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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

JCOVDEN

COVID-19 vaccine (Ad26.COV2-S [recombinant])

Procedure no: EMEA/H/C/005737/P46/073

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	17/10/2022	17/10/2022
☐	CHMP Rapporteur Assessment Report	21/11/2022	18/11/2022
☐	CHMP members comments	05/12/2022	05/12/2022
☐	Updated CHMP Rapporteur Assessment Report	08/12/2022	N.A
☒	CHMP adoption of conclusions:	15/12/2022	15/12/2022

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1. Introduction

The MAH submitted the final clinical study report (date: 23 August 2022) of the VAC31518COV2001 Study (involving paediatric participants) and a short critical expert overview in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that VAC31518COV2001 (also referred to as COV2001) is part of a clinical development program. VAC31518COV2001 was a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older, and in healthy adolescents aged 12 to 17 years inclusive. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

JCOVDEN (also referred hereafter as Ad26.COV2.S) is a monovalent vaccine composed of a recombinant, replication incompetent human adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein, stabilized in its prefusion conformation.

JCOVDEN is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The approved posology is a single dose of $5x10^{10}$ vp in 0.5 mL, to be administered intramuscularly (IM). The conditional marketing authorization was granted on 11 March 2021. In December 2021, JCOVDEN was further authorized as homologous booster or as heterologous booster following completion of primary vaccination with an approved mRNA COVID-19 vaccine. In November 2022, JCOVDEN was authorized as heterologous booster following completion of primary vaccination with an adenoviral vector-based COVID-19 vaccine.

The posology used in the paediatric population in study COV2001 was 2.5×10^{10} vp dose.

2.3. Clinical aspects

The MAH submitted in this procedure the final clinical study report (CSR) for study COV2001 and a short critical expert overview.

VAC31518COV2001 was a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older, and in healthy adolescents aged 12 to 17 years inclusive. Methods and results for the sub-populations of adult participants of COV2001 have already been assessed in other procedures (EMEA/H/C/005737/0000, EMEA/H/C/005737/II/0033 and EMEA/H/C/005737/II/0053).

2.3.1. Clinical study – COV2001

Methods – analysis of data submitted

Study detailed title: *"A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels and Vaccination Intervals of Ad26.COV2.S in Healthy Adults Aged 18 to 55 Years*

Inclusive and Adults Aged 65 Years and Older and to Evaluate 2 Dose Levels of Ad26.COV2.S in Healthy Adolescents Aged 12 to 17 Years Inclusive".

Study number: VAC31518COV2001, EudraCT 2020-002584-63, NCT04535453

Sponsors: COV2001 was conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V.) in collaboration with the United States (US) Government and the COVID-19 Response Team (formerly Operation Warp Speed [OWS]), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health, and the COVID-19 Prevention Trials Network.

Study period:

Adolescents: 3 March 2021 (Date first participant signed informed consent) to 9 March 2022 (Date of last contact of the last participant in the study)

ICH GCP:

The MAH states that COV2001 was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Study design and protocol amendments:

COV2001 was a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older, and in healthy adolescents aged 12 to 17 years inclusive.

The study was conducted in Germany (3 sites), Spain (3 sites), The Netherlands (3 sites), and United Kingdom (4 sites).

Concerning the adolescent population (12 to 17 years of age, inclusive), the aim of COV2001 was to evaluate the safety, reactogenicity and immunogenicity of Ad26.COV2.S in a 1- and 2-dose vaccination regimen (2.5×10^{10} vp and 5×10^{10} vp dose levels, 56-day interval) followed by a booster vaccination 12 months after the first vaccination.

The initial planned total sample size was approximately 660 adolescent participants to be enrolled in a randomized and staggered manner. Randomization was to be stratified by study site and age group, with half of the participants 12 to 15 years, inclusive, and half of the participants 16 to 17 years, inclusive.

The sample size for the adolescent participants was originally calculated based on assessment of non-inferiority (NI) of immune responses as compared to adults. More specifically, demonstrating NI of immune responses induced by the 1-dose or 2-dose vaccination regimen schedule of Ad26.COV2.S (at $2.5x10^{10}$ vp or $5x10^{10}$ vp) in adolescents as compared to 1 dose or 2 doses of Ad26.COV2.S $5x10^{10}$ vp in adults were among the objectives of COV2001.

The safety profile of the Ad26.COV2.S vaccine doses (2.5×10^{10} vp and 5×10^{10} vp dose levels) in adolescents was planned to be assessed separately by age group and by escalating dose, with the 2 adolescent age groups (12 to 15 years and 16 to 17 years) assessed independently and enrolment progressing in a sequential manner. The safety and tolerability of the Ad26.COV2.S vaccine was assessed in the first instance in a group of sentinels at Day 4 post-vaccination, and subsequently, in the larger safety cohort at Day 8 post-vaccination. The Day 4 and Day 8 post-vaccination safety profiles of the Ad26.COV2.S vaccine at the 2.5×10^{10} vp dose level in the sentinel and safety cohorts were to be assessed in participants at 16 to 17 years of age, by the Safety Monitoring Committee (SMC) before progressing to enrolment of the sentinel group of participants at 12 to 15 years of age.

