Background document on the Janssen Ad26.COV2.S (COVID-19) vaccine

Background document to the WHO Interim recommendations for use of Ad26.COV2.S (COVID-19) vaccine

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Contents

Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 15 March 2021 meeting, which resulted in the issuance of the WHO interim recommendations for use of the Ad26.COV2.S (COVID-19) vaccine. Both the recommendations and the background document are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

Context

The Janssen vaccine is a recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein and is based on the Ad26 vector platform. The adenoviruses are a group of viruses that cause infections in the respiratory and gastrointestinal tracts; the adenovirus vector used in the experimental vaccine has been modified, so that it can no longer replicate in humans and cause illness. In developing the vaccine, Janssen employed the same vector used in the first dose of its prime–boost vaccine regimen against Ebola virus disease (Ad26 ZEBOV and MVN-BN-Filo). As of 31 December 2020, Ad26-based vaccines have been used to vaccinate 193 831 participants in clinical studies and vaccination programmes. These more than 193 000 participants included people from different age groups (elderly, adults, children and infants), individuals positive for human immunodeficiency virus (HIV), and pregnant and breastfeeding women, and the data show a favourable safety profile. Ad26-based vaccines elicit strong humoral immune responses with both neutralizing activity and non-neutralizing antibody functionalities, and cellular immune responses involving both CD8+ T cells and CD4+ T-cells, the latter with a predominantly Th1 phenotype, irrespective of the transgene encoded immunogens (1-4). Overall, these vaccines have been shown to have an acceptable clinical safety profile to date.

Data taken into consideration are those included in the US Food and Drug Administration *Vaccines and Related Biological Products Advisory Committee (VRBPAC)* meeting documentation, available under the following links: www.fda.gov/media/146217/download and www.fda.gov/media/146218/download.

Characteristics of Ad26.COV2.S (COVID-19) vaccine

The Janssen COVID-19 Vaccine is a replication-incompetent adenovirus type 26 (Ad26)-vectored monovalent vaccine encoding the SARS-CoV-2 spike (S) protein from the Wuhan-Hu-1 isolate (GenBank accession number MN908947), stabilized in its prefusion conformation. The vector cannot replicate in human cells because the E1 gene was deleted from the genome. To manufacture vaccines that are based on replication incompetent adenoviral vectors, a specific cell line is used that complements for the missing E1 gene. This cell line is derived from a single human primary cell, obtained in 1985 from fetal retina tissue (at 18 weeks of gestation adhering to the Dutch laws that were in effect). The cell line was established by transformation of the primary cells using the Adenovirus E1 gene which resulted in a cell line that constitutively expresses E1, and that is thus able to complement the adenoviral vector that misses E1, allowing the vector to replicate during the manufacturing process. Another consequence of the E1 transformation is that the cell line can be propagated indefinitely and as a result, there is no need to go back to the primary cells in any part of the scientific discovery or manufacturing process. The Ad26 vector expressing the S protein is grown in PER.C6G TetR cell line, in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients and filled into vials.

Composition

One dose (0.5 ml) contains 5 x 10^{10} AD26.COV2.S viral particles (vp).

The vaccine also contains the following inactive ingredients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-beta-cyclodextrin (HBCD), polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid.

The vaccine does not contain preservatives.

Dosing regimen

Ad26.COV2.S is administered as a single intramuscular injection (0.5 ml dose).

Stability and shelf-life

The vaccine is provided to country at -20°C with a shelf life of 24 months in a multi-dose vial containing 5 doses (0.5ml each). The vaccine could be stored at 2°C to 8°C for 3 months. Once thawed the vaccine should not be re-frozen. The vials should be protected from light. After the first dose has been withdrawn, the vial should be held between at 2°C to 8°C for up to 6 hours in compliance with WHO Multidose open vial policy. Any remaining dose of opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

Drug product description

The Janssen Ad26.COV2.S vaccine is a colourless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection.

Container

Each multidose 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 vaccine does not require reconstitution.

