redacted] Immunogenicity evidence was scarce to date [redacted]

[redacted] complemented the analysis of [redacted] highlighting that the AZ approach is relatively good. Since the Phase II clinical trial participants were 18-50 years of age, further trials should include the 65+ contingent as the latter is more susceptible to contracting the disease. The recent publication includes some data on prophylactic use of paracetamol. The most effective schedule appears to be based on two doses, a first administration followed by a booster. Emerging data on duration of protection or sterilising immunity is an outstanding issue. [redacted]

On the J&J candidate, [redacted] stated that the Phase II CT is starting this July, hence no solid opinion of this vaccine as yet. However, it may well be as promising as the AZ candidate. In conclusion, both the AZ and the J&J candidates may prove to be good options, based on currently available information.

[redacted] started by introducing [redacted]

[redacted] agreed [redacted] AZ product is more advanced in development but the J&J product is from a company that is well aware of the adenoviral platform and has a lot of expertise. Whilst both parties draw on their solid background, 1:1 comparability of their products may well be hindered by the fact that assays [redacted] are likely different [redacted]. For the AZ candidate, immunogenicity looked good, although painkillers may be needed for mitigating side-effects. She mentioned NOVAVAX having a potentially serious candidate as well in the long run.

[redacted] thanked for the contributions and moved on to the mRNA platform category**.**

[redacted] explained that the assessments [redacted] pertained to the candidates put forward by Moderna, BioNTech and CureVac, [redacted].

With regards to Moderna's and BioNTech's candidates, the mRNA used has a modification which enhances the odds of inducing an immune response. [redacted]. Moderna is starting their Phase III clinical trials. In animal studies, Moderna's candidate has shown partial protection against the disease, yet not against infection; in human studies, it has triggered a relatively high reactogenic reaction [redacted]. A dose of 100 microgram is the highest tolerated by vaccinnees**.** The recruitment is completed for Phase II CT [redacted], with Phase III planned covering 30 000 vaccinees in the US. Moderna decided to cancel their European CT planned [redacted]. [redacted] highlighted that [redacted]

[redacted]

With regard to BioNTech, [redacted] results of [redacted] out of [redacted] potential candidates in the pipeline was chosen to be presented by the company, so-called [redacted]. [redacted] BioNTech [redacted] decided [redacted] a 35 microgram dose which triggered moderate immunogenicity and high reactogenicity of a lipid, [redacted].

On CureVac's candidate, the full length SARS-CoV-2 vaccine, [redacted] highlighted that it was much more immunogenic and only 2, 4, 8 microgram dose compared to 100 microgram for Moderna – all these vaccines are to be considered with a booster. CureVac started phase I CT in DE and in BE [redacted]. [redacted] [redacted]. A doubt was cast over CureVac's ability to produce large quantities of vaccines. [redacted] [redacted]. [redacted]

[redacted] confirmed that Moderna started Phase III CT on [redacted] July, with previous Phases in DE and BE. [redacted] suggested it was premature to say which candidate would perform in real life. The information received from Moderna indicated an acceptable safety profile, although [redacted]% of participants experienced fever as a side-effect after administration of the booster. [redacted] saw this as a mild pitfall. The 100 microgram doses are administered in people from 20 to 55 years of age. They should also cover the over-75 years of age contingent.

Regarding BioNTech, the short shelf life after defrosting was mentioned.

For CureVac, [redacted] gave indications that more data on immunogenicity is needed although trials in humans seem promising thus far.

[redacted] agreed that rather big differences in the data currently available exist with hardly any results for CureVac, rendering ranking difficult. Moderna recently published a study in the *New England Journal of Medicine* for their mRNA-1273 candidate with similar results in the older group as in other studied groups. Moderna also shared some confidential [redacted] data for which a publication is forthcoming.

Regarding the BioNTech product, [redacted] did not completely agree with [redacted] counterpart. [redacted]

On CureVac's product, the [redacted] may well have more information and theoretically, it could be a good candidate but lagging behind currently. The only official data seen by [redacted] was limited [redacted].

In conclusion, Moderna and BioNTech are promising candidates for [redacted], with good immunogenicity profile and good tolerability also in the older age group. [redacted].

[redacted] then proceeded to the Sanofi-Pasteur and NOVAVAX category (the subunit vaccines).

[redacted] explained that Sanofi-Pasteur are a large producer and have [redacted] vaccines in their portfolio as well as the expertise of producing vaccines as their core business. In terms of timing, [redacted] acknowledged that they [redacted] planning to start their Phase I CT in [redacted]. The technology is adapted from that developed for one of their seasonal influenza vaccines (technology acquired from Protein Sciences). The antigen is administered with a squalene-containing adjuvant [redacted]. [redacted] In terms of production capacity, purification of antigens from insect cells infected with a recombinant baculovirus encoding the SARS-CoV-2 S protein (a well-controlled procedure adapted from that developed for seasonal influenza vaccine). Sanofi-Pasteur has the necessary infrastructure to ensure very large-scale production.

