Date: 28 July 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

COVID-19 Vaccine Janssen

International non-proprietary name: Human adenovirus serotype 26* encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S).

The product contains genetically modified organisms (GMOs).

Pharmaceutical form: Suspension for injection

Dosage strength(s): One dose (0.5ml) contains not less than 8.92 log10 infectious units (Inf.U).

Route(s) of administration: Intramuscular injection

Marketing Authorisation Holder: Janssen-Cilag AG

Marketing Authorisation No.: 68235

Decision and Decision date: approved on 22.03.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

Ad26	adenovirus type 26
Ad26.COV2-S	adenovirus of the serotype 26, encoding the full-length severe acute respiratory syndrome coronavirus 2 spike protein
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AdVac	adenoviral vaccine
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CLS	Capillary leak syndrome
CMAs	critical material attributes
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	coronavirus disease-2019, caused by SARS-CoV-2
CPPs	Critical process parameters
CQAs	critical quality attributes
CRP	C - reactive protein
CYP	Cytochrome P450
DART	developmental and reproductive toxicology
DDI	Drug drug interaction
DNA	deoxyribonucleic acid
DP	Drug Product
DS	Drug Substance
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FIH	first-in-human
FP	Finished Product
FTP	Fast-track authorisation procedure
GLP	Good Laboratory Practice
GMC	geometric mean concentrations
GMO	genetically modified organism
GMT	geometric mean titer
HC	Health Canada
HCP	Host Cell Protein
HEK293 Cells	Human embryonic kidney 293 cells
HER	human embryonal retina
HIV	human immunodeficiency virus
HPLC	High performance liquid chromatography
HSA	Health Sciences Authority (Singapore)
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICU	intensive care unit

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Ig	Immunoglobulin
INN	International nonproprietary name
IPC	In-process controls
ITT	Intention-to-treat
LLOQ	lower limit of quantification
LoQ	List of Questions
LVHD	Large Volume High Density
MAAEs	medically-attended adverse events
MAH	Marketing Authorisation Holder
Max	Maximum
MCB	master cell bank
MHRA	Medicines & Healthcare products Regulatory Agency (UK)
Min	Minimum
MRHD	Maximum recommended human dose
MVS	Master Virus Seed
N/A	Not applicable
NAS	New Active Substance
NHP	non-human primates
NO(A)EL	No observed (adverse) effect level
PARs	Proven acceptable Ranges
PBPK	Physiology based pharmacokinetic
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PBMCs	peripheral blood mononuclear cells
PopPK	Population pharmacokinetic
PP	per protocol
PPQ	process performance qualification
PSP	Pediatric Study Plan (US-FDA)
RCA	replication competent adenovirus
RMP	Risk Management Plan
RNA	ribonucleic acid
RSV	respiratory syncytial virus
S	Spike
SAE	Serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration (Australia)
Th	T helper
Th(1/2)	T helper (cells) (type 1/type 2)
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UK	United Kingdom
US	United States
VAERD	vaccine-associated enhanced respiratory disease
VE	vaccine efficacy
vp	virus particles
WCB	working cell bank
WHO	World Health Organization
wtVNA	wild-type virus neutralization assay

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WVS	Working Virus Seed

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance "*Human adenovirus serotype 26* encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S)*" of the medicinal product mentioned above.

Temporary authorisation for human medicinal products
The applicant requested a marketing authorisation in accordance with Art. 9a, para. 1 TPA. However, based on the submitted clinical data material and the results of the evaluation, Swissmedic granted a temporary authorisation in accordance with Art. 9a TPA and with regard to the guidance document "Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4".

Authorisation for a COVID-19 medicinal product
Connected with the COVID-19 pandemic, the applicant requested a rolling submission procedure.

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2.2 Indication and Dosage

2.2.1 Requested Indication

COVID-19 Vaccine Janssen is indicated for active immunization for the prevention of coronavirus disease-2019 (COVID-19) in adults greater than or equal to 18 years of age.

The use of the vaccine should be in accordance with official recommendations.

2.2.2 Approved Indication

COVID-19 Vaccine Janssen is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The use of this vaccine should be in accordance with official vaccination recommendations.

COVID-19 Vaccine Janssen ist indiziert für die aktive Immunisierung von Personen im Alter von 18 Jahren und älter zur Prävention der durch das SARS-CoV-2 verursachten COVID-19-Erkrankung. Die Anwendung dieses Impfstoffs sollte in Übereinstimmung mit den offiziellen Impfempfehlungen erfolgen.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
COVID-19 Vaccine Janssen is administered as a single dose of 0.5 mL by intramuscular injection only

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	03.12.2020
Formal control completed	3 December 2020
List of Questions (LoQ)	Rolling Lists of Questions
Answers to LoQ	Rolling Answers to List of Questions
Predecision	19 March 2021
Answers to Predecision	22 March 2021
Labelling corrections	Not Applicable
Answers to Labelling corrections	Not Applicable
Final Decision	22.03.2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).
The following link provides the number of cases and deaths globally and per country: Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data
As of 22 March 2021, as Janssen COVID-19 Vaccine was under evaluation by Swissmedic, there had already been over 120,000,000 confirmed cases of SARS-CoV-2 infection globally with approximately 2.9 million deaths. By 1 June 2022, this number had increased to 527,211,631 confirmed cases of COVID-19 cumulatively worldwide, including 6,289,371 deaths reported by WHO.
While hospitalizations and deaths can occur in any age group, a majority occur in people aged 50 and over, with incidence increasing exponentially with age.
Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immunocompromised status, cancer and obesity are some of the risk factors for developing severe COVID-19.
People with COVID-19 have reported a wide range of symptoms, ranging from no, or mild, symptoms to severe illness and death. Symptoms may appear 2-14 days after exposure to the virus, and may include fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea. Severe COVID-19 can cause dyspnoea, pneumonia and ARDS (Acute Respiratory Distress Syndrome), thromboembolism and other conditions that may require ICU care. In addition to respiratory sequelae, severe COVID-19 has been linked to severe health problems such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute renal injury, neurological complications such as encephalopathy and acute ischaemic stroke. Severely infected persons may develop post-acute COVID-19 syndrome and may need months of rehabilitation. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

4 Quality Aspects

4.1 Drug Substance

The active substance of the Janssen COVID-19 vaccine is Ad26.COV2.S, a recombinant, replication-incompetent (E1 and E3 deleted) adenovirus of the serotype 26 (Ad26), encoding the full-length severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) spike (S) protein.
The wild-type full-length S gene information was obtained from a SARS-CoV-2 clinical isolate. The spike protein has been optimized by introducing two point mutations resulting in a stabilised protein.
The recombinant Ad26 vector, Ad26.COV2.S, is replication incompetent after administration due to deletions in the E1 gene (ΔE1A/E1B). The E1 deletion renders the vector replication-incompetent in noncomplementing cells such as human cells. In Ad5 E1 complementing cell lines (e.g., HEK293, PER.C6 TetR, and HER96 cells lines) the virus can be propagated.
In addition, a part of the E3 gene region has been removed (ΔE3) to create sufficient space in the viral genome for insertion of foreign antigens and the Ad26 E4 orf6 has been exchanged by the Ad5 homologue to allow production of replication-incompetent Ad26 vectors in Ad5 E1 complementing cell lines.
The PER.C6 TetR-cell line-is used for virus production. This cell line was derived from human embryonal retina (HER) cells.
The cell banking system is a 3-tiered PER.C6 TetR cell banking system, consisting of the MCB, the WCB and the LVHD cells.
Extensive testing at different levels has been performed which confirms that the PER.C6 TetR master cell bank (MCB) and working cell bank (WCB) have been properly qualified. Testing of cell banks for viral and non-viral adventitious agents and screening also for retroviruses has been sufficiently described and is acceptable. Tumorigenicity and oncogenicity studies have also been performed.
Additional characterisation testing also confirmed correct identity and genetic stability of the cell bank system. Information on storage and stability testing of cell banks is provided.

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Production of replication-incompetent Ad26.COV2.S virus by PER.C6 TetR cells transduced with linearised pAd.26.E1.CMVdel134-TO.COR200007 has been described. All virus seed material originates from the same MVS batch. Generation of the recombinant virus and production and testing of the MVS and WVS has been described in detail. The MVS and WVS were characterised for infectivity titre, genetic stability and stable expression of the transgene. Using appropriate sequencing methods, identical sequences of MVS, WVS and AS were demonstrated, thus confirming genetic stability. The correct expression of the transgene was also confirmed.
The active substance (AS) is manufactured in a 10-stages process. All steps of the AS manufacturing process are described in detail. The process starts with thawing of a vial of the cell substrate. Cells are expanded and then inoculated with the recombinant adenoviral construct, followed by further expansion in production bioreactors. After virus production the cells are lysed and virus is collected. Purification steps include a DNA precipitation step, a clarification, an anion exchange chromatography step and diafiltration.
Following the formulation of the DS, sterile filtration was carried out with subsequent filling into suitable primary containers and deep-frozen storage of the AS.
As regards the control strategy, the AS manufacturing process is controlled using process parameters and in-process controls (IPC). Critical process parameters (CPPs), proven acceptable ranges (PARs), critical quality attributes (CQAs), and critical material attributes (CMAs) have been assigned. They have been verified during AS process performance qualification (PPQ). The proposed operating ranges for the CPPs are acceptable.
The release and stability specifications for Ad26.COV2.S AS comprise appropriate physico-chemical tests and tests for identity, purity, potency, and safety.
The analytical methods used have been adequately described, non-compendial methods have been appropriately validated in accordance with ICH guidelines. Compendial methods were verified to be suitable for use with the current product and that no interference/inhibition occurs.
The active substance is stored below -40°C in polycarbonate bottles. The proposed shelf life is supported by long-term (below -40°C) and accelerated (2-8°C) stability data from other Ad26 viral vectors produced using the same platform technology and stored in the same polycarbonate containers. The AS is typically very stable when stored below -40°C; no trends have been observed so far.
Shipping systems are proposed and have been suitably validated for the transport of the inoculum and the AS.
As a post-approval commitment, additional stability data of Ad26.COV2.S have to be submitted.

