DUTCH SCIENTIFIC BOARD COVID-19 VACCINES

RECOMMENDATIONS ON JANSSEN VIRAL VECTOR VACCINE

30 September 2020

This Note was provided to the Ministry of Public Health, Welfare and Sport and the Program Management COVID-19 on September 30th 2020

PARTICIPANTS

Scientific 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 confidential information via the EC JNT as well as through meetings with representatives of Janssen on June 16 and September 4th 2020. The investigational Janssen COVID-19 vaccine (JNJ-78436725) is a non-replicating viral vector vaccine against SARS-CoV-2. The vaccine is designed to present protein S capable of eliciting powerful immune responses when administered within an adenoviral vector.

The Janssen Pharmaceutical Companies of Johnson & Johnson developed the investigational vaccine (also known as Ad.26.COV2.S) in Leiden. Johnson & Johnson is an established multinational manufacturer with its headquarters in the US and is supported by BARDA (USA), to develop a adenoviral vector vaccine against COVID-19.

VACCINE PRESENTATION

Description of vaccine candidate

Ad26.COVS2.S is a replication incompetent recombinant human adenovirus serotype 26 (Ad26) vector based vaccine with a stabilized SARS-CoV-2 Spike (S) protein. The choice of Ad26 is based on the low prevalence of type 26 adenovirus immunity in the human population globally. The same vector has also been used in their licensed Ebola vaccine (Ad26.ZEBOV) that received marketing authorization from the EMA July 2020 and in their RSV, HIV and Zika vaccine candidates. Ad26 based vaccines are generally well tolerated and highly immunogenic. Pre-existing immunity to the vector is low in Western countries, higher in Africa but with low titers which did not interfere with vaccine response to Ebola vaccine based on the same Ad26 vector.
After comparison of several variants, a full length stabilized SARS-CoV-2 Spike protein, derived from the first clinical isolate of the Wuhan strain, was chosen as antigen.

Pre-clinical and clinical studies

A phase 1/2a randomized, double-blinded, placebo controlled clinical study to assesses the safety, reactogenicity and immunogenicity of Ad26.COV2.S started on July 22nd 2020 in Belgium and US (NCT04436276). The study evaluates a one- and two-dose (8-week interval) schedule with two different vaccine doses ($5x10^{10}$ or $1x10^{11}$ viral particles (vp)) per intramuscular vaccination in adults 18–55 or >65 years of age. Interim analysis showed solicited local and systemic adverse events in 27-64% that resolved within a few days. Fever has been reported by 19% of participants mostly mild to moderate, 5% grade 3, resolved in 1-2 days. After only a single dose, seroconversion rate in wt virus neutralisation assay at day 29 after immunization reached 83-100%. On day 14 post immunization, Th1 cytokine producing S-specific CD4+ T cell responses were measured in 80% of a subset of participants with no or very low Th2 responses, indicative of a Th1-skewed phenotype. CD8+ T cell responses were also robust for both dose levels. They concluded that the safety profile and immunogenicity after a single dose are supportive for further clinical development of Ad26.COV2.S at a dose level of $5x10^{10}$ vp, as a potentially protective vaccine against COVID-19.
A phase 2 trial comparing 1 dose and 2 homologous doses, with different intervals, schedules in participants age 18-55 years and 65 and older (n=375) is ongoing. Sites in the Netherlands (Leiden, Utrecht, Groningen), Germany and Spain.

A randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older has started September 23nd and will run in various countries on three continents (the US, Brazil, Chile and others). Recruitment will start with 18-65 year old individuals followed by 65 and older individuals (25-40% of total). First 2500 participants with no co-morbidities, if no safety concerns also a group with comorbidities such as hypertension and diabetes will be included. The event driven study started in US and will enrol up to 60.000 participants. Primary outcome number of participants with first occurrence of molecularly confirmed moderate to severe/critical COVID-19 with seronegative status. With an assumed

VE of 65%, 126 cases are expected to be completed by March/April 2021, but with VE>65% this will be earlier. Interim analysis is planned after 20 cases.
A second phase 3 study will test a 2 dose schedule with 2 month interval in up to 30.000 participants, with sites in several European countries (UK, Spain, France, Belgium, Netherlands), Mexico, Argentina, South Africa depending on incidence rate.

Several interactions with EMA and FDA are planned.

