EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2020
EMA/639119/2020EMA/639119/2020
Health Threats and Vaccines Strategy

COVID-ETF recommendation on the start of rolling review for Ad26.COV2.S Janssen-Cilag International NV (Ad26.COV2.S)

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Background on the product

The Ad26.COV2.S vaccine contains the recombinant Ad26 vector Ad26.COV2.S as drug substance. The recombinant Ad26 vector Ad26.COV2.S is replication incompetent and contains a modified full-length SARS-CoV-2 spike (S) protein with stabilizing modifications.

Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus, and filovirus. One vaccine based on Ad26 platform has been granted a MA in the EU (Zabdeno, Ad26.ZEBOV).

The Ad26.COV2.S drug product (DP) is supplied as a sterile liquid suspension for injection with a target concentration of 1.0×10^{11} virus particles (vp)/mL. Each vial contains a fill volume of 3.1 mL to allow for an extractable volume of 2.5 mL as 5 extractions of 0.5 mL. The primary packaging consists of a 2R Type I glass vial with a chlorobutyl closure and an aluminium seal with a flip-off cap. The DP contains no preservative.

The initial shelf life of the Ad26.COV2.S drug product (DP) is 24 months when stored frozen at the recommended storage condition of -25 to -15°C, and within these 24 months, 3 months when stored at 2-8°C

The drug product is intended for administration by the intramuscular (IM) route. The indication under this application is active immunization against coronavirus disease-2019 (COVID-19) in adults aged 18 years or older.

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The Ad26.COV2.S drug substance is manufactured by Janssen Vaccines & Prevention B.V. in Leiden, the Netherlands. The drug product is manufactured by Grand River Aseptic Manufacturing, Inc. in Grand Rapids, USA. Batch release is performed by Janssen Biologics B.V. in Leiden, the Netherlands.

Summary of the data available

Quality

Most of the module 3 data are currently already available for both DS and DP. These include description of the process and process controls, process development, control of starting materials, specifications analytical methods, method validations,... Stability data will be provided later. Also some other data may not be available for the initial submission (RR1), but these will be provided in the next submissions (AtoQ,RR3).

Non-Clinical:

J&J Ad26.COV has been shown to be immunogenic in mice, rabbits, hamsters and NHP models, inducing neutralizing antibody response, as well as CD4 and CD8 T cell responses. Further, in hamster and NHP SARS-CoV-2 challenge models, a single administration of J&J Ad26.COV significantly reduced symptoms in hamsters and viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to controls in both species. Data on durability of the immune response (6 and 8 months after vaccination), immunogenicity and efficacy in aged monkeys and vaccine titration in hamsters could be submitted in the third RR package or at cMAA depending on the time of efficacy signal.

A biodistribution study has not been performed, following consideration of the results of other biodistribution studies of replication-deficient adenoviruses. This platform data are considered sufficient to support development.

Studies evaluating any toxicity due to Ad26COV have not been conducted to date. In a toxicology study on related Ad26-based vaccines, no toxicologically relevant effects were noted. The Applicant however started a specific Ad26COV - GLP Repeat-dose toxicity/local tolerance study.

Finally, the applicant conducted a combined embryo-foetal and pre- and postnatal development study in female rabbits with another Ad26-based vaccine, there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A specific Ad26COV DART study will be conducted.

The results of both safety studies will be submitted during rolling review.

Clinical:

Platform data available

Replication-incompetent Ad26 is being used as a vector in the development of vaccine candidates against diseases such as malaria, RSV, HIV, Ebola virus, Zika virus, and filovirus. The Applicant's clinical AdVac® safety database includes safety data from 26 completed clinical studies using Ad26-based vaccines in which 4,224 adult participants were vaccinated with an Ad26-based vaccine. One vaccine based on Ad26 platform has been granted a MA in the EU is Zabdeno, Ad26.ZEBOV, (5x10exp10 virus particles) for the prevention of Ebola (MA under exceptional circumstances).

Clinical development plan

Phase 1/2a (COV1001), Phase 1 (COV1002) and Phase 2 (COV2001) clinical studies to assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S are ongoing. Two Phase 3 studies (COV3001, COV3009) are ongoing as well.