4.2 Drug Product

COVID-19 Vaccine Janssen (Ad26.COV2.S FP) is supplied as a sterile colourless to slightly yellow, clear, liquid suspension for injection. The FP is intended for administration by the intramuscular route. Each dose of 0,5 ml contains not less than 8.92 Log10 Infectious Units (Inf.U) and not less than 2.5 x 10^{10} viral particles (VP). The target concentration is 5 x 10^{10} VP per dose.
Excipients of the FP are: 2-hydroxypropyl-β-cyclodextrin (HBCD), citric acid monohydrate, ethanol, hydrochloric acid, polysorbate-80, sodium chloride, sodium hydroxide, trisodium citrate dihydrate and water for injections.
The type of excipients and the quantitative composition of Ad26.COV2.S FP were selected based on early formulation development studies and on prior knowledge from formulation studies with similar adenoviral products.
All excipients comply with the European pharmacopoeia and no novel excipients are used in the finished product formulation
The manufacturing process for the finished product consists of thawing of the AS, pre-filtration, pooling, and dilution of the drug substance aliquots using a pre-filtered buffer solution. The formulated bulk is homogenized, sterile filtered in-line and aseptically filled into vials, stoppered and capped. Subsequently, the vials are visually inspected, frozen and shipped for labeling and packaging. The final FP is stored under frozen conditions at -20±5 °C.
Extensive description of the manufacturing process development and of process characterization studies was provided and critical process parameters (CPPs) and Proven Acceptable Ranges (PARs)

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were defined. Manufacturing history including process changes and transfer to commercial facilities was sufficiently described. Comparability of material for clinical supply with commercial batches has been demonstrated as based on the release testing and extended characterization studies.
The specification tests and acceptance criteria were provided and include relevant tests such as appearance, identity, purity, potency assay, subvisible particles, pH, osmolality, endotoxin, sterility, container closure integrity and extractable volume.
Analytical methods are described with sufficient details. Non-compendial methods have been validated in accordance with current ICH requirements. Compendial methods have been demonstrated to be suited for the current finished product.
The finished product is supplied in a glass vial (type I glass) with a rubber stopper (chlorobutyl with fluoropolymer coated surface), aluminium crimp and coloured flip-off plastic cap. Each vial contains a fill volume that allows extraction of 5 doses of 0,5 ml. 10 multi-dose vials of the vaccine are packed in one carton.
Materials of primary packaging comply with the Ph. Eur. requirements.
The proposed shelf life of the Ad26.COV2.S FP is 24 months when the FP is stored frozen at -20±5 °C, in original, unopened containers. Within these 24 months, a 3 months storage at 2-8°C is acceptable.
The chemico-physical stability of the FP for 6 hours at 2 – 25°C was also demonstrated by in-use stability studies.
The FP must be stored in the original packaging in order to minimise exposure to light.
The shelf life claim is based on a shelf-life model that uses prior AdVac/PER.C6 Platform knowledge. When sufficient real-time stability of the Ad26.COV2.S FP data are available, the shelf life claim will be reassessed.

GMO / environmental risk assessment

Ad26.COVS.2 active substance is a recombinant Adenovirus26 that has been rendered replication-incompetent by deletion of the E1 region of the wild type Ad26. Ad26.COVS.2 is produced in an E1 complementing cell line, without any DNA sequence overlap between the Ad26.COV.S vector and the cell line, thereby precluding the formation of replication competent adenovirus (RCA). RCA testing of drug substance DS was conducted for several small- and large-scale processes and the results complied with the acceptance criteria specifications.

4.3 Quality Conclusions

From the quality perspective the data presented in the application support the conclusion that the manufacture of Janssen Covid-19 vaccine (Ad26.COV2.S FP) is robust and sufficiently controlled to yield a finished product of consistent quality.
To increase production capacity, additional manufacturing sites for the active substance and the finished product are under evaluation and will be implemented, validation of the complex manufacturing processes is ongoing.
The manufacturing process of active substance and finished product incorporate adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination.
As a post-authorisation measure, acceptance criteria of the drug substance and the finished product have to be re-assessed and limits tightened as appropriate with increased manufacturing experience, at the latest when the temporary marketing authorization will be converted into a regular marketing authorization.

5 Nonclinical Aspects

Ad26.COV2.S1 is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector (Ad26) endoding the SARS-CoV-2 Spike (S) protein, stabilized in its prefusion conformation. The S protein was derived from a SARS-CoV-2 clinical isolate from Wuhan. Two amino acid changes in the S1/S2 junction knock out the furin cleavage site and 2 proline substitutions in the hinge region stabilise the prefusion conformation.

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5.1 Pharmacology

With respect to pharmacodynamics, studies were performed in mice, hamsters, rabbits and non-human primates (NHP). In **BALB/c mice**, immunisation with single intramuscular doses of Ad26.COV2.S (10^8, 10^9, 10^{10} viral particles) induced a humoral immune response with S protein-binding antibodies and corona virus-neutralising antibodies. The IgG2a/IgG1 ratio supported a favourable Th1 response. The analyses of the cellular immune response supported an induction of a Th1 type response characterised by an increased INFγ secretion as compared to IL-4, IL-5 or IL-10 and CD8 T-cell activation. Studies in **New Zealand White rabbits** confirmed the induction of a humoral and cellular immune response after one intramuscular vaccination with Ad26.COV2.S. A booster vaccination 56 days after the first immunisation further increased the immune response. **Syrian Golden hamsters** were used as a disease model. Intranasal inoculation of 10^2 $TCID_{50}$ SARS-CoV-2 strain BetaCoV/Munich/BavPat1/2020 resulted in a peak viral load in the lung around day 4 with clearance from lung tissue and throat within 7 days. SARS-CoV-2-induced a lung pathology that was evident 4 days post inoculation, associated with a transient body weight loss peaking at day 6 post infection. Intramuscular immunisation with 1/5th and 1/50th human dose of Ad26.COV2.S induced a humoral response with the generation of S protein-binding and virus-neutralising antibodies. A second immunisation induced only a transiently enhanced immune response. One or two dose immunised animals were challenged one month after immunisation with SARS-CoV-2 and analysed 4 days after challenge. Immunisation resulted in lower viral loads in the lung and reduced body weight loss. A reduction of viral loads was less apparent in upper respiratory tracts. Bibliographic data also showed that immunisation reduced viral loads in the gastrointestinal tract, liver, kidney and spleen. The potential development of vaccine-associated enhanced respiratory disease (VAERD) was studied using low suboptimal doses (10^7, 10^8 vp) of the Ad26.COV2.S vaccine before intranasally challenging the animals with SARS-CoV-2. No signs of VAERD, such as increased lung pathology or accumulation eosinophils, were observed. In adult **rhesus monkeys** (non-human primates, NHP) the immunogenicity of Ad26.COV2.S and protection after intranasal challenge with SARS-CoV-2 strain USA-WA1/2020 were studied. NHPs are not a model for disease as after inoculation of SARS-CoV-2 viruses no or only minimal virus-induced pathology was noted. NHPs can, however, be accepted to study protection from infection with SARS-CoV2. A single dose vaccination (from 2x 10^9 up to 10^{11} vp, corresponding to a 2x human dose) resulted in a dose-dependent humoral response characterised by S protein-binding antibodies and neutralising antibodies. With respect to the cellular immune response, IFNγ induction was measured in SARS-CoV2 peptide stimulated PBMCs. No IL-4 was induced, pointing to a Th1 skewed immune response. Protection from viral load in the upper and lower respiratory tracts was dose dependent. In the lung, signs of inflammation were reduced in vaccinated animals and no viral replication was measured in vaccinated animals. Dose-dependent breakthrough infections in the upper respiratory tract were noted. However, there was no evidence of VAERD. Long-term protection was evaluated and confirmed until 6 months. Based on literature, the immune response and protection from viral challenge could also be demonstrated in aged monkeys. An analysis of the correlate of protection in NHPs suggests that the humoral immune response correlates with protection from infection.

5.2 Pharmacokinetics

The biodistribution of Ad26.COV2.S was not investigated. Biodistribution was analysed for two Ad26-based viral vectors (Ad26.ENVA.01, Ad26.RSV.preF) which do not encode SARS-CoV2 S protein. This can be accepted as the biodistribution of adenoviral vectors does not dependent on the encoded transgene. For both vectors, the available data do not suggest a broad distribution after injection. the vaccine was primarily localised at the site of injection, lymph nodes and in spleen. Time points prior to 11 days after vaccination were not analysed. It was not studied what cell types were transduced after intramuscular injection of Ad26.COV2.S. Available bibliographic data suggest that many cell types are potentially transduced by Ad26.COV2.S, including antigen presenting cells. In conclusion, the pharmacokinetic data can be accepted based on the WHO guidelines on non-clinical evaluation of vaccines and based on the absence of critical toxicological effects.

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5.3 Toxicology

The evaluation of the toxicity of Ad26.COV2.S was performed in one GLP studies in rabbits after three intramuscular injections. No aged animals were included and no long-term safety (longer than one month) was established. No toxicity of S protein expression and no immunotoxicity were analysed. The local effects included reversible inflammatory reactions at the injection sites and enlargement of draining lymph nodes and spleen due to increased cellularity in germinal centers. Clinical pathology changes included transient increases in C-Reactive Protein (CRP) and fibrinogen concentrations, increases in globulin concentrations along with a decrease in albumin/globulin ratio. All these effects can be considered expected inflammatory immune responses after injection of a vaccine. Transient changes in body weight and increases in temperature were observed in vaccinated animals.

No genotoxicity or carcinogenicity studies were performed. This can be accepted considering the type of product.

A developmental and reproductive toxicology (DART) study was performed in rabbits. The immunization of rabbits with Ad26COVS1 did not induce maternal or developmental toxicity.

5.4 Nonclinical Conclusions

The submitted data show that a single dose of Ad26.COV2.S is immunogenic and has the potential to protect from SARS-CoV-2. No critical toxicological effects were identified. From the preclinical perspective, the benefit-risk balance is in favour of the benefit for the Ad26.COV2.S vaccine.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

No specific pharmacokinetic studies were conducted with Ad26.COV2.S. Pharmacodynamic effects for vaccines are assessed through the evaluation of immunogenicity. No studies on the secondary pharmacodynamics or on pharmacodynamic drug interactions have been performed.

Mechanism of Action

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector that encodes a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) full-length Spike protein in a stabilized immunogenic conformation.
Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating both neutralizing and cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19.

Immunogenicity results

A correlate or threshold of protection for COVID-19 has not been established in vaccinated humans. However, immunogenicity data available from 3 ongoing studies (COV1001, COV1002 and COV2001) support the efficacy observed in the pivotal **study COV3001.** Currently, binding and neutralizing antibody responses have been identified as the predominant correlates of protection.
The main immunogenicity objectives of the ongoing studies are to assess humoral immune responses in terms of neutralizing antibodies, measured by wtVNA, and S-specific binding antibodies, measured by S-ELISA, and to assess cellular immune responses, measured by ICS and/or ELISpot.

Studies COV1001, COV1002 and COV2001

A single dose of Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 Spike-binding antibody (S-ELISA) response by Day 15 (14 days post dose 1) and Day 29 (28 days post dose 1) in adult participants ≥18 to ≤55 years and ≥65 years of age. A neutralizing antibody response was observed as of Day 15 with responder rates of 83%-100% (GMT: 184-242 IC50) in Study COV1001 Cohort 3, in study COV2001, 83% (GMT: 166 IC50) in adults ≥18 to ≤55 years and 71% in adults ≥65 years of age (GMT: 120 IC50). By Day 29, responder rates and GMTs had increased compared to Day 15. In study COV1001 Cohort 3, a SARS-CoV-2 S-binding antibody response was observed as of Day 15 with responder rates of 73%-77% (GMC: 108-136 EU/mL) with increasing responder rates and GMCs by Day 29.

