RECOMMENDATION FOR AN EMERGENCY USE LISTING OF Convidecia™ COVID-19 Vaccine (Ad5-nCoV-S [recombinant]) SUBMITTED BY CanSino Biologics Inc.

Abstract

In early 2020, CanSino Biologics Inc. (CanSinoBIO) and its collaborator Beijing Institute of Biotechnology (BIB) jointly developed COVID-19 vaccine (Ad5-nCoV [recombinant]), trade name Convidecia™, to respond to the COVID-19 pandemic situation. Building on the adenovirus vector technology platform, previously used for the licensed Ebola virus disease vaccine (Ad5-EBOV), this COVID-19 vaccine (Adenovirus Type 5 Vector) is a recombinant replication-defective human Ad5 vector-based vaccine expressing spike S protein from SARS-CoV-2. The vaccine can deliver the spike S protein of SARS-CoV-2 virus in a safe form, thereby stimulating the immune system to produce antibodies and cellular immune responses against the virus that causes the COVID-19 disease.

The manufacturing site of COVID-19 vaccine (Ad5-nCoV [recombinant]) is located in TEDA West District, Tianjin, People's Republic of China. The World Health Organization (WHO) inspection team conducted a site inspection from 18 to 23 October 2021. All good manufacturing practices (GMP) issues raised by the WHO and international GMP team inspectors were satisfactorily addressed. On 1 March 2022, the GMP inspection was considered as closed.

Nonclinical studies indicated that Ad5-nCoV was safe and well tolerated in several animal models. Challenge studies with SARS-CoV-2 in mice, ferrets and nonhuman primates demonstrated that the vaccine induced a good immune response and protected the animals. No evidence suggesting a risk of antibody-dependent enhancement was observed. A Development and Reproductive Toxicity (DART) study in SD rats showed no evidence of maternal or fetal toxicity or teratogenicity.

CanSinoBIO conducted a phase 1 and a phase 2 clinical trials with Ad5-nCoV, both in China, with different vaccine dosages and involving 108 and 508 participants, respectively. Based on the immunogenicity, safety and reactogenicity findings, the dosage containing 5×10^{10} viral particles (vp) per dose was chosen and assessed in a phase 3 placebo-controlled randomized clinical trial, conducted in Argentina, Chile, Mexico, Pakistan, and Russia. This study involved more than 44000 participants, randomized 1:1 to the vaccine or to placebo, administered in a single intramuscular dose. The vaccine efficacy estimate was 57.5% (95% CI 39.7 to 70.0), based on 45 cases of RT-PCR-confirmed symptomatic COVID-19 observed in the vaccine arm and 105 in the placebo arm at least 28 days after vaccination. Vaccine efficacy for severe COVID-19 was estimated to be of 91.7% (95% CI 36.1 to 98.9), based on 1 and 12 cases, respectively, in the vaccine and placebo arms. In individuals 60 years of age and older, vaccine efficacy at least 28 days after vaccination was shown to be not statistically significant [17.5% (95% CI -127.6 to 70.1) for symptomatic COVID-19, and 76.1% (95% CI -114.3 to 97.3) for severe COVID-19]. The vaccine was well tolerated and no safety concerns were raised from the clinical studies and initial post-authorization use

after over 58 million doses were distributed globally. Immunogenicity data, from the clinical trials showed good neutralizing and binding antibody responses.

COVID-19 Vaccine (Ad5-nCoV-S [recombinant]), Convidecia™, is intended for people over 18 years of age, in a single dose of 0.5 mL administered by an intramuscular injection in the deltoid muscle of the upper arm of an individual. There is no sufficient data from clinical trials to support its use for people aged 60 and above.

On 25 February 2021, the Chinese National Medical Products Administration (NMPA) granted conditional market approval to Convidecia™. The vaccine obtained emergency use authorization (EUA) in Mexico, Pakistan, Hungary, Chile, Argentina, Ecuador, Kyrgyzstan, Indonesia, United Arab Emirates and Malaysia (Conditional Market Authorization) in 2021.

This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).

Introduction

1.1. Background

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the WHO and public, and the virus was categorized in the β-coronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have since then spread globally. On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC) and on 11 March the WHO characterized the COVID-19 outbreak as a pandemic.

The SARS-CoV-2 is an enveloped non-segmented positive-sense RNA virus. This novel coronavirus uses the same receptor, angiotensin-converting enzyme 2 (ACE2) as that for SARS-CoV, and mainly spreads through the respiratory tract. The main symptoms of the disease contain fever, dry cough and fatigue. Some patients have symptoms such as nasal congestion, runny nose, sore throat, myalgia, and diarrhea. Severe patients usually have dyspnea and/or hypoxemia one week after the onset of symptoms, and most severe patients can quickly turn to acute respiratory distress syndrome, septic shock, metabolic acidosis that difficult to correct, and coagulation dysfunction and functional failure of multiple organs causing the death of affected individuals.

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020[1] to assess what is known about the new severe acute respiratory coronavirus - 2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic. Life-saving vaccines would not have become a reality without remarkable and rapid collaboration with researchers at universities. Collaboration between academia and industry is well established in many parts of the world. However, the speed and scale of achievement during the pandemic is rare, if not unprecedented. Collaborations of this kind must continue beyond the pandemic.[2]

The pandemic has boosted public awareness of science–industry partnerships and to greater understanding of research, manufacturing, and quality-assurance processes.