Preclinical studies

Nonclinical immunogenicity and efficacy

A single dose of Ad26.COV2.S induced a rapid onset of SARS-CoV-2 neutralizing and S protein-binding antibodies in all species tested (mice, rabbits, Syrian hamsters, and nonhuman primates). Cellular immunity was seen in mice and nonhuman primates, with CD4+ T cells, predominantly of the Th1 phenotype, and IgG-producing CD8+ T cells.

In Syrian hamsters, a single dose of Ad26.COV2.S significantly reduced viral load in the lungs after SARS-CoV-2 challenge, in comparison with mock-vaccinated and challenged controls. In nonhuman primates, undetectable viral load in the nose was observed in the majority, and undetectable viral load in the lungs was recorded for all animals. (5, 6).

Duration of protection: Almost all vaccinated macaques had undetectable lung viral load after challenge 6 months after vaccination (7).

Vaccine enhanced respiratory disease (VAERD): In all Syrian hamsters and nonhuman primates vaccinated with Ad26.COV.2S and subsequently challenged with SARS-CoV-2, no increased lung histopathology, infectious viral load, or clinical signs were observed, indicating the absence of any signs of VAERD (8).

Biodistribution

The biodistribution profile of the Ad26 vector platform was evaluated in New Zealand White rabbits. The Ad26 vector did not widely distribute following intramuscular administration. Vector DNA was detected at the site of injection, in draining lymph nodes, and (to a lesser extent) in the spleen. The Ad26 vector showed clearance from these tissues.

Toxicology

In a repeat-dose toxicity and local tolerance study in New Zealand White rabbits, IM administration of Ad26.COV2.S at 1×10^{11} vp/dose on three occasions, with a 14-day interval period, was well tolerated. There were no adverse vaccine-related effects noted.

Developmental and reproductive toxicity

In a combined embryo-fetal and pre- and postnatal development toxicity study, 3 doses of Ad26.COV2.S at $1x10^{11}$ vp/dose were administered at $1x10^{11}$ intramuscularly to female New Zealand White rabbits during the premating and gestation period. There was no adverse effect of Ad26.COV2.S on fertility, or embryo-fetal and postnatal development.

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from five ongoing studies:

- COV1001: a phase 1/2 trial in 1045 adults (1-dose and 2-dose regimens, with booster in 1 cohort);
- COV1002: a phase 1 safety and immunogenicity study in 250 adults (2-dose regimen);
- COV2001: a phase 1a safety and immunogenicity study involving 550 adults and 660 adolescents (1-dose and 2-dose regimens) (enrolment of adolescents has not yet started);
- COV3001: a phase 3 efficacy and safety trial in 40 000 adults (1-dose regimen) (enrolment complete);
- COV3009: a phase 3 efficacy and safety trial in 30 000 adults (2-dose regimen) (enrolment ongoing);

The primary analysis of vaccine efficacy from the study COV3001 is used here as the main source of data.

Studies in other populations (i.e, pregnant women, children with and without comorbidities) are planned in the near future.

Immunogenicity studies in humans

Study COV1001 (healthy adults ages 18 to 55 in the United States and Belgium): A single dose of Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 spike binding antibody response that was detected by Day 15 and is increased by Day 57. Ad26.COV2.S was able to elicit cellular responses in participants with a Th-1 phenotype. Ad26.COV2.S, given as a single dose was found to have an acceptable safety and reactogenicity profile in adults aged 18 years and above and did not raise safety concerns in any of the assessed populations.

Study COV1002 (healthy adults ages 20-55, and ≥65 years of age and above in good health, in Japan): Two doses were given at a 56-day interval. Neutralizing antibody responses by day 29 post-vaccination with a single dose were similar to Study COV1001.

Study COV2001 is an ongoing, randomized, double-blind, placebo-controlled Phase 2a study, conducted in Germany, Spain, and the Netherlands in healthy adults ⩾18 to ⩽55 years of age, and adults in good or stable health ⩾65 years of age. The primary objectives of this study are to assess safety and reactogenicity and humoral immune response of Ad26.COV2.S across different doses and intervals (for 2-dose regimens). Recently, adolescents aged 12 to 17 years were included.