Across studies **COV1001, COV1002 and COV2001,** at Day 29, a SARS-CoV-2 neutralizing antibody response was observed in at least 88% of participants ≥18 to ≤55 years and at least 93% of participants ≥65 years of age. In the placebo groups, no humoral response was observed at Day 29.

Study COV3001

Regional differences

To examine whether there were any regional differences in vaccine efficacy, Ad26.COV2.S immunogenicity was evaluated by measuring S-specific binding antibodies at Day 1 and Day 29 post vaccination in participants randomly selected from these sites. In total, samples from 380 participants (252 Ad26.COV2.S and 128 placebo) were analysed, of which 118 were from South African sites, 188 from Brazilian sites, and 74 from US sites. For these participants, age was equally distributed between 18-59 years and above 60 years of age. Overall, **no regional difference** was observed in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S between Brazilian, South African and US participants. S-specific binding antibody concentrations for participants at Brazilian, South African and US sites increased from baseline (GMC < LLOQ) to Day 29 with GMCs of 402 (95% CI: 302; 505), 388 (95% CI: 297; 506) and 412 (95% CI: 306; 554), respectively, representing geometric mean increases from baseline of more than 6-fold to 9.3-fold. The responder rates were similar across sites from all 3 countries with >93% for the active vaccine groups.

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Th1/Th2 ratio calculation

Following vaccination with Ad26.COV2.S, the Th1/Th2 ratio was calculated to evaluate T cell phenotype bias in participants with an antigen specific T cell response. A single dose of Ad26.COV2.S elicited SARS-CoV-2 CD4 and CD8 T-cell responses by Day 15 (14 days dose 1) and up to Day 29 (28 days post dose 1) in adult participants ≥18 to ≤55 years and ≥65 years of age. In all participants with a CD4 T-cell response, the response was skewed towards the Th1 phenotype.

Detectable median Th1 responses (percentage of CD4 T cells producing IFN-γ and/or IL-2 but not IL-4, IL-5 and/or IL-13) were observed as of Day 15, which remained similar by Day 29, with, ≥71% of participants in Cohort 1a and ≥68% of participants in Cohort 3 with a positive sample at Day 29. Median Th2 responses (percentage of CD4 T cells expressing IL-4 and/or IL-5/IL-13 and CD40-L) were undetectable at any of the timepoints in either cohort.
CD8 T cell responses (percentage of CD8 T cells producing IFN- γ and/or IL-2) were observed as of Day 15, with ≥ 46% and ≥ 27% of participants who had a positive sample in Cohort 1a and Cohort 3, respectively. By Day 29, an increase in CD8 T cell responses was observed compared to Day 15, with >60% of participants in Cohort 1a and >50% of participants in Cohort 3 having a positive sample.
In addition, ELISpot data from Cohort 1a showed a Th1 (IFNγ) response by Day 15 in >73% of the participants. 14% to 27% of participants showed a Th2 (IL-4) response by Day 15, however, the Th1/Th2 ratio was above 1 for all participants showing a Th1 and/or Th2 response.
This is desirable as a Th1-cell-skewed response indicates a lesser risk of antibody-dependent enhancement (ADE), which could exacerbate COVID-19.

6.2 Dose Finding and Dose Recommendation

The dose levels of Ad26.COV2.S to be assessed in the clinical study programme (5×10^{10} vp and 1×10^{11} vp) was based on experience with other Ad26-vectored vaccines in clinical studies including Ad26.ZEBOV (Ebola virus program); Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV program); Ad26.CS.01 (malaria program); Ad26.RSV.FA2 and Ad26.RSV.preF (RSV program); and Ad26.ZIKV.001 (Zika virus program).

Initial immunogenicity and safety data from the first-in human (FIH) study COV1001 demonstrated that a single dose of Ad26.COV2.S at 5×10^{10} virus particles (vp) and 1×10^{11} vp induced a durable immune response and had an acceptable safety profile.

The data showed that:

- a single dose at either dose level was sufficiently immunogenic and similar in different age groups;
- the $5x10^{10}$ and $1x10^{11}$ vp dose level had comparable immunogenicity profiles; and
- the reactogenicity profile up to 28 days post-dose 1 was acceptable at both dose levels and more favorable at the $5x10^{10}$ vp dose level as compared to the $1x10^{11}$ vp dose level in adults 18 to 55 years of age. In addition, both dose levels had an acceptable safety profile and no safety concerns were identified.
- The $5x10^{10}$ vp dose level had a more favorable reactogenicity profile as compared to the $1x10^{11}$ vp dose level in participants 18 to 55 years of age. Solicited local and systemic AEs of grade 3 or higher were more frequently reported at the $1x10^{11}$ vp dose level than with the $5x10^{10}$ vp dose level. In participants ≥65 years of age, similar reactogenicity was observed with the $1x10^{11}$ vp dose level versus the $5x10^{10}$ vp dose level.

These data led to the decision to proceed with the single dose in the phase 3 study at a 5×10^{10} vp dose level. Thus, the proposed vaccine regimen is a single Ad26.COV2.S dose at $5x10^{10}$ vp, corresponding to not less than 8.92 $\log_{10}$ infectious units. It cannot be excluded that a two-dose regimen of $5x10^{10}$ vp would be more efficacious, which is being investigated in the study COV3009.

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6.3 Efficacy

The primary efficacy endpoint was vaccine efficacy (adjusted 95% CI) against molecularly confirmed moderate to severe/critical COVID-19 occurring at least 14 days and at least 28 days after a single Ad26.COV2.S dose in participants who were seronegative at time of vaccination. The secondary efficacy endpoint was the vaccine efficacy against Severe/Critical COVID-19 occurring at least 14 days and 28 days after a single Ad26.COV2.S dose.

Efficacy data are available from the ongoing **pivotal randomized, double-blind, placebo-controlled Phase 3 study COV3001** in adult participants ≥18 years of age, including at least 30% of adults ≥60 years. The primary efficacy analysis of study COV3001 was performed once the required 2-month (8 weeks) median follow-up was reached on 22 January 2021. The study assesses a single dose Ad26.COV2.S ($5x10^{10}$ vp) vaccine regimen.

In COV3001, 44,325 participants were randomized of whom 43,783 were vaccinated (21,895 in the Ad26.COV2.S group and 21,888 in the placebo group) and 39,321 (19,630 in the Ad26.COV2.S $5x10^{10}$ group and 19,691 in the placebo group) were included in the per-protocol (PP) set (the PP set includes those participants who received study vaccine, were seronegative at the time of vaccination, and had no other major protocol deviations). The median follow-up after vaccination was 58 days and 21,491 (54.7%) participants in the PP set had at least 2 months (8 weeks) of follow-up. The majority of participants came from North America (46.7%; all from US) and Latin America (40.6%, including Mexico, Colombia, Peru, Chile, Brazil and Argentina); the other participants came from South Africa (12.7%). 45.0% of participants were female and 54.9% were male. 38.6% of female participants were of childbearing potential; 285 (3.7%) breastfeeding women were enrolled.

The median age was 52.0 years (range: 18; 100 years). 33.5% of participants was ≥60 years of age and 22.9% of participants was ≥18 to <40 years of age. The median BMI was 27.00 kg/m^2 (interquartile range: 23.90; 30.70 kg/m^2). 9.6% of participants were SARS-CoV-2 seropositive at baseline. These participants were excluded from the PP set. 40.8% of participants had one or more comorbidities at baseline. A total of 1,218 (2.8%) HIV-infected participants were enrolled. No relevant differences in demographics and baseline characteristics were observed between the Ad26.COV2.S group and the placebo group.

Primary analysis of co-primary endpoint: Vaccine efficacy against moderate to severe/critical COVID-19

Vaccine efficacy (adjusted 95% CI) against molecularly confirmed moderate to severe/critical COVID-19 was 66.9% (59.03; 73.40) when evaluated at least 14 days after vaccination and was 66.1% (55.01; 74.80) when evaluated at least 28 days after vaccination.

The prespecified criteria for a successful primary analysis have been met for both co-primary endpoints and, therefore, efficacy of Ad26.COV2.S against moderate and severe/critical COVID-19 has been established from 14 days after vaccination onwards.

The vaccine was efficacious against molecularly confirmed moderate to severe/critical COVID-19 in both age groups (≥18 to <60 years of age and ≥60 years of age), from 14 days after vaccination onwards.

In the age groups ≥18 to <60 years of age and ≥60 years of age, VE (95%CI) against molecularly confirmed moderate to severe/critical COVID-19 was 63.7% (53.87; 71.58) and 76.3% (61.58; 86.04), respectively, when evaluated at least 14 days after vaccination (Table 13) and was 66.1% (53.30; 75.77) and 66.2% (36.74; 82.99), respectively, when evaluated at least 28 days after vaccination.

Onset of Protection against molecularly confirmed moderate to severe/critical COVID-19:

Vaccine efficacy against molecularly confirmed moderate to severe/critical COVID-19 increases over time and persists up to at least Day 56:

- VE (95% CI) from Day 2 to Day 14 was 8.4% (-27.17; 34.05)
- VE (95% CI) from Day 15 to Day 28 was 67.7% (55.37; 77.03)

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- VE (95% CI) after Day 29 was 66.1% (55.01; 74.80)
- VE (95% CI) after Day 42 was 69.3% (51.35; 81.22)

Primary analysis of co-primary endpoint: Vaccine Efficacy against severe/critical COVID-19

If analyses are limited only to sever/critical cases, there were 74 molecularly confirmed severe/critical COVID-19 cases with an onset at least 14 days after vaccination and 39 with an onset at least 28 days after vaccination. Vaccine efficacy (adjusted 95% CI) was 76.7% (54.56; 89.09) at least 14 days after vaccination and 85.4% (54.15; 96.90) at least 28 days after vaccination.
The vaccine was efficacious against molecularly confirmed severe/critical COVID-19 in both age groups (≥18 to <60 years of age and ≥60 years of age), from 14 days after vaccination onwards.
In the age groups ≥18 to <60 years of age and ≥60 years of age, VE (95%CI) against molecularly confirmed severe/critical COVID-19 was 61.4% (49.50; 70.81) and 80.2% (62.76; 90.29), respectively, when evaluated at least 14 days after vaccination, and 64.0% (48.76;75.10) and 67.0% (27.76;86.36), respectively, when evaluated at least 28 days after vaccination.
Onset of Protection against molecularly confirmed moderate to severe/critical COVID-19:

- VE (95% CI) from Day 2 to Day 14 was 66.6% (12.10; 89.14)
- VE (95% CI) from Day 15 to Day 28 was 65.3% (23.69; 85.71)
- VE (95% CI) after Day 29 was 85.4% (54.15; 96.90)
- VE (95% CI) after Day 42 was 92.4% (49.62; 99.82)

Vaccine efficacy against molecularly confirmed COVID-19 requiring medical intervention

Molecularly confirmed COVID-19 cases requiring medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings) were collected using the medical resource utilization (MRU) form.
At the time of the primary analysis (cut-off 22 January 2021), not all MRU forms were available and, therefore, cases occurring with an onset of approximately 29 days (or less) prior to the cut-off for data base lock may not have been included in this analysis.
Based on the MRU form, there were less than 23 COVID-19 cases requiring medical intervention, and, therefore, no inferential testing was performed. At least 14 days after vaccination, there were 2 cases of molecularly confirmed COVID-19 requiring medical intervention in the Ad26.COV2.S group and 8 cases in the placebo group.