When reactogenicity data after the first vaccination of the initial 33 adolescent participants (sentinels as part of the safety cohort) in the 16- to 17-year-old age group at a dose level of 2.5×10^{10} vp was evaluated, it was concluded that reactogenicity was higher in adolescents than in adults vaccinated with Ad26.COV2.S at the 5×10^{10} vp dose level but considered acceptable by the Independent Data Monitoring Committee (IDMC) (4 April 2021) and MHRA (7 April 2021). Shortly thereafter, the entire Ad26.COV2.S COVID-19 vaccine program was paused to evaluate a safety concern of thrombosis with thrombocytopenia syndrome (TTS) in adults. During this pause, the immunogenicity data for these 33 adolescent participants was evaluated.

Immunogenicity in adolescent population with 2.5×10^{10} vp dose was higher than in adults vaccinated with Ad26.COV2.S at the 5×10^{10} vp dose level. Based on the reactogenicity and immunogenicity data from the 2.5×10^{10} vp dose in the adolescent participants, the MAH (sponsor of COV2001) decided to not evaluate the 5×10^{10} vp dose level in the adolescent population. The MAH also decided to stop enrolment and vaccination of adolescents and to stop to further evaluate vaccination of the paediatric population in a separate dose-finding study (Protocol Amendment 6).

The 33 adolescents already enrolled at the time of protocol Amendment 6 continued to be followed in accordance with the planned schedule of activities, but further enrolment of adolescent participants was stopped.

Hence for this procedure, data related to the safety, reactogenicity, and immunogenicity of a single dose of 2.5×10^{10} vp of Ad26.COV2.S in the adolescent population 16- to 17-year-old were submitted.

Objectives:

Note that due to the recruitment stop for the adolescent population (protocol Amendment 6), only the modified objectives and endpoints as presented in protocol Amendment 6 were specified by the MAH for this procedure and they are listed below.

The primary objective for the adolescent participants in this study was:

- To assess the safety and reactogenicity of a single dose of Ad26.COV2.S, administered IM at the 2.5×10^{10} dose level.

The secondary objectives for the adolescent participants in this study were:

- To assess the humoral immune response to a single dose of Ad26.COV2.S at the 2.5×10^{10} vp dose level, 28 days after vaccination.
- To assess the humoral immune response to Ad26.COV2.S at the 2.5×10^{10} vp dose level, at all blood collection timepoints.

Data analysed:

The submitted final analysis CSR includes results from the final analysis for the adult and adolescent participants, when all included participants had completed the last visit, or discontinued earlier.

More specifically for adolescent participants, the submitted final CSR includes

- Safety and reactogenicity data for the adolescent participants, which included data collected up to the end of study: solicited AEs through 7 days post-dose 1; unsolicited AEs through 28 days post-dose 1; deaths, SAEs, AEs leading to vaccine discontinuation, suspected AESIs throughout the study.
- Available immunogenicity data (wtVNA, psVNA, S-ELISA) for the adolescent participants collected up to the end of study: neutralizing antibody responses (wtVNA, psVNA) and binding antibody responses (S-ELISA) up to Day 169. Note that the Day 337 time point is not included

in the tables and graphs because all participants were positive for N-serology or were excluded from the Per Protocol Immunogenicity (PPI) population due to major protocol deviations at Day 337 as evidenced in the Full Analysis Set (FAS) dataset.

- Available SARS-CoV-2 infection data (PCR test, N-ELISA) for the adolescent participants collected up to the end of study: PCR tests were performed on nasal swabs collected by or from participants with COVID-19-like symptoms and N-ELISA was performed at Days 1, 169, and 337.

Criteria for safety evaluation:

Adverse events and special reporting situations, whether serious or non-serious, related to study procedures or non-investigational sponsor products were reported for all participants from the time a signed and dated Informed Consent Form (ICF) was obtained until the end of the study/early withdrawal.

There was a 1-hour on-site post-vaccination assessment for the presence of any acute reactions and solicited events (listed below). On a daily basis, for 8 days post vaccination (i.e. day of vaccination and the subsequent 7 days), participants were asked to record symptoms of the following adverse events (AEs) in a diary:

- Solicited local AEs: injection site pain/tenderness, erythema (measured using the ruler supplied), and swelling, (measured using the ruler supplied).
- Solicited systemic AEs: fatigue, headache, nausea, myalgia, and pyrexia/fever.
- Body temperature was to be measured at approximately the same time each day using the thermometer supplied.

Unsolicited AEs were recorded from the time of each vaccination until 28 days post vaccination and were captured on the Adverse Event pages of the electronic case report form (eCRF). Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination) which were ongoing on the day of the subsequent vaccination were recorded as such.

All SAEs and AEs leading to discontinuation from the study/vaccination were recorded for all participants from the moment of first vaccination until completion of the participant's last study-related procedure. Any respiratory tract infection fulfilling the criteria of an SAE were reported as such during the entire study. If the molecular test was positive for SARS-CoV-2, the SAE was excluded from the SAE analysis in the clinical study report and was tabulated separately.

All AEs were to be followed until resolution or until clinically stable. The outcome of AEs at the end of study is provided in participant listings submitted in this procedure.

In the event of a serious or unexpected adverse event, the medical monitor was notified. Suspected unexpected associated serious adverse reactions (SUSARs) were immediately reported to the Independent Ethics Committee (IEC) by the investigator, and to the appropriate health authorities by the sponsor.