Collaboration is central for initiatives and efforts in the race to fight COVID-19, with particular focus on fostering rapid development of safe and effective COVID-19 vaccines. The World Health Organization's list of COVID-19 vaccine developments indicates that nearly one third of all vaccine candidates were developed by partnerships, which tended to use next-generation's vaccine platforms more than solo efforts. These partnerships vary from materials-transfer partnerships to knowledge-sharing partnerships.[3]

1.2. COVID-19 vaccines

Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its native conformation) was identified as the immunodominant antigen of the virus[4]. Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease[5].

The current global COVID-19 public health emergency underscored the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

The information available on COVID-19 candidate vaccines [6] and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed based on

[1] https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research

[2] *Nature* 594, 302 (2021)

[3] Vaccine. 2021 Oct 8; 39(42): 6291–6295

[4] Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7(3):226-236.

[5] Tseng CT, Sbrana E, Iwata-Yoshikawa N, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7(4):e35421.

[6] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g., MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are constantly reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials.

During the past years, there was an unprecedent global effort to develop safe and effective vaccines against COVID-19. These vaccines represent some of the most important tools in responding to the pandemic, when combined with proven public health and social measures. Very encouraging results on the safety and efficacy of candidate vaccines have been reported for several candidates. However, the current epidemiological scenario is becoming increasingly complicated with the surge of virus variants due to mutations associated with increased viral transmission and in some cases neutralizing antibody escape. These variants make effective changes in the virus's 'Spike' protein, which the virus uses to enter human cells and some of these variants are posing real challenges for vaccine's efficacy.

In this complex scenario, vaccines that could exert protective immunity after a single dose are preferred. However, current epidemiological data has proved that the immunity after a primary vaccination schedule tends to wane and additional dose(s) might be required, making the current scenario more complicated, especially from the vaccine availability, accessibility, and coverage point of view. Although COVID-19 vaccines remain effective in preventing severe disease, recent data suggest their effectiveness at preventing infection or severe illness wanes over time, especially in people ages 65 years and older. The recent emergence of the Omicron variant further emphasizes the importance of vaccination, boosters, and prevention efforts needed to protect against COVID-19. On the other hand, data from clinical trials showed that a booster shot increased the immune response in trial participants who finished a primary series vaccination with WHO listed vaccines. With an increased immune response, people should have improved protection against getting infected with COVID-19 or at least helped prevent severe disease.

1.2.1. The Ad5-nCoV Vaccine (Convidecia™)

CanSinoBIO's Convidecia™ (Ad5-nCoV vaccine) is a genetically engineered vaccine with the replication-defective adenovirus type 5 vector expressing the SARS-CoV-2 coronavirus spike protein. The Emergency Use Listing (EUL) applicant developed a proprietary cell line to be used for viral vector production. It uses a weakened common cold virus (adenovirus, which infects human cells readily but is incapable of causing disease) to deliver genetic material that codes for the SARS-CoV-2 spike protein in cells. These cells then produce the spike protein that will stimulate the immune response to fight off the coronavirus.

In principle, Convidecia™ is similar to other replication-defective viral vector vaccines.

The Drug Product

The Drug Product composition is briefly described below:

Components	Content per dose (0.5 mL)	Function
Ad5-nCoV	3.5 – 6.0 x 10^{10} VP	Active ingredient
Excipients: mannitol, sucrose, magnesium chloride, sodium chloride, polysorbate 80, glycerine and water for injection.		

Each vaccine batch should have a potency of not less than 1.7 x 10^9 IFU/dose at release.

The vaccine formulation does not contain preservatives, adjuvants nor substances of animal origin.

The EUL applicant conducted its Phase III clinical trials in Argentina, Chile, Mexico, Pakistan and Russia with over 40 000 participants.

In February 2021, data from Phase III trials showed that the vaccine is effective for the prevention of symptomatic COVID-19 and severe disease. Convidecia™ is a single-dose regimen and the refrigerator storage requirement (2° to 8 °C) could make it a favourable vaccine option for many countries.

1.3. Emergency Use Listing

The EUL is a time limited risk-benefit assessment for emergency use of vaccines, medicines, and in vitro diagnostics during a public health event of international concern (PHEIC) when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the manufacturer is expected to gather more information on the human safety and efficacy to apply for the prequalification of the vaccine.

The issuance of an EUL for a product reflects WHO's recommendation for its use following a thorough scientific risk benefit assessment. However, each WHO Member State has the exclusive prerogative to allow the emergency use of a product under EUL within their country.

2. Assessment process

Convidecia™, manufactured by CanSinoBIO, was assessed under the WHO EUL procedure based on the submitted data on quality, safety, efficacy, risk management plan (RMP) and programmatic suitability. The WHO EUL dossier was submitted on 24 August 2021 and the review was performed by the WHO vaccine prequalification experts and assessors from different countries and regions. Emphasis was placed on the risk-benefit of the vaccine and therefore on the RMP because of the need to consider the perspectives and concerns of regulators from different regions, that might otherwise not be considered by the NRA of reference for WHO, the NMPA of China.