Booster vaccination (second dose) after basic immunisation

Following approval in March 2021, Swissmedic approved a booster vaccination (second dose) after basic immunisation with COVID-19 Vaccine Janssen in December 2021. In 5 clinical trials conducted in Belgium, Brazil, Colombia, France, Germany, Japan, the Netherlands, the Philippines, South Africa, Spain, the United Kingdom, and the United States, approximately 9,000 individuals received two doses of COVID-19 Vaccine Janssen administered at least 2 months apart. Approximately 2,700 individuals had at least 2 months of follow-up following booster vaccination. No new safety signals were detected, and data from these individual studies indicate that the reactogenicity of a booster dose of COVID-19 Vaccine Janssen is similar to that of the first dose of COVID-19 Vaccine Janssen.

A randomized, double-blind, placebo-controlled phase 3 study (COV3009) evaluated the safety of a booster dose (second dose) of COVID-19 Vaccine Janssen administered approximately 2 months after baseline immunisation. 31,300 subjects were enrolled in this study, of which 15,708 subjects were scheduled to receive two doses of COVID-19 Vaccine Janssen. During the double-blind phase, only 8,655 subjects received two doses of COVID-19 Vaccine Janssen, and 7,053 subjects received one dose of COVID-19 Vaccine Janssen.
A reactogenicity subgroup of 6,068 subjects was included in the analysis, of whom 3,016 subjects received one dose of COVID-19 Vaccine Janssen and 3,052 subjects received placebo. Of these, 2,984 individuals received a second dose (1,559 COVID-19 Vaccine Janssen and 1,425 placebo) and were included in the second dose analysis.
The mean age of participants was 53.0 years (range: 18-99 years). Demographic characteristics were comparable in both groups of subjects (COVID-19 Vaccine Janssen or placebo).

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A randomized, double-blind, placebo-controlled Phase 2 study (COV2001) evaluated the frequency and severity of local and systemic adverse effects within 7 days of administration of a booster shot of COVID-19 Vaccine Janssen. This booster vaccination was administered to healthy adults 18 to 55 years of age and adults 65 years of age and older in good or stable health approximately 2 months after baseline immunisation. 137 subjects received both the basic immunisation and the booster vaccination at 2-month intervals. The mean age was 48 years. Forty-eight subjects (34%) were 65 years and older.

The COV1001 study enrolled 190 subjects who received a first dose and booster of COVID-19 Vaccine Janssen at 2 months and 19 subjects who received a first dose and booster of COVID-19 Vaccine Janssen within 6 months.

Additional data on the safety of two doses of COVID-19 Vaccine Janssen administered less than 6 months apart are available from a larger number of subjects (N=548) from the three Phase 1/2a studies.

An overall assessment of safety analyses from studies in which two doses of COVID-19 Vaccine Janssen were administered revealed no new safety concerns after booster vaccination, compared with adverse effects reported after basic immunisation with a single dose.

Booster vaccination after basic immunisation with an mRNA-COVID-19 vaccine

Following approval in March 2021, Swissmedic approved a heterologous booster vaccination (second dose) after basic immunisation with COVID-19 Vaccine Janssen an mRNA-COVID-19 vaccine in December 2021.

The safety of booster vaccination with COVID-19 Vaccine Janssen in persons who received an mRNA COVID-19 vaccine as baseline immunisation (heterologous booster vaccination) can be derived from safety data on vaccination with two doses of COVID-19 Vaccine Janssen (baseline immunisation and booster vaccination) (homologous booster vaccination), as well as from data from a U.S.-based independent open-label phase 1/2 clinical trial (NCT04889209) of heterologous booster vaccination. This study enrolled adults who had received baseline immunisation with two doses of Spikevax (Moderna) (N=151), with a single dose of COVID-19 Vaccine Janssen (N=156), or with two doses of Comirnaty (Pfizer) (N=151) at least 12 weeks prior to study entry and had no history of SARS-CoV-2 infection. These individuals were randomized in a 1:1:1 ratio to receive booster vaccination with one of the three vaccines, Spikevax, COVID-19 Vaccine Janssen, or Comirnaty. Adverse events were assessed over a 28-day period after booster vaccination. An overall review of adverse events reported after COVID-19 Vaccine Janssen heterologous booster vaccination revealed no new safety concerns compared with adverse events reported after COVID-19 Vaccine Janssen first vaccination or homologous booster vaccination.

Regional differences

In the US, VE against moderate to severe/critical COVID-19 was 74.4% (65.00; 81.57) and 72.0% (58.19; 81.71), when considering cases from at least 14 days and at least 28 days after vaccination, respectively. Vaccine efficacy (95% CI) against severe/critical COVID-19 in the US was 78.0% (33.13; 94.58) as of Day 15 and 85.9% (-9.38; 99.69) as of Day 29. Preliminary sequence data confirm that approximately 96% of these COVID-19 cases were due to the Wuhan-Hu1 reference sequence+D614G variant and approximately 3% were due to the CAL.20C variant.

In South Africa, high efficacy was observed against severe/critical COVID-19 and robust VE was observed for moderate to severe/critical COVID-19. This is especially important since preliminary sequence data confirm that approximately 95% of the COVID-19 cases that occurred in the study in South Africa were due to the SARS-CoV-2 variant 20H/501Y.V2 (belonging to the B.1.351 lineage), implying that Ad26.COV2.S is efficacious against this newly emerging and rapidly spreading strain. Vaccine efficacy (95% CI) against severe/critical COVID-19 was 73.1% (40.03; 89.36) as of Day 15 and increased to 81.7% (46.18; 95.42) as of Day 29. An effect was also seen on mortality, since all COVID-

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19-associated deaths in the study, all in the placebo group, occurred in participants from South Africa. Vaccine efficacy (95% CI) against moderate to severe/critical COVID-19 was 52.0% (30.26; 67.44) as of Day 15 and 64.0% (41.19; 78.66) as of Day 29.

In Brazil, VE estimates were higher than those in South Africa were and similar to those in the US. Preliminary sequence data confirm that approximately 70% of the COVID-19 cases in the study that occurred in Brazil appeared to be due to a variant from the P.2 lineage. This implies that efficacy in Brazil is not impacted by the high prevalence of the variant of the P.2 lineage as it was quite similar to the VE observed in the US, where D614G was highly prevalent.

6.4 Safety

Overall, all safety data (including reactogenicity) from the **Phase 3 study COV3001** from 43,783 participants (including 6,736 participants in the safety subset, the subset of the full analysis set (FAS) for the analysis of solicited and unsolicited AEs) who received either vaccine or placebo with a median of 2 months of follow-up after vaccination show that a single dose of Ad26.COV2.S at a dose level of $5x10^{10}$ vp has an acceptable safety and reactogenicity profile in participants ≥18 years of age. Lower reactogenicity was observed for older adults (≥ 60 years of age) compared to younger adults (≤ 18 to <60 years of age) among participants vaccinated with Ad26.COV2.S. Reactogenicity to Ad26.COV2.S in adults ≥18 years of age was demonstrated to be transient and most solicited AEs generally resolved in 1 to 2 days post vaccination.

Solicited AEs
Overall, for adults, solicited local and systemic AEs were more frequently reported in the Ad26.COV2.S group than in the placebo group. The frequency of Grade 3 solicited local AEs was low overall, but higher after vaccination with Ad26.COV2.S compared to placebo. The frequency of Grade 3 solicited systemic AEs was low overall, but higher after vaccination with Ad26.COV2.S compared to placebo.

During the 7-day post-vaccination period, the frequency of solicited local AEs was higher in participants in the Ad26.COV2.S group compared to participants in the placebo group. The most frequently reported solicited local AE (>45% of participants in the Ad26.COV2.S group) was vaccination site pain. Both vaccination site erythema and swelling were reported in <8% of participants in the Ad26.COV2.S group.

Most solicited local AEs were Grade 1 or Grade 2 in severity. The frequency of Grade 3 solicited local AEs was low overall, but higher in participants in the Ad26.COV2.S group compared to participants in the placebo group. The most frequently reported Grade 3 solicited local AE was vaccination site pain reported in <0.5% of participants in the Ad26.COV2.S group. No Grade 4 solicited local AEs were reported.
Solicited local AEs were considered to be related to the study vaccine by definition. All solicited local AEs were transient in nature; vaccination site erythema and vaccination site pain had a median duration of 2 days after vaccination with Ad26.COV2.S and vaccination site swelling had a median duration of 3 days after vaccination with Ad26.COV2.S.

During the 7-day post-vaccination period, the frequency of solicited systemic AEs was higher in participants in the Ad26.COV2.S group compared to participants in the placebo group. The most frequently reported solicited systemic AEs (≥30% of participants in the Ad26.COV2.S group) were fatigue, headache, and myalgia. Other solicited systemic AEs were reported in <15% of participants in the Ad26.COV2.S group.

Most solicited systemic AEs were Grade 1 or Grade 2 in severity. The frequency of Grade 3 solicited systemic AEs was low overall, but higher in participants in the Ad26.COV2.S group compared to participants in the placebo group. All Grade 3 solicited systemic AEs were reported in <2.0% of participants in the Ad26.COV2.S group. No Grade 4 solicited systemic AEs were reported.

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Pyrexia was reported in 9.0% of participants in the Ad26.COV2.S group compared to 0.6% of participants in the placebo group. Grade 3 pyrexia was reported in 0.2% of participants in the Ad26.COV2.S group of which the majority occurred in the younger age groups. No Grade 3 pyrexia was reported in the placebo group. All fevers were reported to have started on the day of vaccination (Day 1) or the day after (Day 2) and had a median duration of 1 day after vaccination with Ad26.COV2.S. Antipyretics were recommended post-vaccination for symptom relief as needed. Paracetamol (acetaminophen), metamizole sodium, and ibuprofen were the most frequently used medications, with higher frequencies observed in the Ad26.COV2.S group compared to placebo. Of the 302 participants who experienced fever in the Ad26.COV2.S group, 202 (66.9%) used antipyretics. In the full analysis set, 1,128/21,895 (5.2%) participants in the Ad26.COV2.S group used analgesics or antipyretics up to 7 days post vaccination.

Most solicited systemic AEs were considered to be related to the study vaccine by the investigator. Most solicited systemic AEs were transient in nature and had a median duration of 1 to 2 days after vaccination with Ad26.COV2.S.