Adverse events were graded for severity using a modified version of the Food & Drug Administration (FDA) grading table, based on version of September 2007. Adverse events not identified in the grading table were graded as described in the protocol.

From the time of local approval of protocol Amendment 5 onwards, TTS was considered to be an Adverse Events of Special Interest (AESI). Suspected AESIs (thrombotic events and thrombocytopenia [defined as platelet count below 150,000/µL]) were recorded from the moment of vaccination until the

end of the study/early withdrawal. An AESI Adjudication Committee with appropriate expertise was established to evaluate each suspected AESI and determine whether it was a case of TTS.

Testing for anti-platelet factor 4 antibodies was added as an exploratory endpoint to fully evaluate coagulation parameters in adult (Protocol Amendment 5) and adolescent (Protocol Amendment 6) participants. The results of activation of coagulation and APS assessments were presented in a separate Hematology Laboratory Results report as an addendum to the primary analysis CSR. Additional results from this analysis will be reported separately as available.

Immunogenicity evaluation:

Planned humoral immunogenicity assays included:

- SARS-CoV-2 neutralization antibodies to the reference strain by using:
    - Wild-type Virus neutralisation assay (WT-VNA) (Victoria/1/2020 strain) of Public Health England (PHE): Qualified assay
    - Pseudovirion VNA (psVNA) (B.1 D614G) of Monogram: Validated assay
- Binding antibodies against the SARS-CoV-2 Spike protein by using the validated S-ELISA assay of Nexelis.
- Binding antibodies against the SARS-CoV-2 Nucleocapsid protein to detect previous infection with SARS-CoV-2 by using the validated N-ELISA of Nexelis.

Humoral immunogenicity assays have already been assessed in previous procedures (EMEA/H/C/005737/0000, EMEA/H/C/005737/II/0033 and EMEA/H/C/005737/II/0053).

At time of analysis of the COV2001 adolescent samples with the WT-VNA, this assay was qualified. However, the validation report of the WT-VNA was assessed in procedure EMEA/H/C/005737/II/0053. It was concluded that the conclusions obtained from previous wtVNA assessments in VAC31518COV1001, VAC31518COV1002 and VAC31518COV2001 are not impacted by the wtVNA validation and change in LLOQ (refer to EMEA/H/C/005737/II/0033).

Due to poor correlation of the psVNA with the wtVNA and lack of sensitivity of the psVNA, the MAH considered the wtVNA as the main assay to measure virus neutralisation, which is supported.

Statistical methods:

Sample size for the adolescent participants was originally calculated based on assessment of non-inferiority of immune responses as compared to adults. However, in view of reactogenicity and immunogenicity data after the first vaccination of the initial 33 adolescent participants (sentinels as part of the safety cohort) in the 16- to 17-year-old age group at a dose level of 2.5×10^{10} vp, the sponsor decided to stop further enrolment.

Analysis Sets:

For purposes of analysis, the following populations were defined:

- The Full Analysis Set (FAS) included all participants with at least one vaccine administration documented.
- The Per Protocol Immunogenicity (PPI) population included all randomized and vaccinated participants for whom immunogenicity data were available. Samples taken after a participant met the criteria for a major protocol deviation expected to impact the immunogenicity

outcomes were excluded from the PPI analysis. In addition, samples obtained after missed vaccinations or participants with natural SARS-CoV-2 infection occurring after screening (if applicable) were excluded from the analysis. SARS-CoV-2 infection was defined as a positive PCR test or positive N-serology.

Safety:

No formal statistical testing of safety data was planned. Safety data (summaries of AEs, hematology results, vital sign measurements, physical examinations, and pregnancy testing) were analyzed descriptively by vaccine group. All safety analyses were done on the FAS.

Immunogenicity:

Descriptive statistics (geometric mean and confidence intervals [CIs], or median and interquartile range Q1-Q3, as appropriate) were calculated for continuous immunologic parameters. Several definitions of serological response were applied (fold increases in GMT [VNA] or GMC [ELISA]). Graphical representations of immunologic parameters were made as applicable. Frequency tabulations were calculated for discrete (qualitative) immunologic parameters, as applicable.

For the wtVNA assay, a participant was considered a responder if at least one of the following conditions was met:

- The baseline sample value was less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample was greater than the LLOQ (>LLOQ).
- The baseline sample value was greater than the LLOQ (>LLOQ) and the post-baseline sample value represented an at least 4-fold (≥4-fold) increase from the baseline sample value.

Results

Participant flow, Recruitment and Baseline data

Of the 44 participants screened in the adolescent cohort, 33 were randomized, received 1 dose of the study vaccine, and were included in the FAS (2.5×10^{10} group [N=30] and PL group [N=3]). None of the participants discontinued study vaccination.

Within this adolescent group there were more female participants (66.7%) than male participants. The majority were white (97%) and BMI ranged from 17.0 to 28.2 kg/m2.

Number analysed

Per Protocol Immunogenicity (PPI) set analysis.

SARS-CoV-2 serostatus at baseline was determined by Day 1 S- or N-serology assessed by ELISA, or screening PCR test, with a subject being declared seropositive if one of these tests was positive. 3 participants were positive using these 3 assays and were removed from the per protocol immunogenicity (PPI) set analysis.