With respect to the candidate put forward by NOVAVAX, [redacted] informed that [redacted] certainly one to be followed very closely. The antigen is a complete recombinant Spike protein of SARS-CoV-2, stabilised in a pre-fusion conformation. The antigen is presented as trimers on lipid nanoparticles, normally more immunogenic than those on lipid form. The candidate is capable of producing high titers [redacted] even at the lowest dosage tested. Matrix-M™ adjuvant (saponin, cholesterol and phospholipid-based). Preclinical studies in mice and challenge experiments in non-human primates. Results of an infectious challenge study in macaque monkeys show a reduction in viral load in the upper respiratory track and lungs of vaccinated animals, suggesting a protective effect of the vaccine candidate. It is of note that the dose of virus used for the infectious challenge corresponds to the dose used by Moderna, but is lower than the dose used by AstraZeneca. Phase I CT commenced in May in Australia, Phase II ongoing currently in US and Australia. Production capacity is very high, with recently acquired capacity in CZ. NOVAVAX clearly capable of producing large amounts of vaccine. Plan to produce [redacted] doses in [redacted]. [redacted]

On Sanofi, [redacted] issued a note of caution regarding its AS03 adjuvant. GSK used this adjuvant in their pandemic vaccine and it induced narcolepsy in adolescents in 2009-2010. Many studies published since then and it seems that narcolepsy was not caused by the adjuvant itself, but by an antigen (one produced in BE, one in Canada) and only one of these seems to have caused narcolepsy. [redacted]

[redacted] quoted a study published in 2018 in the journal "Vaccine" which did not find an association between Sanofi's pandemic flu vaccine and narcolepsy in children and adults. No data in humans yet from Sanofi's candidate. As regards NOVAVAX, it seems that the vaccine can induce an immune response in vaccinees.

[redacted]

found NOVAVAX's Matrix-M™ formulation of interest. Perhaps a plus for the NOVAVAX product is the T-cell response

In concluding remarks, highlighted the importance of spreading the vaccine portfolio over different platforms. The mRNA candidates are for authorisations, . Manufacturers in this category draw on their experience with this platform, known for its effectiveness in respiratory infectious diseases.

thanked all speakers and opened the Q&A session.

Expert pointed out that direct comparisons of vaccine candidates should be avoided. Having read all published papers, wondered whether the limited number of participants in the BioNTech study data would be an issue and if the multivalent display in their mRNA design engendered any reactions. also invited comments on their lipid envelope.

acknowledged the intrinsic difficulty in drawing comparisons, generally speaking but a platform by platform comparison is feasible. There were a lot of data in animal studies. Difficult to have a definitive conclusion but it seems reasonable to take different elements into account.

Expert enquired about storage temperatures.

explained that Moderna's candidate consists in a powder to be reconstituted. It should be stored at -20 to -40° C . The BioNTech candidate indicated -80°C for long-term storage. Whilst CureVac's candidate has two-dose vials stored frozen at -80°C for long-term storage, stability at 4°C can be preserved for several months. NOVAVAX has ten-dose vials (reconstituted for use), storage at -80° for several years but also at higher temperatures for administration. AZ has ten-dose vials, stable at 4°C for 6 months. J&J has ten-dose vials, stable for several months at 4°C to 10°C.

enquired how these temperatures might impact a vaccine's workability in primary care centres in LMI countries.

responded that for Ebola vaccines in Africa, storage was in liquid nitrogen (in a cold chain container), keeping the temperature quite well.

(SE) suggested that a more traditional adjuvanted protein vaccine would be needed for the elderly. enquired whether adjuvants could be avoided at all.

replied that the jury is still out on that aspect. Similar uncertainties remain for the other categories.

shared that current plans involve seeking to organise small immunogenic studies for the very old – over 75 years of age. Some manufacturers want to work with on this. wondered whether informing manufacturers of this forum's endorsement may bring value added.

suggested that an independent organisation might compare samples from different CTs.

The Chair (EC) highlighted that Nobody knows what the future will hold. The Steering Board, along with the EC, can make informed, educated guesses and this is what we are seeking to do via the portfolio. A demand we are making recurrently is Phase III CT data. We note the suggestion to contact NOVAVAX but doubts remain over their ability to deliver to the EU . A more traditional candidate such as the one put forward by Sanofi (or NOVAVAX), AZ or J&J is of interest. In the mRNA category, we will need to rely on other elements, not just scientific ones. Moderna is having a very commercial proposition, BioNTech/ Pfizer guarantees scalability whilst on CureVac, seemingly a good product but having difficulties to understand if they can produce at scale. The panel could have been clearer on the mRNA category.

clarified that was referring to getting biological samples in this unprecedented vaccine development race with everyone wanting to be able to make a good judgment on products. deemed it fair to ask the companies to collaborate in a standardised assay to measure the data,

[redacted] Expert shared [redacted] concerns that the companies may well be apprehensive in this regard. [redacted].

[redacted] Expert expressed concerns over the respect of purely scientific criteria in the ongoing negotiations.

The Chair (EC) explained that the matter is rather more complex in that the Steering Board decides which companies to open negotiations with. For NOVAVAX, for example, no contact has been established [redacted]

[redacted] continued that the panel is not fully clear in their comparative assessment also because the information is not equally available. [redacted]

The Chair (EC) concluded discussions thanking all for their participation [redacted]. [redacted] also pointed out no objections from the Steering Board to the AZ candidate; good comments for J&J but a duplication of the AZ platform. For the innovative mRNA group, any of them would do for different reasons: scientific reasons for some or other reasons for others. The EC heard the panel's views on the scientific data for CureVac's candidate. [redacted] The JNT has not declined any of the candidates discussed today so this discussion will feed productively into future ones.

The co-Chair (AT) thanked [redacted] (NL) and the Commission for putting this session together. [redacted] closed off the debate [redacted]. Much too early to make a decision on turning down a candidate, although we are closing in on a portfolio. [redacted]

Participants

[redacted] (AT, Co-Chair)

[redacted] (NL)

[redacted] (BE)

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[redacted] (DK)

[redacted] (EE)

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[redacted] (SK)

Sandra Gallina (EC, Chair)

[redacted] (EC)

[redacted] (EC)

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[redacted] (EC)

[redacted] (EC)

[redacted] (EC)

[redacted] (EC, Minutes)