Unsolicited AEs

For adults, there was no apparent difference in unsolicited AEs reported in the Ad26.COV2.S group compared to the placebo group. All unsolicited AEs reported during the 28-day post-vaccination phase had a frequency below 10%. The frequency of unsolicited AEs was similar in participants in the Ad26.COV2.S group compared to participants in the placebo group. The most frequently reported unsolicited AEs by PT (≥ 1.0% of participants in the Ad26.COV2.S group) were headache, fatigue, myalgia, and vaccination site pain, which were also recorded as solicited AEs. The most frequently reported unsolicited AEs by PT (≥ 1.0% of participants in the Ad26.COV2.S group), not recorded as solicited AEs, were chills, nasal congestion, arthralgia, cough, and diarrhea. Other unsolicited AEs were reported in <1.0% of participants in the Ad26.COV2.S group.

Most unsolicited AEs were Grade 1 or Grade 2 in severity. During the 28-day period post-vaccination, there were 19 (0.6%) participants with unsolicited AEs of at least Grade 3 in the Ad26.COV2.S group compared to 18 (0.6%) participants in the placebo group. Of these unsolicited AEs of at least Grade 3, 5 (0.1%) were considered to be related to the study vaccine in the Ad26.COV2.S group.

The frequency of unsolicited AEs that were considered related to study vaccine by the investigator was higher in participants in the Ad26.COV2.S group 242/440 (55%) compared to participants in the placebo group 154/407 (37.8%).

Serious AEs

Up to the cut-off date of 22 January 2021, fewer deaths were observed in the Ad26.COV2.S group (3 [<0.1%]) compared to the placebo group (16 [0.1%]). Out of the 16 deaths reported in the placebo group, 6 were confirmed to be associated with COVID-19. There were no deaths confirmed to be associated with COVID-19 in the Ad26.COV2.S group. Furthermore, a numerical imbalance was observed in the overall number of non-fatal SAEs between the Ad26.COV2.S group (90) and placebo group (137). Of these 227 SAEs, 7 SAEs (reported for 7 participants) in the Ad26.COV2.S group and 3 SAEs (reported for 2 participants) in the placebo group were considered to be related.
Additional analysis of non-COVID-19 associated SAEs showed a balanced distribution of SAEs between both vaccine groups with 83 (0.4%) participants reporting at least 1 non COVID-19 associated SAE in the Ad26.COV2.S group compared to 96 (0.4%) participants in the placebo group. There were no discontinuations from the study reported due to AEs or MAAEs.

AEs of special interest

There were no pre-specified adverse events of special interest for Ad26.COV2.S clinical development. Allergic reactions are of interest as severe reactions (eg, hypersensitivity reactions and anaphylaxis) are known to occur with any injectable vaccine. Up to the cut-off date of 22 January 2021, severe allergic reactions (including anaphylaxis) have not been reported in the studies and have not been

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identified as a safety issue in the data available for Ad26-based vaccines. In COV3001, the most frequently reported AEs within the broad SMQ 'nonanaphylactic allergic reactions' (≥6 participants in the Ad26.COV2.S group) were rash (24 participants active vaccine, 16 placebo), urticaria (8 participants active vaccine, 3 placebo), and hypersensitivity (6 participants active vaccine, 4 placebo). Review of other AEs of interest showed a numerical imbalance observed between the Ad26.COV2.S group and placebo group for:

- Tinnitus: six cases of tinnitus were reported in the Ad26.COV2.S group and none in the placebo group;
- Convulsions/seizures: Four cases were reported in the Ad26.COV2.S group (1 serious) and one case (non-serious) in the placebo group, all of which were considered not related to the study vaccine by the investigator);
- Thrombotic and thromboembolic events: The overall incidence of thrombotic and thromboembolic events (arterial and venous) was similar across Ad26.COV2.S (n=14, 0.1%) and placebo groups (n=10, <0.1%).);
- Demyelinating disorders: four cases of demyelinating disorders were reported in the Ad26.COV2.S group (2 cases peripheral neuropathy, 1 benign monoclonal hypergammaglobulinemia, 1 Guillain-Barré syndrome) compared with 5 cases in the placebo group (2 cases peripheral neuropathy, 1 Guillain-Barré syndrome and 2 sensory loss.

Post-marketing Data

Post-marketing surveillance is ongoing since temporary marketing authorisation was granted. It is based on national and international data from spontaneous reporting (pharmacovigilance) and from post-authorisation studies, see the RMP summary on Swissmedic's website RMP summaries (swissmedic.ch).

The occurrence of Guillain-Barré syndrome (GBS) and transverse myelitis (TM) has been reported very rarely following vaccination with COVID-19 Vaccine Janssen. Healthcare professionals should be alert for signs and symptoms of GBS and TM to ensure proper diagnosis, initiate appropriate supportive measures and treatment, and rule out other causes. A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, have been reported following vaccination with the Janssen COVID-19 Vaccine. Capillary leak syndrome (CLS) has been identified during post authorization use.

Very rare adverse events were identified through the international and Swiss pharmacovigilance systems. See current prescribing information (https://www.swissmedicinfo.ch/) and Swissmedic homepage (https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19.html).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Benefit

In the randomized, double blind, placebo-controlled pivotal phase 3 Study COV3001, 21,895 participants received Ad26.COV2.S and 21,888 participants received placebo. 39,321 participants (19,630 in the Ad26.COV2.S $5x10^{10}$ group and 19,691 in the placebo group) were included in the PP set.

The primary efficacy endpoint, vaccine efficacy (adjusted 95% CI) against molecularly confirmed moderate to severe/critical COVID-19 occurring at least 14 days and at least 28 days after a single Ad26.COV2.S dose in participants who were seronegative at time of vaccination was 66.9% (59.03; 73.40) and 66.1% (55.01; 74.80), respectively.

The secondary efficacy endpoint, vaccine efficacy against Severe/Critical COVID-19 occurring at least 14 days and 28 days after a single Ad26.COV2.S dose, was 76.7% (54.56; 89.09) and 85.4% (54.15; 96.90), respectively.

VE increases over time

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The onset of efficacy against moderate to severe/critical COVID-19 was evident as of 14 days after a single Ad26.COV2.S dose, persisting for the current duration of follow-up (median 58 days). The onset of efficacy against severe/critical COVID-19 was evident as early as of 7 days after a single dose, persisting for the current duration of follow-up (median 58 days). Of note, after Day 42, only 1 confirmed severe/critical COVID-19 case was reported in the Ad26.COV2.S group (on Day 48) while 13 cases were reported in the placebo group. This is consistent with available immunogenicity results from Phase 1/2a, which show that, following a single dose of Ad26.COV2.S, neutralizing and binding antibody titers were detected from Day 15 and increased from Day 29 through Day 57 with no indication of significant waning up to Day 85.

The VE against moderate to severe/critical COVID-19 occurring at least 14 and at least 28 days after vaccination was 67.6% (59.38; 74.30) and 68.8% (58.98; 76.58), respectively, in participants without comorbidities and 64.2% (52.68, 73.14) and 58.6% (40.57; 71.55), respectively, in participants with comorbidities. VE against severe/critical COVID-19 was ≥ 75.6% as of 14 days after vaccination and ≥ 75.2% as of 28 days after vaccination, irrespective of the presence of comorbidities.

Across the Phase 1 and 2 studies, Ad26.COV2.S elicited a SARS-CoV-2 neutralizing antibody response in at least 83% and 88% of participants ≥18 to ≤55 years and at least 71% and 93% of participants ≥65 years of age at Day 15 and Day 29, respectively. Similarly, Ad26.COV2.S elicited a SARS-CoV-2 Spike-binding antibody response in at least 99% of participants ≥18 to ≤55 years at Day 29 and 73% and 95% of participants ≥65 years of age at Day 15 and Day 29, respectively. In study COV1001, Ad26.COV2.S elicited CD4 and CD8 T cell responses in participants ≥18 to ≤55 years and participants ≥65 years of age, by Day 15 and up to 28 days after a single dose. All measurable CD4 T cell responses were predominantly of the Th1 phenotype.

In participants ≥18 to ≤55 years of age, neutralizing and binding antibody responses increased from Day 29 to Day 57 and were maintained up to at least Day 85 in study COV1001. In participants ≥65 years of age, neutralizing and binding antibody responses were maintained from Day 29 up to at least Day 87. For both age groups, later timepoints are being evaluated.

Uncertainties concerning benefits

Fifty-two COVID-19 related hospitalizations were identified (including ICU admission, mechanical ventilation and ECMO). 2 versus 29 COVID-19 related hospitalizations with onset of at least 14 days after vaccination (VE: 93.1% with 95% CI [72.74; 99.20]) were observed in the Ad26.COV2.S group compared to placebo. As of 28 days after vaccination, 0 versus 16 COVID-19 related hospitalizations (VE: 100% with 95% CI [74.26; 100.00)]) were observed in the Ad26.COV2.S group compared to placebo. However, not all confirmed COVID-19 cases that required medical intervention were included in this preliminary analysis. Of the cases that could be included, the number were too small to perform inferential testing. Thus, a trend was observed that the vaccine contributed to the prevention of COVID-19 requiring medical intervention, but clinical significance has not yet been confirmed.

- Clinical efficacy is crucial, especially with regard to the primary efficacy endpoints concerning the new variants. Efficacy with the current new, and anticipated new, virus variants, have to be clarified.

- Ad26.COV2.S VE was not effective among subjects of at least 60 years of age and with comorbidities, having a vaccine efficacy of 42.3% with a wide 95% CI (-13.1, 71.6) when considering cases from at least 28 days after vaccination. Therefore, more follow-up data to better understand the observed differences in vaccine efficacy between subgroups of age and comorbidities needs to be collected.

- In humans, clinical experience of effectiveness is limited to 2 months. Although animal models indicate efficacy for more than 2 months, longer-term efficacy and safety must be demonstrated before definitive approval.

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- Overall, in the PP set, 60.1% of the participants had no comorbidity associated with increased risk of progression to severe COVID-19 at baseline. The study population thus appears to be quite healthy, especially considering the older study participants included. The effectiveness especially in individuals with more and with severe comorbidities, and immunocompromised subjects, needs to be studied.

Risks and associated uncertainties

The safety of COVID-19 Vaccine Janssen was evaluated in an ongoing Phase 3 study (COV3001). A total of 43,783 subjects were enrolled in this study, of whom 21,895 adults aged 18 years and older received basic immunisation with a single dose of COVID-19 Vaccine Janssen (Full Analysis Set [FAS]). The median age of the subjects was 52.0 years (range: 18-100 years). Safety analysis was performed once the median follow-up time of 2 months after vaccination was reached. Longer safety follow-up of >2 months is available for more than 23,000 adults in the full analysis set (11,948 adults in the Ad26.COV2.S group and 11,955 in the placebo group). 1,044 adults were followed up for 3 months and 65 for 4 months.

The most common local adverse event reported was pain at the injection site (48.6%). The most common systemic adverse events were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). Fever (defined as body temperature ≥38.0°C) was observed in 9% of participants. Most adverse events occurred within 1-2 days of vaccination and were mild to moderate in severity and short in duration (1-2 days).