Clinical immunogenicity

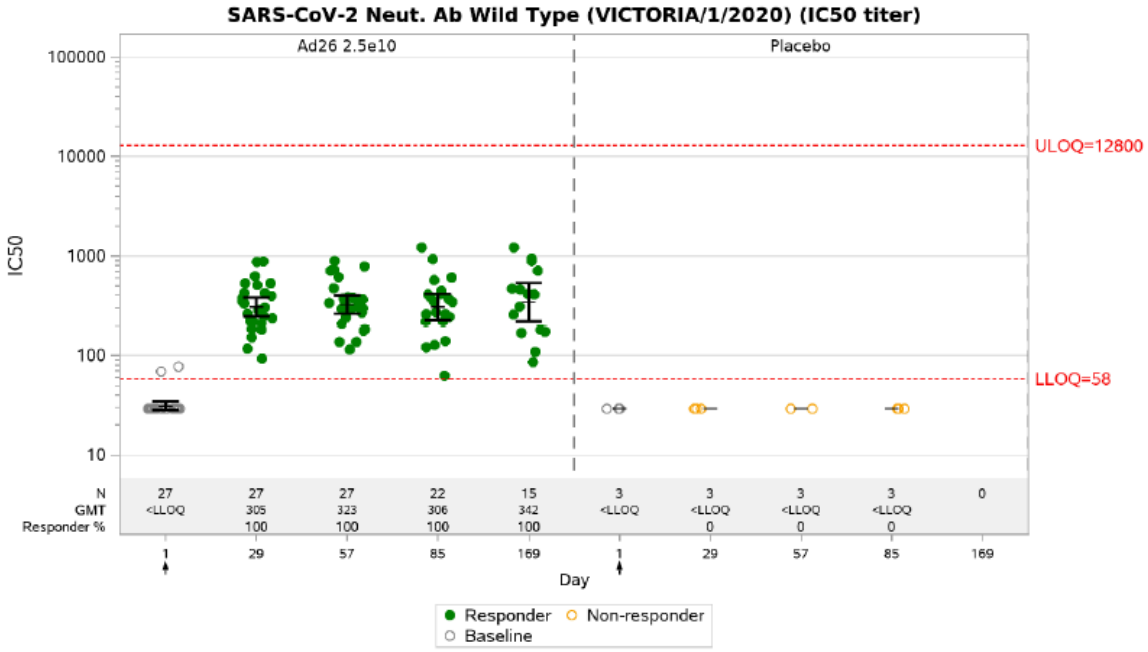
The MAH submitted humoral immunogenicity (neutralizing and binding antibody) results up to Day 169. The MAH specifies that the Day 337 time point was not included in the tables and graphs because all participants were positive for N-serology or were excluded from the PPI population due to major protocol deviations at Day 337.

The data of the immunogenicity analyses performed in adolescents (16 to 17 yoa) at all time points measured (Day 29, 57, 85, and 169) collectively indicate that administration of a single dose of $2.5x10^{10}$ vp of Ad26.COV2.S elicits specific neutralising and binding humoral responses up to 6 months, which is the last timepoint measured in adolescent participants.

Based on the data obtained using wtVNA, an increase in neutralizing antibody levels was observed from baseline up to 6 months post vaccination in Ad26.COV2.S immunised adolescents (responder rate of 100%), while no increase in neutralizing antibody response was observed in the placebo group (N=3). IC50 geometric mean titers of 305, 323, 306 and 342 were respectively measured on Days 29, 57, 85 and 169 (Figure 1). Detectable baseline levels of SARS-COV-2 IC50 were detected in 2/27 adolescent participants who received the single dose of Ad26.COV2.S, potentially indicative of exposure to SARS-COV-2 prior to enrolment. Both participants were responders at all timepoints measured.

Based on the data obtained using the psVNA assay, an increase in neutralizing antibody levels was observed from baseline up to 6 months post vaccination in adolescents participants who received Ad26.COV2.S ($2.5x10^{10}$ vp). No increase in (psVNA) neutralizing antibody response was observed in the placebo groups. On Days 29, 57, 85 and 169, GMTs of 103, 146, 186 and 168, respectively, were observed. Responder rates based on psVNA data were respectively of 59%, 78%, 82% and 80% on Days 29, 57, 85 and 169.

Figure 1 SARS-CoV-2 Neutralization Wild-type VNA - VICTORIA/1/2020 (IC50): Plot of the Actual Values Over Time; Adolescent Subjects, 16-17 years old; Per Protocol Immunogenicity Set (Study VAC31518COV2001)



Mod5.3.1.1/VAC31518COV2001/Final Analysis CSR/Fig26
Note: Geometric mean titers with 95% CI shown in the figure.
Note: Ad26 2.5e10: Ad26.COV2.S 2.5x10 [10] vp.
The status of wtVNA assay is qualified. The assay range may change as the assay becomes validated.
The Day 337 timepoint is not included in this graph because all participants were positive for N-serology or were excluded from the PPI population due to major protocol deviations at D337 as evidenced in the FAS dataset.
CI: confidence interval, FAS: Full Analysis Set, LLOQ: lower limit of quantification, vp: virus particle, ULOQ: Upper limit of quantification, wtVNA: wild-type virus neutralization assay

Binding antibody responses specific to the SARS-CoV-2 S antigen were also measured by ELISA (Table 1). Data obtained from the 27 adolescent participants who received Ad26.COV2.S ($2.5x10^{10}$ vp) showed an increase in binding antibody concentrations 28 days post Ad26.COV2.S vaccination, representing an increase in GMI from baseline of approximately 13-fold. On Days 29, 57, 85 and 169, geometric mean concentrations (GMCs) of 682, 770, 773 and 796 were respectively observed with overlapping 95% CI. The responder rate was of 100%. No increase in binding antibody response was observed in the placebo groups.