The information package submitted to WHO for the vaccine followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD).

During the assessment process, different rounds of questions were addressed satisfactorily by the EUL applicant. Furthermore, the WHO GMP site inspection has been recently (1 March 2022) closed as satisfactory.

3. Scientific Review

3.1. Quality overview

Manufacture, control of materials and drug substance

The Ad5-nCoV vaccine contains S protein as vaccine antigen. The S protein gene of SARS-CoV-2 (Strain Wuhan-Hu-1, GenBank No. NC_045512.2) was synthesized for Ad5-nCoV construction. To increase expression, codon optimization was performed on the gene of S protein. The sequence of S protein expressed by Wuhan-Hu-1 (GenBank No. NC_045512.2) was compared with the novel coronavirus S protein sequence submitted on the National Center of Biotechnology Information (NCBI) official website. The results were consistent. The sequence alignment of the S protein is 99.9% identical to the target protein of Ad5-nCoV. The EUL applicant provided the gene sequence of S protein of Ad5-nCoV and complete amino acid sequence of the spike protein.

The applicant had developed a technology to genetically modify virus packaging. The core of this proprietary technology lies in the genetically engineered HEK293 in which adenoviral replication is kept intact while viral protein expression during adenovirus packaging process is significantly suppressed. The system allows maximum adenovirus production with minimum protein expression during viral packaging. This system is extremely useful for packaging adenoviral vectors with genes of interests.

The cell line used in the production process of Ad5-nCoV vaccine, HEK293SF-3F6, was derived from HEK293 cells which constitutively support growth of the replication-defective adenoviral virus. The cell line developed to produce the adenovirus vector and the recombinant protein is serum free.

Currently, the 800L Drug Substance manufacturing processes have been commercialized in the Building 020 at CanSino Biologics Inc. Tianjin site. There are two identical, new manufacturing lines at 800L for Drug Substance, Line 1 and Line 2. The drug substance manufacturing process of Ad5-nCoV basically consists of the following steps:

- Virus inoculum preparation.
- Cell preparation and propagation.
- Virus infection.
- Purification.
- Drug substance preparation.

Cell substrate and virus lot systems are described, and quality and safety controls identified. These two manufacturing systems have been tested in accordance with international requirements and are qualified for the manufacturing of the vaccine.

The cell banks have been tested according to international requirements (e.g., Eur. Ph. 10th.) Certificate of analysis of the primary cell line, reports of the master cell bank and the working cell bank are provided by the EUL applicant.

Raw materials are controlled according to vendors' specifications, in-house methodology or as per international pharmacopeial compendiums.

The results of the completed process validation studies (800L scale) demonstrated that the manufacturing process can consistently yield the desired drug substance, suitable for its intended purpose. All values recorded for the process operating parameters during the manufacturing process of Adenovirus Type 5 Vector drug substance meet the defined operating ranges. All in-process control results obtained during the drug substance production meet the acceptance criteria. In addition, all QC results are within the release acceptance criteria. In conclusion, each step of the manufacturing process of SARS-CoV-2 S protein drug substance at 800L process is reproducible and considered validated.

The specifications for Recombinant COVID-19 Vaccine (Adenovirus Type 5 Vector) virus inoculum, harvest and drug substance have been established based the actual testing results from multiple batches of Ad5-nCoV intermediates and drug substance. All quality attributes in the specifications meet the requirements of different pharmacopoeias (e.g., Eur. Ph.; Ch. P.) and guidance documents (e.g., EMA).

The release specifications of the drug substance include attributes for safety, identity, potency, purity and impurities as well as general tests such as pH, appearance, and viral particle size. Testing methods are considered qualified or validated.

The approved quality specifications for the drug substance and the testing methods includes the content of viral particles (VP), infectious viral titer (IFU), ratio VP/IFU, analysis for replication competent adenovirus (RCA) as well important identity, purity and safety tests.

Quality specifications for the release and the stability testing of the drug substance are provided and discussed in detail by the EUL applicant.

Container Closure System

For drug substance manufactured by the 800L perfusion process and commercial drug substance shipment, sterile plastic bags are used. These container closure systems are widely used in the manufacturing of biopharmaceutical products. These are SARTORIUS STEDIM Biotech sterile and single used bags. The study report on compatibility of SARTORIUS STEDIM Biotech bags with Ad5-nCoV drug substance is provided and found satisfactory. In addition, sterile storage bags from another manufacturer (Pall Austar Sterile Single Use Bag) have been tested for the drug substance storage as an alternative to the supply of Sartorius bags. Thus, stability studies of the drug substance were designed with these two bags as well.

Stability

The long-term stability studies at 2 - 8 °C for drug substance lots at 50 L and 800L commercial scale support the claim of 6 months when stored at 2 - 8 °C. Studies are on-going.

Manufacture and control of the Drug Product

Composition, manufacture and controls of excipients, intermediates, and drug product

Convidecia™ is a Recombinant COVID-19 Vaccine (Adenovirus Type 5 Vector or Ad5-nCoV) that contains replication-defective recombinant human type 5 Adenovirus expressing spike protein (S protein) of SARS-CoV-2, which is produced by processing steps including viral amplification in HEK293SF-3F6 cells, purification, formulation, and filling.