In older adults (763 adults ≥65 years), reactogenicity was generally milder and reported less frequently.

The safety profile was generally consistent among participants with or without prior evidence of SARS-CoV-2 infection at baseline; 2,151 adults who were seropositive at baseline received COVID-19 Vaccine Janssen (9.8%).

A numerical imbalance in reported events can be observed, where Ad26.COV2.S as contributing factor could not be excluded: Embolic and thrombotic events (vaccine: 0.06% (n=14), placebo: 0.05% (n=10); deep vein thrombosis: vaccine n=6, placebo n=2; pulmonary embolism: vaccine n=4, placebo n=1, sinus venous thrombosis: vaccine n=1, placebo n=0), tinnitus (vaccine n=6, placebo n=0), urticaria (vaccine n=8, placebo n=3). Serious adverse events, likely related to the vaccine, were observed (hypersensitivity reaction, vaccine site pain on Day 1 that progressed to greater portion of arm, extreme generalized weakness, fever, headache on Day 2). A causal association with the vaccine cannot be ruled out for the following SAEs: facial paralysis (Bell's palsy), Guillain-Barré syndrome, Pericarditis. Long-term safety data and safety in certain subpopulations (e.g. pregnant and lactating women, immunocompromised, individuals previously infected with SARS-CoV-2) could not be established with these interim data.

Benefit / Risk Assessment

COVID-19 Vaccine Janssen was the third COVID-19 vaccine to receive a temporary marketing authorisation in Switzerland. The results presented in this preliminary data analysis demonstrate that a single dose of Ad26.COV2.S is effective in the prevention of moderate to severe/critical COVID-19 as well as in the prevention of severe/critical COVID-19 occurring at least 14 days and at least 28 days after a single Ad26.COV2.S dose. Clinical efficacy is consistent with the demonstrated humoral and cellular immune responses. Some uncertainties remain regarding longer-term duration of humoral and cellular immune response, long-term efficacy and effectiveness in various subgroups.

In general, reactogenicity was acceptable with the most common local and systemic adverse reactions injection site pain, headache, fatigue and myalgia. Most local and systemic, solicited and unsolicited adverse events were mild to moderate, transient in nature and had a median duration of 1 to 2 days after vaccination. Some uncertainties remain regarding adverse events likely to be related to

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vaccination (hypersensitivity reactions), adverse events for which Ad26.COV2.S could not be excluded as contributing factor (thromboembolic events, tinnitus, facial paralysis (Bell's palsy), Guillain-Barré syndrome, Pericarditis), imbalances between the Ad26.COV2.S group and the placebo group (embolic and thrombotic events (deep vein thrombosis, pulmonary embolism, sinus venous thrombosis), tinnitus and urticaria), long-term safety data, and safety in certain subpopulations (e.g. pregnant and lactating women, immunocompromised, individuals previously infected with SARS-CoV-2).

In view of the current pandemic situation, and against the background of proven overall efficacy with an acceptable safety profile in this preliminary data analysis, the benefit-risk profile for Ad26.COV2.S in the proposed indication of an active immunisation to prevent coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 in adults ≥18 years of age is favourable for a temporary authorisation. A definitive approval can be considered when the described uncertainties regarding humoral and cellular immune response, efficacy and safety can be resolved.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to COVID-19 Vaccine Janssen was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
COVID-19 Vaccine Janssen has been authorised temporarily, see section “Properties/Effects”.

COVID-19 Vaccine Janssen

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

Composition

Active substances

Human adenovirus serotype 26* encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S).
* Produced in the PER.C6 TetR Cell Line and by recombinant DNA technology.
The product contains genetically modified organisms (GMOs).

Excipients

2-hydroxypropyl-β-cyclodextrin (HBCD), citric acid monohydrate, ethanol, hydrochloric acid, polysorbate-80, sodium chloride, sodium hydroxide, trisodium citrate dihydrate, water for injections.
Sodium content per dose of 0.5 mL: 1.91 mg. Each dose (0.5 mL) contains approximately 2 mg of ethanol.

Pharmaceutical form and active substance quantity per unit

Suspension for injection (injection). Colourless to slightly yellow, clear to very opalescent suspension (pH 6-6.4).
This is a multi-dose vial which contains 5 doses of 0.5 mL.
One dose (0.5 mL) contains not less than 8.92 $\log_{10}$ infectious units (Inf.U).

Indications/Uses

COVID-19 Vaccine Janssen is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.
The use of this vaccine should be in accordance with official vaccination recommendations.

Dosage/Administration

Usual dosage

Individuals 18 years of age and older
COVID-19 Vaccine Janssen is administered as a single-dose of 0.5 mL by intramuscular injection only.

Special dosage instructions

Elderly (65 years of age and older)

No dose adjustment is required in elderly individuals ≥65 years of age (see also *Undesirable effects* and *Properties/Effects*).

Children and adolescents

The safety and efficacy of COVID-19 Vaccine Janssen in children and adolescents (less than 18 years of age) have not yet been established. No data are available.

Mode of administration

COVID-19 Vaccine Janssen is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.
Do not inject the vaccine intravascularly, intravenously, subcutaneously or intradermally.
The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.
For precautions to be taken before administering the vaccine, see *Warnings and Precautions*.
For instructions on handling and disposal of the vaccine, see *Handling instructions and administration* (at the end of the product information).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section *Composition - Excipients*.

Warnings and precautions

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
A traceability card shall be given to the vaccinated person or his/her caregiver, indicating the name of the vaccine, the batch number and the possible reporting points.
Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination.
Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.
Concurrent illness
Vaccination should be postponed in individuals suffering from an acute severe febrile illness or

acute infection.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Janssen may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Protection starts around 14 days after vaccination. As with all vaccines, vaccination with COVID-19 Vaccine Janssen may not protect all vaccine recipients (see *Properties/Effects*).

Excipients

This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL dose, that is to say essentially ‘sodium-free’.

This vaccine contains 2 mg of alcohol (ethanol) per 0.5 mL dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

Interactions

No interaction studies have been performed. Concomitant administration of COVID-19 Vaccine Janssen with other vaccines has not been studied.

Pregnancy, lactation

Pregnancy

There is limited experience with the use of COVID-19 Vaccine Janssen in pregnant women. Animal studies with COVID-19 Vaccine Janssen do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see *Preclinical data*).

Administration of COVID-19 Vaccine Janssen in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and foetus.

Lactation

It is unknown whether COVID-19 Vaccine Janssen is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see *Preclinical data*).

Effects on ability to drive and use machines

COVID-19 Vaccine Janssen has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under *Undesirable effects* may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of safety profile

The safety of COVID-19 Vaccine Janssen was evaluated in an ongoing phase 3 study (COV3001). A total of 21’895 adults aged 18 years and older received COVID-19 Vaccine Janssen. The median age of individuals was 52 years (range 18-100 years). The safety analysis was performed once the median follow-up duration of 2 months after vaccination was reached. Longer safety follow-up of >2 months is available for over 23’000 participants in the FAS (11’948 participants in the Ad26.COV2.S group and 11’955 in the placebo group). Overall, 1’044 participants were followed for 3 months and 65 for 4 months.

In study COV3001, the most common local adverse reactions reported was injection site pain (48.6%). The most common systemic adverse reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%) and nausea (14.2%). Pyrexia (defined as body temperature ≥38.0°C) was observed in 9% of participants. Most adverse reactions occurred within 1-2 days following vaccination and were mild to moderate in severity and of short duration (1-2 days).

Reactogenicity was generally milder and reported less frequently in older adults (763 adults ≥65 years old).

Shown below are the frequency of solicited local and systemic adverse reactions in adults in the ongoing Phase 3 clinical trial (COVID3001) in the 7 days following vaccination.

Table: Solicited local adverse reactions reported in the 7 days following vaccination

Adverse reactions	COVID-19 Vaccine Janssen N=3'356 (%)	Placebo N=3'380 (%)
1 or more local adverse reactions		
- Any	1'685 (50.2)	657 (19.4)
- Grade 3	23 (0.7)	6 (0.2)
Injection site pain		
- Any	1'632 (48.6)	564 (16.7)
- Grade 3[a]	11 (0.3)	2 (<0.1)
Injection site erythema		
- Any	245 (7.3)	131 (3.9)
- Grade 3[b]	7 (0.2)	2 (<0.1)
Injection site swelling		
- Any	178 (5.3)	53 (1.6)
- Grade 3[b]	7 (0.2)	2 (<0.1)

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table: Solicited systemic adverse reactions reported in the 7 days following vaccination

Adverse reactions	COVID-19 Vaccine Janssen N=3'356 (%)	Placebo N=3'380 (%)
1 or more local adverse reactions		
- Any	1'850 (55.1)	1'185 (35.1)
- Grade 3	61 (1.8)	21 (0.6)
Headache		
- Any	1'306 (38.9)	802 (23.7)
- Grade 3[a]	23 (0.7)	9 (0.3)
Fatigue		
- Any	1'283 (38.2)	728 (21.5)
- Grade 3[b]	35 (1)	9 (0.3)
Myalgia		
- Any	1'113 (33.2)	430 (12.7)
- Grade 3[b]	32 (1)	6 (0.2)
Nausea		
- Any	477 (14.2)	327 (9.7)
- Grade 3[b]	6 (0.2)	6 (0.2)
Fever[c]		
- Any	302 (9)	20 (0.6)
- Grade 3	8 (0.2)	0

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38°C. Grade 3 fever: Defined as 39.0°C - 40.0°C.

The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; a total of 2'151 adults seropositive at baseline received COVID-19 Vaccine Janssen (9.8%).

List of adverse reactions

Adverse drug reactions observed during study COV3001 are listed below by frequency category. Frequency categories are defined as follows:
very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1'000 to <1/100), rare (≥1/10'000 to <1/ 1'000), very rare (<1/10'000) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders

Rare: hypersensitivity[a], urticaria.

Not known: anaphylaxis[b].

Nervous system disorders

Very common: headache (38.9%).

Uncommon: tremor.

Respiratory, thoracic and mediastinal disorders

Common: cough.

Uncommon: sneezing, oropharyngeal pain.

Gastrointestinal disorders

Very common: nausea (14.2%).

Skin and subcutaneous tissue disorders

Uncommon: rash, hyperhidrosis.

Musculoskeletal and connective tissue disorders

Very common: myalgia (33.2%).

Common: arthralgia.

Uncommon: muscular weakness, pain in extremity, back pain.

General disorders and administration site conditions

Very common: fatigue (38.2%), injection site pain (48.6%).

Common: pyrexia, injection site erythema, injection site swelling, chills.

Uncommon: asthenia, malaise.

[a] Hypersensitivity refers to allergic reactions of the skin and subcutaneous.

[b] Cases received from an ongoing open-label study in South Africa.