Table 1 SARS-CoV-2 S Binding Antibodies (ELISA Unit [EU]/mL): Descriptive Statistics; Adolescent Subjects, 16-17 Years Old; Per Protocol Immunogenicity Set (Study VAC31518COV2001)

	Ad26 2.5e10	Placebo
Analysis set: Per Protocol Immuno Population	27	3
Baseline		
N	26	3
Geometric mean (95% CI)	< LLOQ	< LLOQ
Positive sample n (%) (95% CI)	0	0
Day 29		
N	27	3
Geometric mean (95% CI)	682 (506; 920)	< LLOQ
Positive sample n (%) (95% CI)	27 (100.0%) (87.2; 100.0)	0 (0.0; 70.8)
Geometric mean increase (95% CI) from Baseline	13.4 (9.8; 18.3)	1.0
Responders n/N* (%) (95% CI)	26/26 (100.0%) (86.8; 100.0)	0/3 (0.0; 70.8)
Day 57		
N	27	3
Geometric mean (95% CI)	770 (593; 1000)	< LLOQ
Positive sample n (%) (95% CI)	27 (100.0%) (87.2; 100.0)	0 (0.0; 70.8)
Geometric mean increase (95% CI) from Baseline	15.4 (11.8; 20.3)	1.0
Responders n/N* (%) (95% CI)	26/26 (100.0%) (86.8; 100.0)	0/3 (0.0; 70.8)
Day 85		
N	22	3
Geometric mean (95% CI)	773 (547; 1093)	< LLOQ
Positive sample n (%) (95% CI)	22 (100.0%) (84.6; 100.0)	0 (0.0; 70.8)
Geometric mean increase (95% CI) from Baseline	15.4 (10.9; 21.7)	1.0
Responders n/N* (%) (95% CI)	22/22 (100.0%) (84.6; 100.0)	0/3 (0.0; 70.8)
Day 169		
N	15	0
Geometric mean (95% CI)	796 (449; 1411)	-
Positive sample n (%) (95% CI)	15 (100.0%) (78.2; 100.0)	-
Geometric mean increase (95% CI) from Baseline	15.8 (8.9; 28.0)	-
Responders n/N* (%) (95% CI)	15/15 (100.0%) (78.2; 100.0)	-

Key: CI = confidence interval.
N = number of subjects with data.
N* = number of subjects with data at baseline and at that time point.
Exact Clopper-Pearson 95% confidence intervals are shown for Positive sample and Responders.
Positive sample refers to a quantifiable response (sample interpretation).
Note: Ad26 2.5e10: Ad26.COV2.S 2.5x10 [10] vp.
The assay status is validated.
The Day 337 time point is not included in this table because all participants were positive for N-serology or were excluded from the PPI population due to major protocol deviations at D337 as evidenced in the FAS dataset.

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The MAH's conclusion that administration of a single dose of $2.5x10^{10}$ vp of Ad26.COV2.S to adolescents 16 to 17 yoa elicits specific neutralising and binding humoral responses up to 6 months is endorsed.

The MAH also performed analyses comparing humoral immunogenicity results from adolescents (16 to 17 yoa) of COV2001 and young adults (18 to 25 years of age) in other studies. At all timepoints compared (Day 29, 57, 85 and 169), SARS-CoV-2 neutralizing and Spike-specific binding antibody

responses in adolescents aged 16 to 17 years after a single dose of Ad26.COV2.S at 2.5×1010 vp were similar to those in young adults aged 18 to 25 years after a single dose of Ad26.COV2.S at 5×1010 vp. As specified by the MAH, the small sample size for adolescents and young adults prevents robust conclusions from being drawn. This is endorsed and comparative analyses were therefore not detailed in this assessment report.

Concerning the data obtained with the wtVNA as compared to the psVNA, the results question the correlation of the results between both methods and the lower sensitivity of the psVNA as previously mentioned in other procedures (EMEA/H/C/005737/II/33 and EMEA/H/C/005737/II/53). This is exemplified in this procedure by the differences in percentages of responder rates estimated by wtVNA (100% at all time-points tested) as compared to psVNA (ranging from 59%, 78%, 82% and 80%).

Efficacy results

Efficacy was not assessed in study COV2001.

Safety results

Safety data for the small set of 33 adolescents aged 16 to 17 years inclusive were submitted.

More specifically, the MAH submitted:

- solicited local and systemic AEs reported during the 7-day post-vaccination phase (Table 2),
- unsolicited AEs reported during the 28-day post-vaccination phase (unrelated and related events) and during the follow-up phase (>28 days post vaccination) (related events only) (Table 5).

Deaths, SAEs, and AESIs (i.e., TTS), as well as AEs leading to permanent discontinuation of vaccination, reported during the study were also discussed by the MAH. There were no SAEs, deaths, or unsolicited AEs leading to vaccine discontinuation reported in the adolescent participants (Table 5). There were no suspected AESIs reported in adolescents.