One dose of Ad5-nCoV vaccine (0.5 mL) contains 3.5×10^{10}vp - 6.0×10^{10} VP Ad5-nCoV as active ingredient.

The product is colourless or slightly white sterile liquid for injection which is filled in 2 ml glass vials. A single dose vial contains 0.5 mL Ad5-nCoV vaccine in a 2 mL glass vial, while a three-dose presentation contains 1.5 mL (three doses, 3 × 0.5 mL) of Ad5-nCoV vaccine in a 2 mL glass vial.

The active ingredient of Convidecia™ is the replication-defective recombinant human type 5 Adenovirus expressing S protein of SARS-CoV-2.

The formulation of the vaccine includes excipients like mannitol, sucrose, polysorbate 80, sodium chloride, magnesium chloride, N-(2-Hydroxyethyl) Piperazine-N'-(2-ethanesulfonic acid) (HEPES), glycerine and water for injection (WFI). The excipients of Ad5-nCoV are selected based on the excipients used in Ad5-EBOV vaccine.

During the manufacturing process of the final bulk, the excipients for final formulation are prepared in a sterile bag, then filtered through a 0.2 μm sterile filter and mixed with the bulk drug substance in a sterile bag. The final bulk is filtered again through 0.2 μm sterile filter and the finished product is then filled aseptically using automated aseptic filling line operated under Class A/B environment in GMP clean rooms in the Building 020 at CanSino Tianjin site. After filling and capping as well as visual inspection, the samples of the final drug product are tested by QC. The final product is stored at 2 - 8°C until the final product is released by QA.

Clinical trial materials were formulated with the same vaccine qualitative composition.

Convidecia™ does not contain adjuvants nor preservatives. The product does not require diluent. Brief description of the vaccine composition is given above (see Section 1.2.1).

None of the excipients used in Ad5-nCoV manufacturing is derived from human origin or from animal source.

The manufacturing process of formulation and final product fill and finish in CanSinoBIO Building 020 is dedicated to for the Ad5-nCoV commercial scale drug product manufacturing. These manufacturing procedures and equipment were found qualified or validated.

The processing steps for the finished product starts with the final formulation of the bulk drug substance with the formulation solution and the filling into 2 mL Type 1 glass vial, following an aseptic procedure. These final operations are conducted under GMP conditions and in GMP compliant facility. Once the vaccine batches pass the established quality control and are approved by quality assurance, the vaccine vials are labelled and packaged.

Currently, the batch size of finished drug product packaged in glass vials is up to 400,000 vials (single dose) or up to 150,000 vials (three doses) per batch in the Building 020. The target fill volume is set within 0.55 - 0.65 mL for single-dose vials. For three-dose vial, the target fill volume per vial is 1.65 - 1.95 mL.

Process validation of the drug product fill and finish process for single-dose and for three-dose vials in the Building 020 have been completed and provided as part of the EUL submission and reviewed during the WHO GMP site inspection. This included four batches of single-dose vials drug product (including one pre-validation batch and three process validation batches), and four batches of three-dose vials drug product (including one pre-validation batch and three process validation batches).

Quality specifications for the release and the stability testing of the drug product are provided and discussed in detail by the EUL applicant. Specifications include identity tests (e.g.: viral vector, target gene, target antigen expression), potency tests (IFU per dose, VP/IFU), safety tests (e.g., adeno associated virus or AAV, bacterial endotoxins, sterility) and appearance.

Container Closure System

Convidecia™ is presented in a Type 1 glass vial of borosilicate glass, halogenated butyl rubber stoppers (brominated) and aluminium caps with plastic composite cover or flip off.

The extractable data of the glass vials and the stoppers showed that the materials mentioned above were suitable for this product.

Stability

The long-term stability studies of the Drug Product have been initiated at 2 - 8°C and planned for 30 months. Current data supports 12 months of shelf-life at this storage condition. Accelerated stability results available so far showed that the Ad5-nCoV drug product is stable for 2 months at 25 ± 2 °C.

The shelf-life will be extended upon availability of the stability updates and satisfactory opinion from the WHO.

3.2. Inspection overview

An international inspection team of experts from WHO, China, South Africa and observers from the medicine regulatory authorities of China i.e., NMPA performed an onsite GMP inspection, the details of which are outlined below:

Name:	CanSino Biologics Inc.
Address:	185 South Avenue, TEDA West District, 300462 Tianjin, China.
Date:	18 to 23 October 2021.
Vaccine:	COVID-19 vaccine (Ad5-nCoV-S [recombinant]) in 2 mL glass vials (single dose (0.5 mL) and 3-dose (1.5 mL) presentation) for intramuscular (IM) Injection.
Production Line:	The inspection focused on the production and control of Recombinant COVID-19 vaccine (Adenovirus Type 5 Vector) in the following main production buildings: o Cell bank, seed bank and seed lot preparation; o QC lab and warehouse; o The vaccine workshop which includes 2 bulk production lines (each with a production scale of 800L), one vial filling and packaging.