Across Phase 1 and 2 studies at Day 29, a SARS-CoV-2 neutralizing antibody response was observed in at least 88% of participants aged 18 to 55 years and at least 93% of participants aged 65 and above. Neutralizing and binding antibody responses continued to increase from Day 29 to Day 57 and were maintained to at least Day 85, with very high responder rates across the age groups. A single dose of Ad26.COV2.S elicited SARS-CoV-2 CD4+ and CD8+ T cell responses by Day 15 and up to Day 29 in the majority of adult participants aged 18 to 55, and aged 65 and above.

Efficacy studies

Study COV3001, which used a 1-dose regimen, provides the primary analyses for this background paper. Study COV3001 is an ongoing, multicentre, randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy, safety and immunogenicity of a single dose (5×10^{10} vp) of Ad26.COV2.S for the prevention of COVID-19 in adults aged 18 years and older. The study is being conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and the USA. A total of 44 325 participants were randomized, of whom 43 783 were given either Ad26.COV2.S or placebo. The study was well balanced among subgroups with regard to age, comorbidities, sex, region, race, and ethnicity. The study was initiated at sites expected to experience high incidence of COVID-19 on 21 September 2020. The time of study enrollment coincided with a marked increase of incidence of COVID-19 and the emergence of new SARS-CoV-2 variants, which were emerging in some of the countries where study COV3001 was being conducted. Efficacy results were based on the primary analysis, which included 19 630 participants who received the vaccine and 19 691 participants who received placebo.

At the time of the primary analysis, 464 central laboratory-confirmed primary endpoint cases with an onset at least 14 days after vaccination included in the per protocol analysis set, of which 259 cases occurred at least 28 days after vaccination. The primary analysis included centrally confirmed cases only. Because of the high in-study incidence of COVID-19 and the time needed for central laboratory confirmation of the local polymerase chain reaction (PCR) test, not all cases could be confirmed by the central laboratory at the time of the primary analysis. As a result, there were two data sets: a data set of centrally confirmed primary endpoint COVID-19 cases (464 after day 14, 259 after day 28) and a data set including all primary endpoint COVID-19 cases with a positive PCR from any source, regardless of central confirmation (682 after day 14, 437 after day 28). Vaccine efficacy (VE) estimates based on the two data sets differed by less than 1% and had similar confidence intervals (CIs). Among the cases that were centrally confirmed, a high concordance was observed (90.3%). For subgroup analyses, COVID-19 requiring medical intervention, and COVID-19-related deaths, the data set including non-centrally confirmed cases was used to increase the robustness of the conclusions. The primary analysis included centrally confirmed cases only.

The co-primary endpoints in study COV3001 were the first occurrence of PCR-confirmed COVID-19, including both moderate and severe/critical COVID-19 cases according to their case definitions, with onset at least 14 days or at least 28 days after vaccination. All other efficacy endpoints were also evaluated in relation to cases that occurred at least 14 days or at least 28 days after vaccination. The primary efficacy analysis was performed after 50% of the participants had been followed for 8 weeks from the day of vaccination, on 22 January 2021, with 464 primary endpoint cases at least 14 days after vaccination and 259 primary endpoint cases at least 28 days after vaccination. Because of the limited number of mild COVID-19 cases, the co-primary endpoints capture almost all observed symptomatic COVID-19 cases. The total number of symptomatic cases (468 at least 14 days after vaccination and 261 at least 28 days after vaccination) was very similar to the total number of moderate and severe/critical COVID-19 cases. Participants will continue to be followed up for up to 24 months, for assessments of both safety and efficacy of the vaccine against COVID-19. Following emergency use authorization, Janssen proposes to change the study design, offering a single dose of Ad26.COV2.S to participants who initially received placebo, resulting in de facto unblinding of participants and investigators.

Table 1. Participant disposition by age group and comorbidities, full analysis set, study COV3001.