Events of special interest

Numerical imbalances, with more events in vaccine than placebo recipients, were observed for the following serious and other adverse events of interest in individuals receiving the vaccine or placebo, respectively:

- Thromboembolic events:
  - Deep vein thrombosis: 6 events (2 serious; 5 within 28 days of vaccination) vs. 2 events (1 serious; 2 within 28 days of vaccination).
  - Pulmonary embolism: 4 events (3 serious; 2 within 28 days of vaccination) vs. 1 event (serious and within 28 days of vaccination).
  - Transverse sinus thrombosis: 1 event (serious and within 28 days of vaccination) vs. 0.
- Seizures: 4 events (1 serious; 4 within 28 days of vaccination) vs. 1 event (0 serious and 0 within 28 days following vaccination).

- Tinnitus: 6 events (0 serious; 6 within 28 days of vaccination, including 3 within 2 days of vaccination) vs. 0.

For these events, a causal relationship with the COVID-19 Vaccine Janssen could not be determined.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System) and the batch number, if available. You can obtain information about this at www.swissmedic.ch.

Overdose

No case of overdose has been reported. In phase 1/2 studies where a higher dose (up to 2-fold) was administered, COVID-19 Vaccine Janssen remained well-tolerated, however, vaccinated individuals reported an increase in reactogenicity (increased vaccination site pain, fatigue, headache, myalgia, nausea and pyrexia).
In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

Properties/Effects

ATC code

J07BX03

Mechanism of action

COVID-19 Vaccine Janssen is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus serotype 26 vector that encodes a SARS-CoV-2 full-length spike (S) glycoprotein and in a stabilised conformation. Following administration, the S-glycoprotein of SARS-CoV-2 is transiently expressed, stimulating both neutralising and other functional S-glycoprotein-specific antibodies, as well as cellular immune responses directed against the S-glycoprotein, which may contribute to protection against COVID-19.

Pharmacodynamics

No further information.

Clinical efficacy

An ongoing, multicentre, randomised, double-blind, placebo-controlled phase 3 study (COV3001) is being conducted in the United States, South Africa and Latin American countries to assess the efficacy, safety, and immunogenicity of a single-dose of COVID-19 Vaccine Janssen for the prevention of COVID-19 in adults aged 18 years and older. The study excluded individuals with

abnormal function of the immune system resulting from a clinical condition, individuals who are under immunosuppressive therapies within 6 months, as well as pregnant women. Participants with stable HIV infection under treatment were not excluded. Licensed vaccines, excluding live vaccines, could be administered more than 14 days before or more than 14 days after the vaccination in the study. Licensed live attenuated vaccines could be administered more than 28 days before or more than 28 days after the vaccination in the study.

A total of 44'325 individuals were randomised in parallel in a 1:1 ratio to receive an intramuscular injection of COVID-19 Vaccine Janssen or placebo. A total of 21'895 adults received COVID-19 Vaccine Janssen and 21'888 adults received placebo. Participants were followed for a median of 58 days (range: 1-124 days) after vaccination.

The primary efficacy analysis population of 39'321 individuals included 38'059 SARS-CoV-2 seronegative individuals at baseline and 1'262 individuals with an unknown serostatus.

Demographic and baseline characteristics were similar among individuals who received the COVID-19 Vaccine Janssen and those who received placebo. In the primary efficacy analysis population, among the individuals who received COVID-19 Vaccine Janssen, the median age was 52.0 years (range: 18 to 100 years); 79.7% (N=15'646) of individuals were 18 to 64 years old [with 20.3% (N=3'984) aged 65 or older and 3.8% (N=755) aged 75 or older]; 44.3% of individuals were female; 46.8% were from Northern America (United States), 40.6% were from Latin America and 12.6% were from Southern Africa (South Africa). A total of 7'830 (39.9%) individuals had at least one pre-existing comorbidity associated with increased risk of progression to severe/critical COVID-19 at baseline (comorbidities included: obesity defined as BMI ≥30 kg/m2 (27.5%), hypertension (10.3%), type 2 diabetes (7.2%), stable/well-controlled HIV infection (2.5%), serious heart conditions (2.4%) and asthma (1.3%)). Other comorbidities were present in ≤1% of the individuals.

COVID-19 cases were confirmed by a central laboratory based on a positive SARS-CoV-2 viral RNA result using a polymerase chain reaction (PCR)-based test. Vaccine efficacy overall and by key age groups are presented in Table below.

Table: Analysis of vaccine efficacy against moderate[b] to severe/critical[c] COVID-19[b] in SARS-CoV-2 seronegative adults – primary efficacy analysis population

Subgroup	COVID-19 Vaccine Janssen N=19'630		Placebo N=19'691		% Vaccine Efficacy (95% CI)[d]
	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	
14 days post-vaccination					
All subjects[a]	116	3'116.57	348	3'096.12	66.9 (59.03; 73.40)
18 to 64 years of age	107	2'530.27	297	2'511.23	64.2 (55.26; 71.61)
65 years and older	9	586.31	51	584.89	82.4 (63.90; 92.38)
75 years and older	0	107.37	8	99.15	
28 days post-vaccination					
All subjects[a]	66	3'102.00	193	3'070.65	66.1 (55.01; 74.80)
18 to 64 years of age	60	2'518.73	170	2'490.11	65.1 (52.91; 74.45)
65 years and older	6	583.27	23	580.54	74.0 (34.40; 91.35)
75 years and older	0	106.42	3	98.06	

[a] Co-primary endpoint as defined in the protocol.

[b] Co-primary endpoint evaluated the first occurrence of moderate COVID-19. Symptoms of moderate COVID-19 were defined based on the following criteria: the individual must have experienced any one of the following new or worsening signs or symptoms: respiratory rate ≥20 breaths/minute, abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level, clinical or radiologic evidence of pneumonia, radiologic evidence of deep vein thrombosis (DVT), shortness of breath or difficulty breathing OR any two of the following new or worsening signs or symptoms: fever (≥38.0°C), heart rate ≥90 beats/minute, shaking chills or rigors, sore throat, cough, malaise, headache, muscle pain (myalgia), gastrointestinal symptoms, new or changing olfactory or taste disorders, red or bruised appearing feet or toes.

[c] Co-primary endpoint evaluated the first occurrence of severe/critical COVID-19. Symptoms of severe/critical COVID-19 were defined based on the following criteria: the individual must have experienced 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 (SpO_2) ≤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 neurologic dysfunction, admission to intensive care unit (ICU), death.

[d] Confidence intervals for 'All Subjects' were adjusted to implement type I error control for multiple testing. Confidence intervals for age groups are presented unadjusted.

Vaccine efficacy against severe/critical COVID-19 is presented in Table below.

Table: Analyses of vaccine efficacy against severe/critical COVID-19[a] in SARS-CoV-2 in seronegative adults – primary efficacy analysis population

	COVID-19 Vaccine Janssen N=19'630		Placebo N=19'691		% Vaccine Efficacy (95% CI)[b]
Subgroup	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	
14 days post-vaccination					
Severe/critical	14	3'125.05	60	3'122.03	76.7 (54.56; 89.09)
28 days post-vaccination					
Severe/critical	5	3'106.15	34	3'082.58	85.4 (54.15; 96.90)

[a] Final determination of severe/critical COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.

[b] Confidence intervals were adjusted to implement type I error control for multiple testing.

Of the 14 vs. 60 severe/critical cases with onset at least 14 days after vaccination in the COVID-19 Vaccine Janssen group vs. placebo group, 2 vs. 6 were hospitalised. Three individuals died (all in the placebo group). The majority of the remaining severe/critical cases fulfilled only the oxygen saturation (SpO_2) criterion for severe/critical disease (≤93% on room air).

Prior to unblinding, supplementary analyses, considered post-hoc, of positive cases using PCR-based tests regardless of confirmation by the central laboratory generally support the results of the primary analysis.

Beyond 14 days after vaccination, 2 vs. 8 cases of molecularly confirmed COVID-19 were hospitalised, respectively in the COVID-19 Vaccine Janssen vs. placebo group. One case in the placebo group required Intensive Care Unit (ICU) admission and mechanical ventilation. The finding was supported by post-hoc analysis of all COVID-19 related hospitalisations implementing a broader search based on all available information from any source (2 vs. 29 cases in the extended data set).

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants, as well as for participants with and without medical comorbidities associated with high risk of severe/critical COVID-19.

Exploratory subgroup analyses of vaccine efficacy against COVID-19 and severe/critical COVID-19 for Brazil, South Africa, and the United States were conducted (see Table below). For the subgroup analyses, all COVID-19 cases accrued up to the primary efficacy analysis data cut-off date, including cases confirmed by the central laboratory and cases with documented positive SARS-CoV-2 PCR from a local laboratory which are still awaiting confirmation by the central laboratory, were included.

Table: Summary of vaccine efficacy against COVID-19 and severe/critical COVID-19 for countries with >100 reported cases

		Severity	
	Onset	COVID-19 point estimate (95% CI)	Severe/critical COVID-19 point estimate (95% CI)
US	at least 14 days after vaccination	74.4% (65.00; 81.57)	78.0% (33.13; 94.58)
	at least 28 days after vaccination	72.0% (58.19;81.71)	85.9% (-9.38; 99.69)
Brazil	at least 14 days after vaccination	66.2% (51.01; 77.14)	81.9% (17.01; 98.05)
	at least 28 days after vaccination	68.1% (48.81; 80.74)	87.6% (7.84; 99.72)
South Africa	at least 14 days after vaccination	52.0% (30.26; 67.44)	73.1% (40.03; 89.36)
	at least 28 days after vaccination	64.0% (41.19; 78.66)	81.7% (46.18; 95.42)

Samples from 71.7% of central laboratory confirmed primary analysis cases had been sequenced [United States (73.5%), South Africa (66.9%) and Brazil (69.3%)]. Of the sequenced samples there is an imbalance in the completeness of the dataset between COVID-19 Vaccine Janssen and placebo. In the United States, 96.4% of strains were identified as the Wuhan-H1 variant D614G; in South Africa, 94.5% of strains were identified as the 20H/501Y.V2 variant (B.1.351 lineage); in Brazil, 69.4% of strains were identified to be a variant of the P.2 lineage and 30.6% of strains were identified as the Wuhan-H1 variant D614G.

The study was not conducted in regions with high prevalence of the new B.1.1.7 variant that first emerged in the UK, therefore no data are available for this variant.

Elderly population

COVID-19 Vaccine Janssen was assessed in individuals 18 years of age and older. The efficacy of COVID-19 Vaccine Janssen was consistent between elderly (≥65 years) and younger individuals (18-64 years).

Temporary authorisation

Due to incomplete clinical data at the time of the evaluation of the marketing authorisation application, COVID-19 Vaccine Janssen is granted a temporary marketing authorisation (Art. 9a Therapeutic Products Act). The temporary marketing authorisation is compulsorily linked to the timely fulfilment of conditions. Once these conditions have been fulfilled, the temporary marketing authorisation can be converted into a full marketing authorisation.

Pharmacokinetics

Not applicable.

Preclinical data

Non-clinical data reveal no special hazards for humans based on conventional studies of repeat-dose toxicity and local tolerance and reproductive and development toxicity.