The inspection focused on the quality management system of the site and the manufacturing and control of the COVID-19 vaccine (Adenovirus Type 5 Vector, Ad5-nCoV) from CanSino Biologics as per WHO Good Practices guidelines and publications.

The inspection covered the following systems and areas:

1. Pharmaceutical quality system
   Management review, Quality risk management, Product quality review, Deviation management, Change control, CAPA management, Complaints, Product recalls, Self-inspection, Quality audits and suppliers' audits and approval, Personnel, Documentation, Batch Release Process and Lot Summary Product review.
2. Production system
   The manufacturing process of COVID-19 vaccine including but not limited to Buffer and media preparations, Seed lots, Cell banks and Inoculum, Drug substance, Formulation and Filling, Visual inspection, Labelling and Packaging, Storage, distribution and shipping, Batch manufacturing record review, Process validation, Sterile filtration and Validation of the aseptic processing through media simulations, Extractables and Leachables.
3. Premises and Equipment system
   The manufacturing and testing areas associated with COVID-19 Vaccine including but not limited to Storage of seeds and cell banks, Buffer and media solution preparations, Cell culture area, Drug substance workshop, Formulation, Filling and packaging, Quality controls and Testing areas, Warehousing Area for final product, raw material, excipient and packaging material, Waste management, Qualification and validation, Water system and pure steam, Heating, Ventilation, and Air Conditioning System, Steam sterilization by the autoclaves, Vial washing machine, Depyrogenation Tunnel, Filling and stoppering machine, Capping machine, Visual inspection equipment, Cleaning and fumigation and Warehouses.
4. Laboratory control system
5. Materials system
6. Packaging and labelling system
7. International shipping arrangement

Upon completion of the inspection a WHO Inspection Report was issued to the manufacturer detailing the findings and listing all deficiencies identified. Manufacturer is provided with a timeline to respond to the report.

During the final review, WHO considered satisfactory the Corrective and Preventive Actions (CAPA) proposed and undertaken by the manufacturer. WHO will verify the effective implementation of the improvements by performing the next inspection of CanSino Biologics within the following 3 years as per WHO routine monitoring program of GMP site inspections.

4. Nonclinical overview

Ad5-CoV vaccine was tested in animal models to confirm its immunogenicity, protective effects and its safety. All pivotal safety-related studies were conducted according to Good laboratory practices (GLP) principles.

Viral adsorption, biodistribution and shedding studies of Ad5-nCoV vaccine were carried out in 10 cynomolgus monkeys with repeated intramuscular injections once every 2 weeks with up to three doses (1.5×10^{11} viral particles [VP]/0.5 mL/monkey). There was no evidence of viral replication or pathogenic effects, and the virus was progressively cleared from the tissues. Based on the biodistribution study the vaccine components of Ad5-nCoV are expected to be confined to the injection site and possibly the draining lymph nodes without any increase in the risk of virus shedding.

Nonclinical immunogenicity and protective activity of Ad5-nCoV were evaluated in young BALB/c mice, hACE2 transgenic mice, SD rats, Hartley guinea pigs, ferrets, and nonhuman primates. The vaccine was shown to induce strong humoral and cellular immune responses in these animal models.

The results of the challenge studies indicated that the Ad5-nCoV vaccine provided good protection against live SARS-CoVv-2 challenge, reduced viral infection significantly, and did not promote antibody-dependent enhancement (ADE) in mice, ferrets and nonhuman primates. This was demonstrated by controlled SARS-CoV-2 replication and the absence of increased lung pathology after viral challenge in animals vaccinated with doses predicted to be fully or partially protective.[7]

A single-dose toxicity study was conducted in rats. Under the conditions of the study, the vaccine was well tolerated after one injection. In repeat-dose studies in rats and in cynomolgus monkeys the Ad5-nCoV vaccine was shown to be safe and well-tolerated even at 3 times the proposed clinical dose (i.e., $15x10^{10}$ VP).

No genotoxicity studies were conducted as these are not required since there are no new excipients or adjuvants in the proposed vaccine formulation. These replication defective adenoviral vectors lack ability to integrate their genome into the host chromosomes, thus the vaccine is not expected to be genotoxic in humans. No carcinogenicity studies were conducted with the proposed vaccine.
A local tolerance study was conducted in New Zealand rabbits. Only temporary local irritation at the injection site was noted.

A Development and Reproductive Toxicity (DART) study in SD rats showed no evidence of maternal or fetal toxicity or teratogenicity.

In general, the data from the nonclinical studies demonstrate that Ad5-CoV vaccine is safe and well tolerated and no nonclinical objections were identified that raised any concern about the use of this vaccine in humans and prevented the conduct of clinical trials.

4.1. Clinical overview

Clinical trials with Ad5-nCoV vaccine were authorized based on previous experiences from clinical trials with an Ebola vaccine candidate (Ad5-EBOV vaccine) and on the results of the nonclinical studies. The phase I and II studies were conducted in China and CanSinoBIO presented the analysis of a multicenter,

[7] Wu S, Zhong G, Zhang J. *et al*. A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications* 2020; 11:4081. DOI: https://doi.org/10.1038/s41467-020-17972-1 (Published online August 14, 2020).

randomized, placebo-controlled phase III clinical trial carried out in five countries (Argentina, Chile, Mexico, Pakistan, and Russia)[8] [9] [10]

In the phase I clinical trial, 108 healthy adults (51% male) aged between 18 and 60 years (mean 36.3) received a single low (5×10^{10} VP), medium (10×10^{10} VP) or high dose (15×10^{10} VP) of Ad5-nCoV vaccine to assess tolerability, safety and immunogenicity.

