This Note was provided to the Ministry of Public Health, Welfare and Sport and the Task Force of the Dutch Government on Covid-19 vaccine initiatives on September 22th 2020

DUTCH SCIENCE BOARD COVID-19 VACCINES

RECOMMENDATIONS ON VALNEVA WHOLE

INACTIVATED VIRAL VACCINE

22 September 2020

PARTICIPANTS

Science Board: 5.1.2e, 5.1.2e, 5.1.2e, 5.1.2e, 5.1.2e, 5.1.2e, 5.1.2e

INTRODUCTION

The Board obtained information via public[1] or confidential[2,3] sources on VLA2001, a vaccine against SARS-CoV-2. The vaccine is designed to present a chemically inactivated preparation of the whole SARS-CoV-2 virus, administered with the proprietary adjuvant CpG1018 (Dynavax), to promote the induction of an effective immune response. This adjuvant is also used in a hepatitis B vaccine (Heplisav-B, Dynavax) holding a FDA license.

VLA2001 is based on the classical platform of a 'whole inactivated viral vaccine', but is still in the preclinical phase. Two Chinese vaccine candidates based on the same platform, from Sinopharm and Sinovac, are much further advanced, in clinical phase 3. The board has seen preclinical Non Human Primate (NHP) data[4] and interim Phase 1 /2 safety and immunogenicity data[5,6] for these Chinese products.

VALNEVA is an established vaccine manufacturer with its headquarters in France. It has operations in Austria, Sweden, the United Kingdom, France, Canada and the U.S. The firm has two registered vaccine products: DUKORAL® against cholera and IXIARO® against Japanese Encephalitis. IXIARO® is the only JE vaccine licensed and available in the United States, and has an EMA registration. The firm is very proactive in presenting its future COVID-19 product to national governments and the EU. UK has a deal with Valneva for 190 M vaccine doses over a period of 5 years. The firm producing the adjuvant, Dynavax, will provide 190 M doses of the adjuvant.

[1] https://valneva.com/
[2] EC JNT
[3] French Scientific Committee meeting with Valneva representatives on June 20th
[4] Preclinical study Sinovac product: https://pubmed.ncbi.nlm.nih.gov/32376603/
[5] Clinical study Sinovac product: https://www.medrxiv.org/content/10.1101/2020.07.31.20161216v1.full.pdf
[6] Clinical study Sinopharm product: https://pubmed.ncbi.nlm.nih.gov/32789505/

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VACCINE PRESENTATION

Description of vaccine candidate

- VLA2001. The candidate vaccine is based on the traditional platform of 'whole inactivated viral vaccines'. After culture on VERO cells, using Univercells technology, the virus is inactivated with β-propriolacton (BPL), preserving the native structure of the S-protein. The same production platform has also been used for a Japanese encephalitis vaccine IXIARO® approved by the FDA and EMA. The strain for the JE vaccine though is an attenuated vaccine, while the SARS-C0V-2 strain for VLA2001 is not. VLA2001 should be given in a 2 dose schedule.

- SARS-CoV-2 strain for production: the strain selected for production is currently preselected from several candidate strain, based on genetic stability and in vitro growth capacity (from strains circulating in Europe). The virus is grown on VERO cells.

- Adjuvant: Dynavax proprietary toll-like receptor 9 adjuvant (CpG1018), is expected to elicit a powerful Th1 type immune response. CpG 1018 is the adjuvant contained in HEPLISAV-B®, the Company's U.S. FDA-approved hepatitis B vaccine. CpG1018 is also used in other COVID19 vaccine candidates developed among which by Sinovac, Medigen (sub-unit vaccine) and Medicago (VLP vaccine)

Pre-clinical and clinical program

- Preclinical studies: immunogenicity testing in mice and infectious challenge experiments (intranasal and intratracheal) in macaque monkeys are planned for the fall of 2020

- Clinical Development:
    - Phase 1/2: start December 2020
    - Phase 3:
    - Regulatory approval anticipated 2021

Formulation, packaging, storage

- Formulation and packaging
    - 10-dose glass vials of adjuvanted product
- Product presentation
    -
- Storage
    - 2-8 °C

- Production capacity:

  Production of virus is in 'Cell Factories' (Univercells technology) which allows large scale production. Estimated production capacity (2021-2022) of 250M doses per year (50M Scotland, 200M at new production site Brownfield, from June 2021), plus other sites to be made operational.

  CpG is supplied by Dynavax (several hundreds of M doses per year)

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CONCLUSIONS

- Pre-clinical and clinical data for VLA2001 are not yet available. The vaccine developed by VALNEVA- is based on a proven 'whole inactivated viral vaccine' technology implemented by an experienced firm, but whose development plan clearly lags behind that of its competitors, e.g. for the Chinese Sinopharm and Sinovac Whole Inactivated vaccine products. These products are based on Chinese SARS-CoV-2 strains, but the production and inactivation platforms are comparable with the VLA2001 product: VERO cell propagation and BPL inactivation (the Sinopharm product is inactivated twice). Both the advanced Sinopharm and Sinovac products are however adjvanted with aluminium hydroxide.