Genotoxicity

COVID-19 Vaccine Janssen has not been evaluated for its genotoxic potential. The components of the vaccine are not expected to have genotoxic potential.

Carcinogenicity

COVID-19 Vaccine Janssen has not been evaluated for its carcinogenic potential. The components of the vaccine are not expected to have carcinogenic potential.

Reproductive toxicity and fertility

Female reproductive toxicity and fertility were assessed in a combined embryo-foetal and pre- and post-natal development study in the rabbit. In this study a first vaccination of COVID-19 Vaccine Janssen was administered intramuscularly to female rabbits 7 days prior to mating, at a dose equivalent to 2- fold above the recommended human dose, followed by two vaccinations at the same dose during the gestation period (i.e. at gestational days 6 and 20). There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. The parental females as well as their foetuses and offspring exhibited SARS-CoV-2 S protein-specific antibody titers, indicating that maternal antibodies were transferred to the foetuses during gestation. No COVID-19 Vaccine Janssen data are available on vaccine excretion in milk.
In addition, a conventional (repeat-dose) toxicity study in rabbits with COVID-19 Vaccine Janssen did not reveal any effects on male sex organs that would impair male fertility.

Other information

Incompatibilities

This vaccine must not be mixed with other medicinal products or diluted.

Shelf life

Unopened vial
2 years when stored at -25°C to -15°C.
Once removed from the freezer, the unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light in the original packaging, for a single period of up to 3 months, not exceeding the printed expiry date (“EXP”).

Once thawed, the vaccine should not be re-frozen.
For special precautions for storage, see below.
Vial after first puncture
Chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours at 2°C to 25°C. From a microbiological point of view, the product should preferably be used immediately after first puncture of the vial; however, the product can be stored between 2°C to 8°C for a maximum of 6 hours or remain at room temperature (maximally 25°C) up to 3 hours after first puncture of the vial.

Special precautions for storage

Store and transport frozen at -25°C to -15°C. The expiry date for storage at -25°C to -15°C is printed on the vial and outer carton after “EXP”.
When stored frozen at -25°C to -15°C, the vaccine can be thawed either at 2°C to 8°C or at room temperature:

- at 2°C to 8°C: a carton of 10 vials will take approximately 12 hours to thaw, and a single vial will take approximately 2 hours to thaw.
- at room temperature (maximally 25°C): a carton of 10 vials will take approximately 2 hours to thaw, and a single vial will take approximately 1 hour to thaw.

The vaccine can also be stored in the original packaging in a refrigerator at 2°C to 8°C for a single period of up to 3 months, not exceeding the original expiry date (“EXP”). Upon moving the product to 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used by the updated expiry date. After the updated expiry date, the vaccine must be discarded. The original expiry date must be crossed out. The vaccine can also be transported at 2°C to 8°C as long as the appropriate storage conditions (temperature, time period) are applied.
Once thawed, the vaccine cannot be re-frozen.
Keep the vials in the original carton in order to protect from light.
Unopened COVID-19 Vaccine Janssen is stable for a total of 12 hours at 9°C to 25°C. It is not a recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the 3-month storage at 2°C to 8°C.
For storage conditions after first puncture of the medicinal product, see *Other information - Shelf life*.

Instructions for handling

Handling instructions and administration, see at the end of this product information.

Authorisation number

68235 (Swissmedic)

Packs

A 2.5 mL suspension in a multi-dose vial (type I glass) with a rubber stopper (chlorobutyl with

fluoropolymer coated surface), aluminium crimp and blue plastic cap. Each vial contains 5 doses of 0.5 mL.
Pack size of 10 multi-dose vials.

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

March 2021

Handling instructions and administration

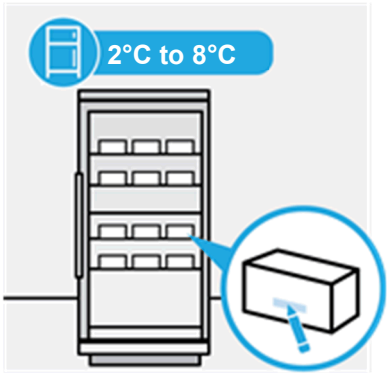
This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

- The vaccine comes ready to use once thawed.
- The vaccine may be supplied frozen at -25°C to -15°C or thawed at 2°C to 8°C.
- Do not re-freeze vaccine once thawed.
- Keep the vials in the original carton in order to protect from light and to record the expiry for the different storage conditions, if applicable.
- Each vial contains a sufficient overfill to ensure that 5 doses of 0.5 ml can be administered.

a. Storage upon receipt of vaccine

IF YOU RECEIVE YOUR VACCINE FROZEN AT -25°C to -15°C you may:

OR



Store in a freezer

- The vaccine can be stored and transported frozen at **-25°C to -15°C.**
- The expiry date for storage is printed on the vial and outer carton after “EXP” (see *Other information – Special precautions for storage*).

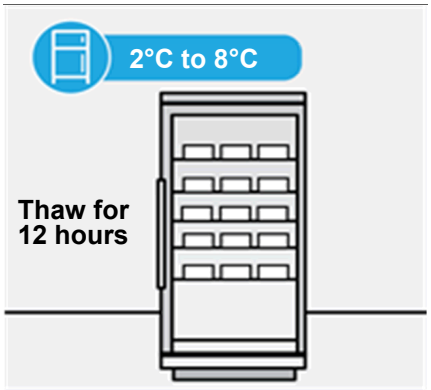
Store in a refrigerator

- The vaccine can also be stored and transported at **2°C to 8°C** for a single period of **up to 3 months**, not exceeding the original expiry date (“EXP”).
- Upon moving the product **to a refrigerator at 2°C to 8°C**, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. **The original expiry date must be crossed out**. (See *Other information – Special precautions for storage*).

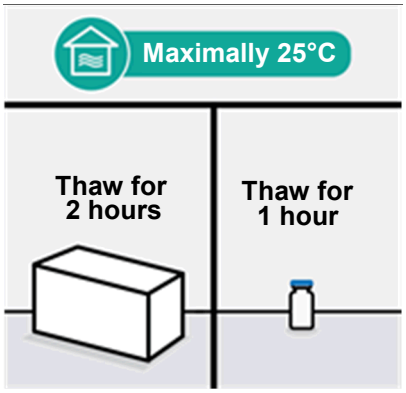
IF YOU RECEIVE YOUR VACCINE THAWED AT 2°C to 8°C you should store in a refrigerator:

Note: If the vaccine is received refrigerated at 2°C to 8°C, check that the expiry date has been updated by the local supplier upon receipt. If you cannot find the new “EXP” date, contact the local supplier to confirm the refrigerated expiry date. Write the **new expiry date** on the outer carton before the vaccine is stored in the refrigerator. **The original expiry date must be crossed out**. (see *Other information – Special precautions for storage*).

b. If stored frozen, thaw vial(s) either in a refrigerator or at room temperature before administration



OR



Thaw in refrigerator

- When stored frozen at -25°C to -15°C, a carton of 10 vials will take approximately 12 hours to thaw or individual vials will take approximately 2 hours to thaw **at 2°C to 8°C**.
- If the vaccine is not used immediately, refer to the instructions in section 'Store in a refrigerator'.
- The vial must be kept in the original carton in order to protect from light and to record the expiry for the different storage conditions, if applicable.

⚠ Do not re-freeze once thawed.

Thaw at room temperature

- When stored frozen at **-25°C to -15°C**, a carton of 10 vials or individual vials should be thawed at room temperature maximally **25°C**.
- A carton of 10 vials will take approximately **2 hours** to thaw.
- Individual vials will take approximately **1 hour** to thaw.
- The vaccine is stable for a total of **12 hours at 9°C to 25°C**. It is not a recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions.
- If the vaccine is not used immediately, refer to the instructions in section 'Store in a refrigerator'.

⚠ **Do not** re-freeze once thawed.

c. Inspect vial and vaccine

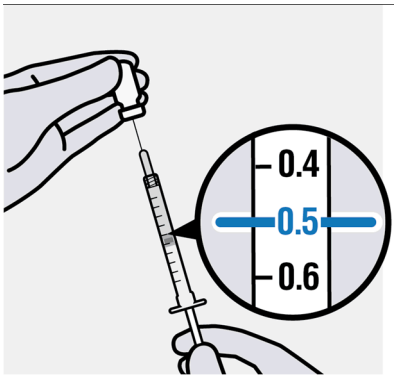
- COVID-19 Vaccine Janssen is a colourless to slightly yellow, clear to very opalescent suspension (pH 6-6.4).
- The vaccine should be inspected visually for particulate matter and discoloration prior to administration.
- The vial should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration.

If any of these should exist, do not administer the vaccine.

d. Prepare and administer vaccine

Swirl the vial gently

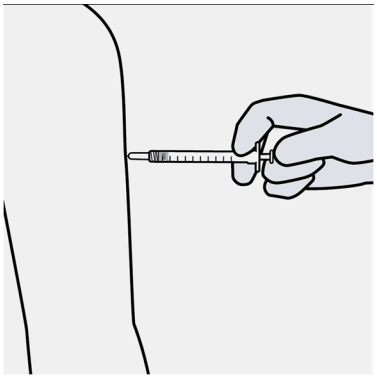
- Before administering a dose of vaccine, swirl the vial **gently in an upright position for 10 seconds**.
- **Do not** shake.



Withdraw 0.5 mL

- Use a sterile needle and sterile syringe to extract a single-dose of **0.5 mL** from the multi-dose vial (see *Dosage/Administration).*

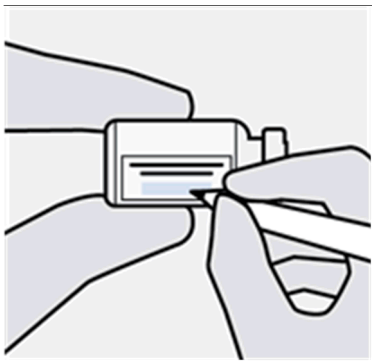
A maximum of 5 doses can be withdrawn from the multi-dose vial. Discard any remaining vaccine in the vial after 5 doses have been extracted.



Inject 0.5 mL

- Administer by **intramuscular injection only** into the deltoid muscle of the upper arm (see *Dosage/Administration*).

e. Storage after first puncture



Record date and time the vial should be discarded

- After first puncture of the vial record the date and time the vial should be discarded on each vial label.

⚠ Preferably, use immediately after first puncture.

- After the first puncture of the vial, the vaccine can be held at **2°C to 8°C** for **up to 6 hours**.
- Discard if vaccine is not used within this time.

OR

- After the first puncture of the vial, the vaccine can be held at **room temperature (maximally 25°C)** for a single period of **up to 3 hours**.
  (see *Other information - Shelf life*).
- Discard if vaccine is not used within this time.

f. Disposal

Any unused vaccine or waste material should be disposed of in compliance with local guidance for pharmaceutical waste. Potential spills should be disinfected with agents with viricidal activity against adenovirus.