In the phase II study, 508 healthy adults (50% male) aged between 18 and 83 years (mean 39.7, SD 12.5) received a single dose the low- (253 participants) or medium-dose formulation of the Ad5-nCoV vaccine (129 participants), or placebo (126 participants). Vaccine safety and immunogenicity were assessed.

Following this, a double-blind, randomized, international, placebo-controlled, endpoint-case driven, phase 3, clinical trial enrolled adults from 18 years of age. Participants enrolled in the trial had no unstable or severe underlying medical or psychiatric conditions, had no history of a laboratory-confirmed SARS-CoV-2 infection and had no history of having received an adenovirus-vectored coronavirus or SARS-CoV-2 vaccine. Pregnant and breastfeeding women were not eligible to participate in the study.
Participants enrolled in the trial were randomized in a 1:1 ratio to receive a single intramuscular dose of 0·5 mL containing 5×10^{10} VP/mL of Ad5-nCoV vaccine or placebo.

Equal proportions of males and females were enrolled in the Ad5-nCoV vaccine group and the placebo group. The primary efficacy objective evaluated Ad5-nCoV in preventing symptomatic, PCR-confirmed COVID-19 infection in all participants who were at least 28 days postvaccination on Jan 15, 2021. The primary safety endpoint was the occurrence of any serious adverse events or medically attended adverse events postvaccination in all participants who received a study injection.
A total of 44 450 participants were randomized by March 15, 2021, the cut-off date for the extended safety and immunogenicity analyses.

By 15 January 2021, 36 982 participants had been enrolled and randomized in the trial in a 1:1 ratio and 36 727 had received a single intramuscular dose of 0·5 mL dose of 5×10^{10} VP/mL of Ad5-nCoV vaccine (18362; 50.0%) or placebo (18365; 50.0%). Over 99.9% of the participants were included in the primary safety analysis. Median follow-up of the safety cohort was 32 days (IQR 17–49). Only 2 and 8 participants allocated for the vaccine and placebo groups had not received the vaccine, because of moving from the study area and or withdrawal of consent. A subset of about 3000 participants (extended safety cohort) was followed up as of 15 March 2021.

Post-authorization effectiveness studies have been conducted in Chile and China.

---

[8] Zhu FC, Li YH, Guan XH, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020; 395: 1845–1854. https://doi.org/10.1016/S0140-6736(20)31208-3. (Published online May 22, 2020).
[9] Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo controlled, phase 2 trial. Lancet 2020; 396: 479–488. https://doi.org/10.1016/S0140-6736(20)31605-6. (Published online July 20, 2020)
[10] Halperin SA, Ye L, MacKinnon-Cameron D, et al. Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial. Lancet 2022; 399:237-248. https://doi.org/10.1016/S0140-6736(21)02753-7. (Published online December 23, 2021)

4.1.1. Vaccine efficacy and effectiveness

Phase III

There were 21 250 participants in the primary efficacy cohort (10 590 [49·8%] in the placebo group and 10 660 [50·2%] in the Ad5-nCoV group), which was defined as participants who were 28 days or more postvaccination on Jan 15, 2021. The median follow-up was 45 days (IQR 36–58). 3230 (30.5%) participants in the placebo group and 3238 (30.4%) participants in the Ad5-nCoV group had at least 8 weeks of follow-up. There were 29 177 participants in the secondary efficacy cohort (14 586 [50.0%] in the placebo group and 14 591 [50.0%] in the Ad5-nCoV group), defined as participants who were 14 days or more postvaccination on Jan 15, 2021. The median follow-up for them was 38 days (IQR 27–53). 3259 (22.3%) participants in the placebo group and 3261 (22.4%) participants in the Ad5-nCoV group had at least 8 weeks of follow-up. The characteristics of the participants in the primary efficacy cohort were similar in the vaccine and placebo groups in terms of age (mean of 37.8 and 37.7, respectively), sex (69.9% and 71.6% males), gender (70.1% and 71.7% males), ethnicity (37.6 and 37.3% Hispanic or Latino, 62.4% and 62.7% other), race (58.4% and 58.7% Asian, 23.4% and 23.2% mixed race, 9.7% and 9.6% White, 8.2% and 8.3% indigenous, applicable to participants from the Americas), and body mass index [BMI] (42.5% and 41.4% 18.5-24.9 range, 33.5% and 33.9% 25.0-29.9 range, 17.5% for both, ≥30).

One dose of Ad5-nCoV vaccine showed a 57.5% (95% CI 39.7 to 70.0) efficacy against symptomatic, PCR-confirmed, COVID-19 infection at 28 days or more postvaccination (21 250 participants; 45 days median duration of follow-up [IQR 36–58]) and 63.7% (95% CI 52.9 to 72.1) efficacy for the same endpoint beginning 14 days postvaccination. Against severe disease, the Ad5-nCoV vaccine showed efficacy of 91.7% (95% CI 36.1 to 99.0) and 96.0% (95% CI 70.5 to 99.5), respectively, 28 days and 14 days postvaccination.

