SCIENTIFIC COMMITTEE ON VACCINES COVID-19

RECOMMENDATIONS ON INACTIVATED VACCINES

Paris, 20 July 2020

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INTRODUCTION

The "inactivated virus" vaccine platform is a traditional platform that is the foundation for many vaccines currently used in human and veterinary medicine. The virus is grown in cell culture and inactivated by chemical or physical treatment. After purification, the inactivated virus is often formulated with an adjuvant to stimulate the immune response and/or to promote the induction of cellular or humoral responses.

The Committee held a meeting with representatives of the SINOVAC and VALNEVA companies on 20 June, 2020. Both companies are developing inactivated SARS-CoV-2 vaccines, with a significant difference in the choice of adjuvant.

SINOVAC is developing the CoronaVac vaccine, with which the firm has obtained encouraging results in non-human primates. Based on the results (safety and immunogenicity) obtained in Phase 1 and 2 clinical trials conducted in China, SINOVAC has initiated a Phase 3 clinical trial in Brazil (in collaboration with Instituto Butantan (Sao Paulo). Further clinical trials are planned in other countries to test the efficacy of

the vaccine. SINOVAC is interested in the international market, particularly the European market, and has set up large-scale production capabilities for its vaccine in China.

VALNEVA is developing a vaccine called VLA2001. After negotiations with other companies for access to an adjuvant (notably for AS03 (GSK) and MF59), VALNEVA finally partnered with Dynavax for the use of the CpG 1018 adjuvant. With a considerable delay compared to SINOVAC, VALNEVA will not enter clinical development before the end of 2020. However, VALNEVA is very proactive with national governments (Sweden, Austria, Spain and France among others) to present its future product. At the same time, VALNEVA is continuing to develop its production capacities and is in discussions with the British government for the establishment of a production plant in Edinburgh.

PRESENTATION OF THE VACCINES AND DEVELOPMENT PLANS

1. SINOVAC: CoronaVac

- SARS-CoV-2 virus inactivated with β -propiolactione, purified and administered with aluminum salts as adjuvant.

- Preclinical Data :

    - The SINOVAC team conducted preclinical testing in a large number of animal models: efficacy in mice, rats, rabbits, guinea pigs, sheep and non-human primates; toxicity in rats, guinea pigs and non-human primates. These studies were carried out in collaboration with various Chinese research institutions (Chinese Academy of Medical Sciences, JOINN laboratories in Beijing).

    - Infectious challenge experiments in non-human primates shows that the CoronaVac vaccine significantly reduces the viral load in the lungs, feces and throat of the animals. At the highest vaccine dose, viral load becomes undetectable after 7 days after inoculation of the virus in the throat of the macaques. Analysis of the lung pathology in vaccinated animals suggests that the CoronaVac vaccine also has a protective effect - even at the lowest dose - on the development of lung lesions due to CoV-2-SARS infection. No disease facilitation (ADE, *Antibody Dependent Enhancement*) was observed under the experimental conditions tested.
      Dose levels tested: 1200U/mL, 600U/mL with an immunization regimen of three (days 0, 7 and 14) or two (days 0 and 14) successive administrations. Dose level of virus used for the challenge experiment: 10^6 $TCDI_{50}$ (administration into the trachea), 7 days after the last vaccine administration.

    - The CoronaVac vaccine induces low level of neutralizing antibodies in non-human primates (neutralization at 1/24 dilution after the boost), but the lack of details provided on the method used to measure these antibodies does not allow for a definitive conclusion. *In vitro* cross-neutralization studies suggest that this vaccine would protect against various strains of SARS-CoV-2.

- Clinical Development

  - Phase 1/2 (NCT04352608): Initiated on April 16, 2020 in China. Phase 1: 144 participants (18-59 years old). Phase 2: 1200 participants (18-59 years old). Recruitment completed.
    Dose levels used and vaccination schedules:
    - Two administrations at days 0 and 14; 600U/dose
    - Two administrations at days 0 and 14; 1200U/dose
    - Two administrations at days 0 and 28; 600U/dose
    - Two administrations at days 0 and 28; 1200U/dose

    Initial analyses show that the CoronaVac vaccine is immunogenic and capable of inducing neutralizing antibodies in vaccinated individuals with no significant difference between dose levels and vaccination schedules used. Surprisingly, Phase 2 immunogenicity results are substantially better than those of Phase 1, particularly with regard to the 14-day dosing schedule.
    CoronaVac appears to induce only moderate reactogenicity, with a slightly higher incidence of adverse events at the 1200U/dose and after the booster vaccination at day 14.

  - Phase 3: NCT04456595: Initiated on 20 July 2020 in Brazil (Collaboration with the Instituto Butantan). 8870 participants (> 18 years old; health care workers - HCWs). The protocol allows for the inclusion of SARS-CoV-2 positive individuals.
    Dose level used and vaccination schedule: two administrations at days 0 and 14; 600U/dose
    Primary endpoint: efficacy of the vaccine against the occurrence of COVID-19 symptoms.
    Target: 150 cases (incidence of COVID-19 among HCWs in Brazil to date: 10%)

  - Additional phase 3 clinical trials are planned in Bangladesh (4500 participants, HCWs, collaboration with icddr,b), Turkey, Chile, Saudi Arabia, Indonesia (to be started if possible before the end of August) also allowing the evaluation of the J0-J28 regimen.

- Production capacity, presentation and storage:
  Production batches of 2M doses from a 1000L fermenter - compatible with large-scale production.
  Two presentations are envisaged: pre-filled syringes and single-dose glass vials for vaccination campaigns. Multi-dose presentations are not authorized in China.