Solicited Local and Systemic Adverse Events

The majority of solicited AEs were of Grade 1 or 2 severity. Solicited AEs of Grade 3 or higher were recorded for 9 (30.0%) participants in the active vaccine group (N=30) and none in the placebo group (N=3).

Table 2 Overall Summary of Solicited Adverse Events; Adolescent Subjects, 16-17 years old; Full Analysis Set (Study VAC31518COV2001)

	Ad26 2.5e10	Placebo
Analysis set: Full	30	3
Post-Dose 1	30	3
Subjects with 1 or more:		
Solicited AE	30 (100.0%)	3 (100.0%)
Solicited AE of worst grade 3 or higher	9 (30.0%)	0
Solicited local AE	29 (96.7%)	1 (33.3%)
Solicited local AE of worst grade 3 or higher	3 (10.0%)	0
Solicited systemic AE	28 (93.3%)	3 (100.0%)
Solicited systemic AE of worst grade 3 or higher	7 (23.3%)	0
Solicited systemic AEs considered to be related to study vaccine[a]	28 (93.3%)	3 (100.0%)
Solicited systemic AEs of grade 3 or higher considered to be related to study vaccine[a]	7 (23.3%)	0

Mod5.3.1.1/VAC31518COV2001/Final Analysis CSR/Tab27
Note: Ad26 2.5e10: Ad26.COV2.S $2.5x10^{10}$ vp.
Key: AE = adverse event
[a] Relationship to vaccine is assessed by the investigator.
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period.

The majority of solicited local AEs were of Grade 1 or 2 severity. The most common solicited local AEs was vaccination site pain, reported in 29 (96.7%) participants in the active vaccine group and 1 (33.3%) participant in the placebo group (Table 3). Solicited local AEs of Grade 3 severity (vaccination site pain) were reported by 3 (10.0%) participants in the active vaccine group and none in the placebo group. No solicited local AE of Grade 4 severity was reported. All solicited local AEs were considered related to the study vaccine by protocol definition.

Table 3: Number of Subjects with Local Solicited Adverse Events by Derived Term and Worst Severity Grade; Adolescent Subjects, 16-17 Years Old; Full Analysis Set (Study VAC31518COV2001)

	Ad26 2.5e10	Placebo
Analysis set: Full	30	3
Post-Dose 1	30	3
Subjects with 1 or more AE		
Any	29 (96.7%)	1 (33.3%)
Grade 1	21 (70.0%)	1 (33.3%)
Grade 2	5 (16.7%)	0
Grade 3	3 (10.0%)	0
Vaccination site erythema		
Any	0	0
Vaccination site pain		
Any	29 (96.7%)	1 (33.3%)
Grade 1	21 (70.0%)	1 (33.3%)
Grade 2	5 (16.7%)	0
Grade 3	3 (10.0%)	0
Vaccination site swelling		
Any	2 (6.7%)	0
Grade 1	2 (6.7%)	0

Note: Ad26 2.5e10: Ad26.COV2.S $2.5x10^{10}$ vp.
Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The event experienced by the subject with the worst toxicity grade is used. If a subject has missing toxicity grade for a specific adverse event, the subject is counted in the 'Any' row for that adverse event.

[tsfaesolloc02adst.rtf] [vac31518/vac31518cov2001/dbr_adult_final/re_csr/tsfaesolloc02adst.sas] 25APR2022, 23:04

The majority of solicited systemic AEs were of Grade 1 or 2 severity. All solicited systemic events were considered to be related to study vaccine: 28 (93.3%) participants in the active vaccine group and 3 (100%) in the placebo group. The most common solicited systemic AEs were headache, fatigue and myalgia, reported in 25 (83.3%), 21 (70.0%) and 16 (53.3%) participants in the active vaccine group, respectively (Table 4). In the placebo groups, headache, fatigue and myalgia, were reported in 3 (100.0%), 1 (33.3) and 1 (33.3%) participants, respectively. All solicited systemic AEs of Grade 3 were considered related to vaccination: 7 (23.3%) participants in the active vaccine group and none was recorded for participants in the placebo group. Four of these 7 participants experienced more than 1 Grade 3 solicited systemic AE. No solicited systemic AEs of Grade 4 severity were reported.

Table 4: Number of Subjects With Systemic Solicited Adverse Events by Derived Term and Worst Severity Grade; Adolescent Subjects, 16-17 Years Old; Full Analysis Set (Study VAC31518COV2001)

	Ad26 2.5e10	Placebo
Analysis set: Full	30	3
Post-Dose 1	30	3
Subjects with 1 or more AE		
Any	28 (93.3%)	3 (100.0%)
Grade 1	6 (20.0%)	3 (100.0%)
Grade 2	15 (50.0%)	0
Grade 3	7 (23.3%)	0
Fatigue		
Any	21 (70.0%)	3 (100.0%)
Grade 1	8 (26.7%)	3 (100.0%)
Grade 2	10 (33.3%)	0
Grade 3	3 (10.0%)	0
Headache		
Any	25 (83.3%)	1 (33.3%)
Grade 1	7 (23.3%)	1 (33.3%)
Grade 2	11 (36.7%)	0
Grade 3	7 (23.3%)	0
Myalgia		
Any	16 (53.3%)	1 (33.3%)
Grade 1	7 (23.3%)	1 (33.3%)
Grade 2	7 (23.3%)	0
Grade 3	2 (6.7%)	0
Nausea		
Any	8 (26.7%)	0
Grade 1	4 (13.3%)	0
Grade 2	3 (10.0%)	0
Grade 3	1 (3.3%)	0
Pyrexia		
Any	5 (16.7%)	0
Grade 1	4 (13.3%)	0
Grade 2	1 (3.3%)	0