Production :

The production platform in an optimized and well controlled PERC-6 cell culture system in 900 liter bioreactors resulting in 5.1.1c doses. Current capacity: 5.1.1c doses/year, rising to approximately 5.1.1c doses/year in 2021. Two bioreactors available in Janssen-Leiden are able to produce 5.1.1c doses. Other production sites are under discussion: United States 5.1.1c 5.1.1c Europe and India.

Formulation, packaging, storage

- Formulation and packaging
  - Multi dose vials
  - 0.5 ml/dose
- Delivery by syringe
- Storage
  - Refrigerator-stable product, i.e. at 2-8 degrees Celsius for a few months, which permits leveraging standard vaccine distribution and delivery infrastructure
  - Stability data based on warehouse storage at -20 degrees.

General considerations

The levels of binding and neutralizing antibodies induced by one dose of Ad26.COV2.S are, for most participants, in the same range as found in convalescent sera from human COVID-19 patients. However, one should be careful with the interpretation of this comparison since the neutralizing capacity of convalescent sera varies considerably between batches since it depends on several factors, including the patients age, disease severity, time of sampling since disease onset and the number of sera included in the batch. Standardization of convalescent sera is urgently needed to also allow comparison of antibody responses elicited by the different candidate COVID-19 vaccines.

Only limited safety data is available for Ad26.COV2.S. There could be a risk for Antibody Disease Enhancement (ADE). Although the phase 1/2 data show that the vaccine induces a cytokine producing S-specific CD4+ T cell response with a Th1-skewed phenotype which reduces the risk for ADE. In addition, special attention for the effect of pre-existing immunity. However, in contrast to eg adenovirus serotype 5 based vaccines, baseline Ad26 neutralizing antibodies in human populations do not suppress the immunogenicity of an Ad26-HIV vaccine.

CONCLUSIONS

Ad26.COVS2.S is a non-replicating recombinant human adenovirus serotype 26 vector based vaccine with a stabilized SARS-CoV-2 Spike (S) protein. The Ad26 vector has also been used in their EU licensed Ebola vaccine.

At this moment the only human data available are phase1/2 safety and immunogenicity data. The study results showed an acceptable safety profile and the induction of neutralizing antibodies after one vaccine dose. Since no generally accepted correlate of protection has been identified yet, clinical efficacy data are required to provide an indication on the vaccines ability to induce protection against disease and/or infection. Extrapolating the 5.1.1c results to humans suggests that vaccination with this vaccine candidate may not or only partially stop transmission of the virus in the community but could protect against severe disease. The vaccine is currently being tested in a phase 3 efficacy trial in the US.

RECOMMENDATIONS OF THE DUTCH SCIENCE BOARD ON COVID-19 VACCINES

The Committee analysed data provided by Janssen. Based on these pre-clinical and preliminary human phase 1/2 safety and immunogenicity data that show that the vaccine seems to be immunogenic with an acceptable safety profile, the Committee considers that the Ad26.COVS2.S vaccine can be successful.

NEDERLANDSE SAMENVATTING AANBEVELINGEN VAN HET WETENSCHAPPELIJK ADVIESPANEL COVID-19 VACCINS T.A.V. JANSSENS VIRALE VECTOR VACCINE

- Janssens COVID-19 vaccin (Ad26.COVS2.S) bestaat uit Janssens niet-replicerende recombinant humaan adenovirus serotype 26 vector met een gestabiliseerd SARS-CoV-2 Spike (S) eiwit.
- Er zijn op dit moment alleen preklinische en preliminaire klinische fase 1/2 data beschikbaar deze beperkte dataset laat zien dat het vaccin een acceptabel veiligheidsprofiel heeft en in staat is neutraliserende antistoffen en een gunstige T-cel respons op te wekken.
- Het feit dat gebruik gemaakt wordt van een technologie waarmee een geregistreerd ebola vaccine gemaakt is maakt de kans groter dat ze in staat zullen zijn ook een succesvol SARS-CoV-2 vaccin te ontwikkelen en produceren.
- Voor het vaccin is een potentieel grote EU productie capactiteit beschikbaar (Leiden, Nederland)
- De board ziet op dit moment geen reden voor een opt-out uit de deal van de EU-commissie met Janssen aangaande levering van SARS-CoV-2 vaccin

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.