Participant group Follow-up	Ad26.COV2.S (21 895)	Placebo (21 888)	All participants (43 783)
18–59 years, total	14 564	14 547	29 111
Participants with at least 8 weeks follow- up	62.8%	63.1%	63.0%
Median follow-up after vaccination (days)	61.0	61.0	61.0
18–59 years, no comorbidities	9332	9371	18 703
Participants with at least 8 weeks follow- up	70.0%	69.9%	70.0%
Median follow-up after vaccination (days)	64.0	64.0	64.0
18–59 years, with comorbidities	232	5176	10 408
Participants with at least 8 weeks follow- up	49.9%	50.8%	50.4%
Median follow-up after vaccination (days)	56.0	57.0	57.0
≥60 years, total	7331	7341	14672
Participants with at least 8 weeks follow- up	38.2%	37.8%	38.0%
Median follow-up after vaccination (days)	52.0	52.0	52.0
⩾60 years, no comorbidities	3627	3595	7222
Participants with at least 8 weeks follow- up	47.6%	49.0%	48.3%
Median follow-up after vaccination (days)	54.0	55.0	54.0

≥60 years, with comorbidities	3704	3746	7450
Participants with at least 8 weeks follow- up	29.0%	27.1%	28.0%
Median follow-up after vaccination (days)	50.0	50.0	50.0

Boxes 1 and 2 provide respectively the primary endpoint case definitions for moderate and severe/critical COVID-19 cases used in the efficacy studies.

Box 1: Case definition for moderate COVID-19[1]

The **case definition for moderate COVID-19** was a positive SARS-CoV-2 reverse transcription (RT)-PCR or molecular test result from any available respiratory tract sample (e.g. nasal, throat, sputum, saliva) or other sample,

and at any time during the course of observation,

either:

- any one of the following new or worsening signs or symptoms:
  - respiratory rate ≥20 breaths/minute,
  - abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level,
  - clinical or radiological evidence of pneumonia,
  - radiological evidence of deep vein thrombosis,
  - shortness of breath or difficulty breathing

or:

- any two of the following new or worsening signs or symptoms:
  - fever (≥38.0°C or ≥100.4°F),
  - heart rate ≥90 beats/minute,
  - shaking chills or rigors,
  - sore throat,
  - cough,
  - malaise, as evidenced by loss of appetite, fatigue, physical weakness, and/or feeling unwell,
  - headache,
  - muscle pain (myalgia),
  - gastrointestinal symptoms (diarrhoea, vomiting, nausea, abdominal pain),
  - new or changing olfactory or taste disorders,
  - red or bruised-looking feet or toes.

[1] The case definitions used were developed by Janssen and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

Box 2: Case definition for severe/critical COVID-19[2]

The ***case definition for severe/critical COVID-19*** was an RT-PCR or molecular test result from samples described above and any one of the following at any time during the course of observation:

- clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg),
- respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)),
- evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors),
- significant acute renal, hepatic, or neurological dysfunction,
- admission to the intensive care unit (ICU),
- death.

Box 3 provides the list of secondary endpoints considered.

Box 3: Secondary efficacy endpoints

Secondary efficacy endpoints included vaccine efficacy to prevent or vaccine impact on:

- Severe/critical COVID-19
- COVID-19 requiring medical intervention
- COVID-19 related death
- Any asymptomatic COVID-19
- Asymptomatic COVID-19 as inferred through seroconversion
- COVID-19 per the U.S. Food and Drug Administration harmonized COVID-19 case definition

All cases meeting the severe/critical criteria were adjudicated by the Clinical Severity Adjudication Committee. Classification of a case as severe/critical by the Clinical Severity Adjudication Committee was considered definitive.

Efficacy against COVID-19

COV3001 demonstrated vaccine efficacy for both co-primary endpoints. A single dose of Ad26.COV2.S protected against moderate to severe/critical COVID-19 in adults ⩾18 years of age, including adults ⩾60 years of age, with an efficacy that was consistent across age groups but with some variability across countries (Table 2). Vaccine efficacy against first