Note: Ad26 2.5e10: Ad26.COV2.S 2.5x10 ^{10} vp.
Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The event experienced by the subject with the worst toxicity grade is used. If a subject has missing toxicity grade for a specific adverse event, the subject is counted in the 'Any' row for that adverse event.
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Unsolicited Adverse Events

Unsolicited AEs were reported in 12/30 (40.0%) adolescent participants in the active vaccine group and 2/3 (66.7%) in the placebo group. The majority of unsolicited AEs in adolescents were Grade 1 or 2 in severity. The most common unsolicited AE was chills, reported in 3 (10.0%) participants in the active vaccine group. One (3.3%) adolescent participant in the active vaccine group experienced an unsolicited AE of Grade 3 or higher that was considered related to vaccination (chills) (versus none in the placebo group).

Table 5: Overall Summary of Unsolicited and Serious Adverse Events; Adolescent Subjects, 16-17 years old; Full Analysis Set (COV2001)

	Ad26 2.5e10	Placebo
Analysis set: Full	30	3
Entire Study	30	3
Subjects with 1 or more:		
SAE	0	0
SAE considered to be related to study vaccine[a]	0	0
AE with fatal outcome	0	0
Post-Dose 1	30	3
Subjects with 1 or more:		
Unsolicited AE	12 (40.0%)	2 (66.7%)
Unsolicited AE with worst grade of 1	9 (30.0%)	1 (33.3%)
Unsolicited AE with worst grade of 2	2 (6.7%)	1 (33.3%)
Unsolicited AE with worst grade of 3 or higher	1 (3.3%)	0
Unsolicited AE considered related to study vaccine[a]	3 (10.0%)	1 (33.3%)
Unsolicited AE with worst grade of 3 or higher considered related to study vaccine[a]	1 (3.3%)	0
AE leading to permanent stop of vaccination	0	0
SAE	0	0
SAE considered to be related to study vaccine[a]	0	0
AE with fatal outcome	0	0

Mod5.3.1.1/VAC31518COV2001/Final Analysis CSR/Tab28
Key: AE = adverse event, SAE = serious adverse event
[a] Relationship to vaccine is assessed by the investigator.
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period.
Note: Ad26 2.5e10: Ad26.COV2.S $2.5x10^{10}$ vp.

Table 6: Number of Subjects with Unsolicited Adverse Events by System Organ Class and Preferred Term; Adolescent Subjects, 16-17 Years Old; Full Analysis Set (Study VAC31518COV2001)

	Ad26.2.5e10	Placebo
Analysis set: Full	30	3
Post-Dose 1	30	3
Subjects with 1 or more AEs	12 (40.0%)	2 (66.7%)
General disorders and administration site conditions	3 (10.0%)	1 (33.3%)
Chills	3 (10.0%)	0
Fatigue	0	1 (33.3%)
Vaccination site pain	1 (3.3%)	0
Nervous system disorders	3 (10.0%)	0
Dizziness	1 (3.3%)	0
Presyncope	1 (3.3%)	0
Syncope	1 (3.3%)	0
Eye disorders	1 (3.3%)	1 (33.3%)
Episcleritis	1 (3.3%)	0
Eye pain	0	1 (33.3%)
Gastrointestinal disorders	1 (3.3%)	1 (33.3%)
Abdominal pain	0	1 (33.3%)
Toothache	1 (3.3%)	0
Infections and infestations	2 (6.7%)	0
Tonsillitis	1 (3.3%)	0
Upper respiratory tract infection bacterial	1 (3.3%)	0
Injury, poisoning and procedural complications	2 (6.7%)	0
Chemical burn	1 (3.3%)	0
Joint injury	1 (3.3%)	0
Reproductive system and breast disorders	1 (3.3%)	1 (33.3%)
Dysmenorrhoea	1 (3.3%)	0
Premenstrual pain	0	1 (33.3%)
Musculoskeletal and connective tissue disorders	1 (3.3%)	0
Arthralgia	1 (3.3%)	0

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period.
Note: Adverse events are coded using MedDRA Version 24.1
Note: Ad26.2.5e10: Ad26.COV2.S 2.5x10 ^{10} vp.

Adapted from: [tsfaeunsol02adst.rtf] [vac31518/vac31518cov2001/dbr_adult_final/re_csr/tsfaeunsol02adst.sas] 25APR2022, 23:04

The MAH has mentioned that, in the active vaccine group, 1 participant had Grade 1 COVID-19 infection which started at Day 111 during the post-dose 1 follow-up period and lasted for 21 days, and 1 participant had Grade 1 COVID-19 infection which started at Day 114 during the post-dose 1 follow-up period and lasted for 15 days. There were no cases in the placebo group. However, that MAH has not clarified which AEs were related to COVID-19. This issue is not further pursued.