- The preclinical NHP data and Phase 1 /2 safety and immunogenicity data for the alum-adjuvanted Sinopharm and Sinovac products indicate that the Whole Inactivated Viral vaccine concept shows protection against SARS-CoV-2 challenge in NHP with no indication of disease enhancement, and has a favorable safety and immunogenicity profile in humans. As the immune response to a vaccine is a result of the combined activity of the antigen(s) and adjuvant, the results of these studies can not be readily translated to VLA2001.

- The expected type of immune response with an CpG adjuvanted vaccine is shifted towards Th1 type immunity, propagating IFNg-type T-cell responses associated with IgG1 type antibody responses, which are both expected to be favourable for protection against COVID-19 and to avoid antibody enhanced disease.

- The Science Board would want to see data on protection in NHP, vaccine-induced systemic and mucosal immunity, durability of the immune response, assessment of the potential risk of ADE associated with the administration of the vaccine candidate and a targeted risk assessment and (pre-)clinical safety program. The Board also likes to see assessment of virus shedding in follow up studies of VLA2001 vaccinated individuals with breakthrough infections.

RECOMMENDATIONS OF THE DUTCH SCIENCE BOARD ON COVID-19 VACCINES

At this stage, VALNEVA has no immunogenicity data available in animals nor humans. Therefore, the Board cannot make an evidence-based recommendation on their candidate vaccine. However, the fact that the company uses proven vaccine and adjuvant technologies and that other companies using a similar whole inactivated virus vaccine production technology, albeit in combination with another adjuvant, have demonstrated protection in NHP and a reasonable safety and immunogenicity profile, increases the chance that the VALNEVA SARS-CoV-2 vaccine will be successful.

The Board draws the attention of policy makers to the fact that, although the CpG1018 adjuvant is also being used in the registered hepatitis B vaccine (HEPLISAV-B®), there still is limited experience with this adjuvant and it is unknown how the immune system will respond to the adjuvant in combination with a SARS-CoV-2 whole inactivated virus preparation. Notably, the adjuvant of VLA2001, CpG1018, is different from the adjuvants used in the advanced Chinese whole inactivated virus vaccine products in development. Therefore the board recommends the preclinical and clinical test phases of the VLA2001 vaccine should be followed with special attention for the adjuvant, as data might reveal unexpected

safety and/or immunogenicity patterns.

Large scale production of a whole virus preparation at BSL3 level and appropriate inactivation is challenging. Although VALNEVA will use existing technology also in place for the Japanese encephalitis vaccine IXIARO® and a proven platform for virus inactivation (BPL), the board points out the anticipated production scale for VLA2001 may exceed the manufacturers ' present production scale. The plans and capacity to scale up timely should be part of the product safety profile discussion with authorities..

NEDERLANDSE SAMENVATTING AANBEVELINGEN VAN HET WETENSCHAPPELIJK ADVIESPANEL COVID-19 VACCINS T.A.V. HET VALNEVA HEEL GEINACTIVEERD VACCIN VLA2001

- VALNEVA's 'heel-geinactiveerd virus vaccin' ('VLA2001) bestaat uit VALNEVA's BPL-geinactiveerd heel SARS-CoV-2 virus preparaat met het CpG1018 adjuvant van DYNAVAX
- Het type immuun respons dat dit adjuvant stimuleert is het Th1 type, dat het meest effectief geacht wordt in bescherming tegen COVID-19
- Er zijn op dit moment geen preklinische en klinische data beschikbaar waardoor een evidence-based advies over hun VLA2001 niet mogelijk is
- Voor de productie van de werkzame componenten van VLA2001 worden technologieën gebruikt waarmee VALNEVA en DYNAVAX al effectieve en veilige vaccins gemaakt hebben die tot de markt zijn toegelaten
- Geinactiveerde virus vaccins zijn een klassiek beproefd platform voor veilige en werkzame vaccins. Chinese producten van ditzelfde type vaccin hebben gunstige veiligheid en immunogeniciteit data laten zien, maar deze producten hadden wel een ander adjuvant
- Onduidelijk is of de ambitieuze registratie termijn en benodigde productie opschaling van zowel virus productie als adjuvant haalbaar zijn voor tijdige inzetbaarheid van dit product.
- Echter een vaccin op meer klassieke basis geproduceerd kan ook een toegevoegde waarde hebben in bepaalde populaties, of patiënten categorieën
- De Adviespanel vindt VLA2001 een interessant, klassiek en nog niet in het EC portfolio opgenomen COVID-19 vaccin concept, en om die redenen, niettegenstaande bovengenoemde onzekerheden, een mogelijke kandidaat voor verdere overweging in het EC portfolio

These recommendations were approved by the Dutch science board COVID-19 vaccines. 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 board. The members of the Dutch science board COVID-19 vaccines are available to the Government to provide additional information, if necessary.