The FIH study COV1001 is a randomized, double-blind, placebo-controlled, Phase 1/2a multicenter study in adults aged ≥18 to ≤55 years and aged ≥65 years (US and Belgium). The safety, reactogenicity, and immunogenicity of Ad26.COV2.S is evaluated at 2 dose levels (5×10^{10} vp and 1×10^{11} vp), administered IM as a single-dose or 2-dose schedule with a 56-days interval. Overall, a target of 1,045 adult participants will be randomly assigned in this study.

COV1002 is a Phase 1 trial ongoing in Japan (n=250).

COV2001 is a Phase 2a ongoing in The Netherlands, Germany, and Spain (n=550) in healthy adults to assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S. The vaccine candidate is evaluated across a range of dose levels ($1x10^{11}$, $5x10^{10}$, $2.5x10^{10}$, $1.25x10^{10}$ vp) and schedules (2 dose vs 1 dose primary regimen, with different compressed or expanded intervals for the 2-dose regimen [1m, 2m, 3m]). Anamnestic responses will be compared by using a later, low-dose vaccination ($1.25x10^{10}$ vp) as a surrogate of antigen exposure upon SARS-CoV-2 infection.

Based on the interim immunogenicity and safety data (28 days post-Dose 1 data from participants aged ≥18 to ≤55 years and available data from participants aged ≥65 years) from study COV1001 (described below), the Applicant decided to proceed with Ad26.COV2.S at a dose level of 5×10^{10} vp in its Phase 3 studies.

Study COV3001 is a randomized, double-blind, placebo-controlled Phase 3, pivotal efficacy and safety study in adults aged ≥18 to <60 years of age and ≥60 years of age, with and without relevant comorbidities. The primary objective of study COV3001 is to demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical COVID-19 when given as a single-dose vaccination regimen, in SARS-CoV-2 seronegative adults. A total of 60,000 subjects are planned to be enrolled in this trial.

Study COV3009 has a similar design but assesses efficacy of Ad26.COV2.S when given as a two-dose vaccination regimen (same dose level as in COV3001; doses given 8 weeks apart), and plans to enrol 30,000 subjects. Even though a single-dose regimen in study COV1001 showed robust immunogenicity, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in a higher and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study.

Preliminary data

Preliminary safety and immunogenicity data from the first interim analysis are available for 402 participants aged ≥18 to ≤55 years and 403 participants aged ≥65 years who received at least one dose of study vaccine. The results from the safety analyses showed that both dose levels had acceptable reactogenicity in participants aged ≥18 to ≤55 and ≥65 years with no significant safety issues during the 28-day observation period. One participant aged ≥18 to ≤55 years experienced a SAE (pyrexia) which was considered to be related to blinded study vaccine.
In both age groups, a single vaccination (both dose levels) with Ad26.COV2.S was shown to induce neutralizing and binding antibody responses, a Th1-skewed phenotype, and specific CD4+ and CD8+ T cell responses.

Temporary pause phase 3 study

The Company halted the COV3001 trial following detection on the 11th of October of a case with initial diagnosis of transverse sinus thrombosis resulting in cerebral haemorrhage detected in a 25-year-old

male that started with symptoms 19 days after receiving the first dose of the vaccine (after experiencing flu-like illness starting Day 9). The sponsor assessed this event to be not causally related to the study vaccine/placebo (no clear cause identified). Based on a cumulative ad hoc safety review the sponsor considers that, from the data available to date, there is insufficient evidence for a causal role of Ad26.COV2.S or any other Ad26 vaccines, in the development of thrombotic, thromboembolic, or neurovascular events.

The DSMB has recommended resuming trial recruitment, and regulators have approved it in US and in various countries in Europe (Belgium, Germany, Nederland, France and Spain, to our knowledge).

Conclusion

Demonstration of the proof of principle (non-clinical) including challenge models and proof of concept (clinical immunogenicity, neutralising antibodies) justify the start of the rolling review.

coRapporteur comments

The Rapporteur's conclusion is fully supported.

COVID-ETF recommendation:

<The available information on the product is <not> considered sufficient to establish proof of concept and warrant start of a rolling review of this application.>

Annex 1

Briefing document or other documents from the Applicant on proof of concept data to support the start of the Rolling Review