Other Safety Observations

The most frequent vital sign abnormalities in adolescent participants were increased respiratory rate and increased pulse rate. All reported abnormalities were Grade 1 or 2 in severity, except for 1 participant in the active vaccine group who had a Grade 3 respiratory rate (post-dose 1 follow-up), which was not considered as AE by the investigator.

There were no cases of Grade 3 pyrexia reported in adolescent participants.

No clinically relevant changes from baseline were identified for any of the laboratory parameters examined in the study.

2.3.2. Discussion on clinical aspects

The clinical results submitted by the MAH for this P46 procedure are limited. These results belong to a single phase 2 trial (COV2001) that was originally designed as a randomized, double-blind, placebo-controlled, multicenter, Phase 2a study in healthy adults aged 18 to 55 years inclusive, adults in good or stable health aged 65 years and older, and in healthy adolescents aged 12 to 17 years inclusive. The aim was to evaluate safety and immunogenicity of a range of dose levels and vaccination intervals of Ad26.COV2.S.

Concerning the adolescent population (12 to 17 years of age, inclusive), the initial planned total sample size was approximately 660 adolescent participants to be enrolled in a randomized and staggered manner to receive placebo or intramuscular JCOVDEN at the $2.5x10^{10}$ or $5x10^{10}$ vp dose level, as a 1-dose or a 2-dose vaccination regimen schedule followed by a booster vaccination 12 months after the first vaccination. Randomization was to be stratified by study site and age group, with half of the participants 12 to 15 years, inclusive, and half of the participants 16 to 17 years, inclusive.

Sample size for the adolescent participants was originally calculated based on assessment of non-inferiority of immune responses as compared to adults. More specifically, demonstrating NI of immune responses induced by the 1-dose or 2-dose vaccination regimen schedule of Ad26.COV2.S (at $2.5x10^{10}$ vp or $5x10^{10}$ vp) in adolescents as compared to 1 dose or 2 doses of Ad26.COV2.S $5x10^{10}$ vp in adults was among the objectives of COV2001.

Only a very limited number of adolescent participants aged 16 to 17 years inclusive were randomized (N=33) to COV2001 and received a single dose of the study vaccine (2.5×10^{10} vp, N=30) or placebo (N=3).

This limited number of paediatric study participant is a consequence of changes in the paediatric development plan of JCOVDEN, as it was decided to stop the further clinical development supporting the paediatric indication.

Concerning the humoral immunogenicity results submitted, the conclusion that these indicate that administration of a single dose of $2.5x10^{10}$ vp of Ad26.COV2.S elicits specific neutralising and binding humoral responses up to 6 months is endorsed.

The MAH concluded that the reactogenicity in the 30 adolescents aged 16 to 17 years vaccinated with the 2.5×10^{10} vp dose was higher than in adults vaccinated with the 5×10^{10} vp dose. Solicited local and systemic AEs were more frequently reported in the adolescents in this study than in adults (Cf. approved Summary Product Characteristics (SmPC)): vaccination site pain (96.7% vs. 54.3%, respectively), headache (83.3% vs. 43%), fatigue (70% vs. 44%), myalgia (53.3% vs. 38.1%), and pyrexia (16.7% vs. 7.2%).

Moreover, the MAH states that "… *the results from the safety and reactogenicity analyses suggest that Ad26.COV2.S administered at 2.5×10^{10} vp dose level in adolescents aged 16 to 17 years had an acceptable safety and reactogenicity profile*".

However, no conclusion on the reactogenicity and safety of JCOVDEN in the tested adolescent population can be drawn with the limited available data.

Overall, submitted data are only descriptive and do not allow to draw robust conclusions on the reactogenicity, safety and immunogenicity of JCOVDEN in this paediatric (adolescent) population.

Of note, another phase 2 paediatric study (COV3006) is ongoing to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a one- or two-dose regimen in healthy adolescents from 12 to 17 years inclusive. Part 1 of this study (dose selection cohort) is ongoing but the Part 2 (expansion cohort) is not planned to be conducted any longer. No data are yet available.

The modification of the Paediatric Investigation Plan (PIP) (EMEA-002880-PIP01-20-M01) into a waiver for the entire paediatric population was recently agreed by the Paediatric Committee (PDCO) based on the grounds of lack of significant therapeutic benefit over existing vaccines. This was based on the consideration that it will be not feasible to clearly define/quantify the risk of thrombosis with thrombocytopenia syndrome in the paediatric population, the course of COVID-19 is generally mild in the paediatric population and other vaccines with a better-known safety profile are authorised in the paediatric population.

3. Overall conclusion and recommendation

Only limited reactogenicity, safety and immunogenicity data obtained in adolescents (16-17 yoa) after a single dose of $2.5x10^{10}$ vp JCOVDEN in study COV2001 were provided. Data are only descriptive, and no robust conclusions can be drawn. As it was decided to stop the further clinical development of JCOVDEN to support the paediatric indication, the post authorisation measure is considered fulfilled.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: JCOVDEN
Active substance: COVID-19 vaccine (Ad26.COV2-S [recombinant]), referred to as Ad26.COV2.S

Study title	Study number	Date of completion	Date of submission of final study report
A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive	VAC31518COV2001	23 August 2022	September 2022 (current submission)
A randomized, observer-blind, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of different dose levels of Ad26.COV2.S administered as a one- or two-dose regimen in healthy adolescents from 12 to 17 years inclusive	VAC31518COV3006	Ongoing	Planned