In participants 60 years or older there were 7 cases/839 and 8 cases/840 of PCR-confirmed symptomatic infection beginning 28 days postvaccination, respectively, in the vaccine and placebo arms; the vaccine efficacy estimate was 17.5% (95% CI -127.6 to 70.1), i.e., no efficacy was demonstrated for this endpoint. Vaccine efficacy beginning 14 days postvaccination was 53·3% (95% CI 0.9 to 78.0), calculated from 10 cases/1323 in the vaccine arm and 21 cases/1347 in the placebo arm. For this age group, vaccine efficacy against severe disease at 28 days or more postvaccination was 76.1% (95% CI -114.3 to 97.3), based on 1 case/839 and 4 cases/840, respectively, in the vaccine and placebo arms, and 90.1% (95% CI 22.3 to 98.7) beginning 14 days after immunization, based on 1 case/1323 in the vaccine arm and 10 cases/1347 in the placebo arm.

Participants with any comorbidity had a vaccine efficacy estimate after 14 days of vaccination of 60.5% (95% CI 35.7 to 75.7), based on 23/3123 cases in the Ad5-nCoV arm and 56/3059 cases in the placebo arm, whereas those with hypertension had a vaccine efficacy estimate of 67.3% (95% CI 30.4 to 84.6), based on 9/1016 cases vs 27/1010 cases in the vaccine and placebo arms, respectively.

Stratification by country was possible for Pakistan and Mexico, where the majority of the participants were included in the trial. Vaccine efficacy estimates were, respectively, 69.10% (95% CI 52.77 to 79.78) and 58.05% (95% CI 40.80 to 70.28).

The participants of the phase III clinical trial were included in an extension of that study, in which they were randomized to receive an additional vaccine dose given 6-8 months after the primary vaccination (or placebo), so that each participant received at least one dose of the Ad5-nCoV vaccine (which is the

case of those initially allocated to the placebo arm). The results of this relative efficacy trial, in which participants who received two vaccine doses will be compared to those who received one, more than 10,000 per study arm, will become available within about two months. The follow-up period was approximately six months. This study should evaluate a period when the Delta and Omicron variants circulated.

Effectiveness

In an unpublished Chilean cohort study, a second dose of the CanSino vaccine showed vaccine effectiveness estimates after 28 days of the second dose of 52.27% (95% CI 49.16, 55.19) against symptomatic COVID-19, 83.73% (95% CI 76.88, 88.54) against hospitalization from COVID-19, and 95.35 (95% CI 85.51, 98.51) against ICU admission from COVID-19. (Data presented to WHO on October 25, 2021, and available at https://cdn.who.int/media/docs/default-source/blue-print/chile_rafael-araos_who-vr-call_25oct2021.pdf?sfvrsn=7a7ca72a_7).

A case-control study was conducted in Ruili City, Yunnan province, China, after an outbreak of COVID-19 caused by the SARS-CoV-2 Delta variant, in which the effectiveness of the Ad5-nCoV Vaccine and of two inactivated COVID-19 vaccines were estimated [REFERENCE: Ma C, Sun W, Tang T, et al. Effectiveness of adenovirus type 5 vectored and inactivated COVID-19 vaccines against symptomatic COVID-19, COVID-19 pneumonia, and severe COVID-19 caused by the B.1.617.2 (Delta) variant: Evidence from an outbreak in Yunnan, China, 2021. Vaccine, 2022. DOI: https://doi.org/10.1016/j.vaccine.2022.03.067. (Published online on April 1, 2022)]. Adjusted vaccine effectiveness estimates for the Ad5-nCoV vaccine were 61.5% (95% CI 9.5 to 83.6) against symptomatic COVID-19 and 67.9% (95% CI 1.7 to 89.9) against pneumonia.

4.1.2. Vaccine safety

Phase I

At least one adverse reaction within the first 7 days after vaccination was reported in 30 (83%) participants in the low dose group, 30 (83%) participants in the middle dose group, and 27 (75%) participants in the high dose group. The most common injection site adverse reaction was pain, which was reported in 58 (54%) vaccine recipients, and the most commonly reported systemic adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]). Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse event was noted within 28 days post-vaccination.

The Ad5 vectored COVID-19 vaccine was tolerable and immunogenic at 28 days post-vaccination.

Phase II

Solicited adverse events were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the low- and medium-dose groups, respectively. Severe adverse events were reported by 24 (9%) participants in the medium-dose group and one (1%) participant in the low-dose group. No serious adverse events were documented.

Phase III

The demographic characteristics of the 36717 participants in the full safety cohort were similar in the vaccine and placebo arms. Among the participants of the vaccine and placebo groups the mean age was 39.2 years (IQR 27–49) and 39.1 years (IQR 27–49), respectively, 10.0% and 10.1% were aged ≥60 years, and 34.4% and 33.5% were female. The majority of the participants were from Pakistan (46.2%) and

Mexico (36.9%), whereas the proportion included from Russia, Chile and Argentina were 10.1%, 5.1% and 1.7%, respectively.