2. VALNEVA: VLA 2001

- SARS-CoV-2 virus inactivated with β-propiolactione and administered with oligonucleotide CpG 1018 (Dynavax) as adjuvant (TLR9 agonist; adjuvant used in the Dynavax hepatitis B vaccine HEPLISAV-B® marketed in the USA). The viral strain to be used to produce the vaccine is currently being selected from among several candidates, based on their genetic stability and *in vitro* growth capacity (from strains circulating in Europe).

- Preclinical strategy: Immunogenicity assays in mice and infectious challenge experiments (intranasal and intratracheal) in macaque monkeys are planned for the fall of 2020.

- Clinical Development:

    - Phase 1: Initiation planned for December 2020 with 150 participants aged 18-55. Vaccination schedule: 2 administrations, (2 or) 3 weeks apart; 2 or 3 dose levels tested. First results expected in April 2021.

    - Phase 2/3: the protocol has not yet been finalized and will be adapted to the situation (in particular based on the evolution of the pandemic and the existence of other approved COVID-19 vaccines). 4000 participants aged 18-55 years. Vaccination schedule: 2 administrations with a (2 or) 3-week interval at the best dose level identified in Phase 1. First results expected in September 2021.

    - If a correlate of protection is identified by then, possible immunobridging strategy for the elderly: 225 participants aged 65-80. Vaccination schedule: 2 administrations with an interval of (2 or) 3 weeks; two different dose levels. First results expected in September 2021.

- Production capacity, presentation and storage:
  Production of the virus in "Cell Factories" (Univercells technology) that allow large-scale production. VALNEVA targets an estimated production capacity (2021-2022) of 250M doses per year (50M in its new site in Scotland, 200M in a new production site in Brownfield which will be operational from June 2021). VALNEVA plans to make other sites operational through partnerships with CMOs.
  The packaging of the product will be carried out at their site in Sweden (Capacity 200M/year) and by CMOs. The CpG 1018 adjuvant is supplied by Dynavax (production capacity of hundreds of millions of doses per year).
  Presentation: 10-dose glass vials of adjuvanted product. Storage at 2-8°C.

CONCLUSIONS

- The immunogenicity (neutralizing antibodies) results in humans reported by SINOVAC for their CoronaVac vaccine are significantly better for the Phase 2 trial than for the Phase 1 trial. According to the SINOVAC team, this does not result from a different age distribution or the presence of pre-existing immunity to SARS-CoV-2 in the vaccinated population. They explain the differences observed by a change in the culture conditions (roller bottles for Phase 1, bioreactor for Phase 2) and by a difference in the purification method for the virus used to manufacture the vaccine. Indeed, the vaccine used in Phase 1 seems to have had a low concentration of Spike protein.

- The methodological aspects supporting the results presented by SINOVAC, in particular the neutralizing antibody titres obtained after vaccination, were not clearly explained. In animal models, the neutralizing antibody titres induced appear to be low. The SINOVAC team did not respond satisfactorily to the Committee's technical questions on this issue and the Committee will go back to them for further details in writing on this point.

- The T-cell response induced by the CoronaVac vaccine has not yet been evaluated, and analyses to characterize Th1/Th2 responses are only planned. The Committee does not consider this response satisfactory in the present context, especially for an alum-adjuvanted inactivated vaccine, as the Th1/Th2 balance is considered important in predicting a potential ADE-like response.

- SINOVAC is interested in the European market. Discussions are underway with Odile Launay's team to set up a clinical trial in France.

- The Committee wishes to draw attention to the choice of adjuvant CpG 1018 *vs* MF59 or AS03 for the VALNEVA VLA 2001 vaccine. This adjuvant is used for other vaccines such as HEPLISAV® (Dynavax's hepatitis B vaccine) for which the FDA has had difficulty in granting approval for use in humans due to safety concerns. In addition, CpG 1018 generally facilitates the induction of Th1-type cellular immune responses rather than robust humoral responses leading to the production of neutralizing antibodies. VALNEVA appears to have made a choice based primarily on the availability of a product that can support large-scale vaccine production. CpG 1018 was recently selected by MEDICAGO (plant-based production technology) and Clover Biopharmaceuticals for the adjuvantation of their respective COVID-19 vaccine candidates, which have just started Phase 1 trials.

COMMITTEE RECOMMENDATIONS

The Committee has a rather favourable a *priori* opinion on the potential of candidate vaccines based on an "inactivated virus" platform. Indeed, this is a traditional and proven platform. The SINOVAC vaccine is clearly the most advanced and the company has had encouraging results in the clinic and in a virulent challenge model in macaque monkeys. However, the Committee stressed that clarification on the level of neutralising antibodies induced by the vaccine, as well as on the characterisation of the T-cell responses in humans, is needed to better assess the potential of this vaccine and the possible risk of induction of an ADE-type reaction.

The Committee is not in a position to make a scientific recommendation on VALNEVA's VLA2001 vaccine: preclinical testing has not yet started and the first clinical data will not be available before 2021.

At this stage, the Committee recommends not to rush to reserve or purchase these two vaccines and suggests to follow closely the progress of VALNEVA and to wait for the efficacy results of the SINOVAC vaccine - which will probably be available in autumn 2020. A clinical trial in France in individuals > 70 years of age could be useful to guide a possible decision to purchase CoronaVac vaccine.

Finally, the Committee questions the acceptability among the French population of a vaccine developed in China (SINOVAC) in the current geopolitical context.

These recommendations were approved by the COVID-19 vaccine scientific committee. In application of the code of ethics, the members confirmed that none of them was in a situation of deportation and they all participated in the collegial debate of the committee.

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