In the primary safety analysis undertaken at the time of the efficacy analysis (36 717 participants), there was no significant difference in the incidence of serious adverse events (14 [0.1%] of 18 363 Ad5-nCoV recipients and 10 [0.1%] of 18 354 placebo recipients, p=0.54) or medically attended adverse events (442 [2.4%] of 18 363 Ad5-nCoV recipients and 411 [2.2%] of 18 354 placebo recipients, p=0.30) between the Ad5-nCoV or placebo groups, or any serious adverse events considered related to the study product (none in both Ad5-nCoV and placebo recipients). In the extended safety cohort, a subset of approximately 3000 participants distributed among the enrolment countries, which collected detailed solicited and unsolicited AEFI data, 1004 (63.5%) of 1582 of Ad5-nCoV recipients and 729 (46.4%) of 1572 placebo recipients reported a solicited systemic adverse event (p<0.0001), of which headache was the most common (699 [44.2%] of Ad5-nCoV recipients and 481 [30.6%] of placebo recipients; p<0.0001). 971 (61.3%) of 1584 Ad5-nCoV recipients and 314 (20.0%) of 1573 placebo recipients reported an injection-site adverse event (p<0.0001), of which pain at the injection site was the most frequent; reported by 939 (59%) Ad5-nCoV recipients and 303 (19%) placebo recipients. Fever was observed in 12.5% (198/1578) in the vaccine arm; 1.7% were classified as grade 3 and above. There were 14 serious adverse events in participants who received Ad5-nCoV vaccine and ten serious adverse events in those who received the placebo; none of them was considered vaccine-related. Four SAE associated with thrombosis (two cases of deep vein thrombosis, one of "acute thrombosis" and one of pulmonary artery thrombosis) were observed during this study, none of them fulfilling the criteria for the diagnosis of thrombosis and thrombocytopenia syndrome (TTS); all the patients recovered. There was also one case of Guillain-Barré syndrome associated to the vaccine who had recovered partially according to information as of December 2021.

Additional study

An investigator-initiated clinical trial (NCT05005156) is ongoing in Argentina in participants living with HIV. As of March 2022, 130 participants had been randomized and 104 received two doses of the Ad5-nCoV vaccine. No safety concerns had been raised as of then. The trial intends to follow-up participants for safety for 52 weeks.

Post-authorization use

Active surveillance data is available from a phase IV trial conducted in China from September 24, 2021, and December 16, 2021, during immunization campaigns in 20,865 individuals 18 years of age and older, including 2350 participants 60 years of age and older. Active surveillance data is available from a phase IV trial conducted in China from September 24, 2021, and December 16, 2021, during immunization campaigns in 20,865 individuals 18 years of age and older, including 2350 participants 60 years of age and older. The incidence of local and systemic adverse events (AE) within 30 minutes after vaccination, which was the study primary endpoint, was 1.20%. The incidence of solicited AE 0-7 days after vaccination was 22.30%, whereas the incidence of unsolicited AE 0-28 days after vaccination was 0.72%. The most commonly observed AE - fatigue, myalgia, dizziness, fever and local reactions – are the same observed during the clinical trials.

Passive surveillance data is also available. As of May 31, 2022, CanSinoBIO had AEFI data on approximately 78 million doses administered globally (34 million in China). A total of 12310 safety reports were received from China, 96.58% of them considered non-serious; there were 416 non-fatal serious

adverse events and 5 deaths. There were 1789 safety reports from overseas; 82.73% of the reports came from Mexico. The large majority of the cases were non-serious, whereas there were 171 non-fatal serious adverse events, and 24 deaths. Additional safety data was available for 1614 cases reported to the Uppsala Monitoring Centre (UMC); out of them, 94.18% were considered non-serious. There were 74 non-fatal serious adverse events, and 20 deaths.

Worldwide, 54 cases considered by the applicant as "thrombosis with thrombocytopenia syndrome (TTS)-related AE" were reported (0.07/100,000) after vaccination. According to the causality assessment, 33 cases were considered "unlikely", 20 as "conditional/unclassified", and 1 case of immune thrombocytopenia was considered possibly caused by the vaccine.

A total of 33 cases of Guillain-Barré syndrome were reported worldwide as of May 31, 2022, with an incidence rate of 0.04/100,000. Out of them, 10 were considered as adverse reactions, 1 as coincidental, and causality could not be determined in 22 patients. There were 3 deaths.

Out of 43 reports of anaphylaxis (14 cases of anaphylactic shock, 6 of Henoch-Schonlein purpura, and 23 of anaphylactic reactions), only 3 cases of anaphylactic shock and 1 case of Henoch-Schonlein purpura were considered as adverse reactions. Causality assessment of the majority of the other cases was not possible due to limited information.

4.1.3. Immunogenicity

Phase I
ELISA antibodies and neutralising antibodies increased significantly at day 14 and peaked 28 days post-vaccination. Anti-RBD ELISA antibody levels (GMTs) after 28 days of vaccination were 615.8 (95% CI 405.4 to 935.5), 806.0 (95% CI 528.2 to 1229.9) and 1445.8 (95% CI 935.5 to 2234.5) for the low-dose, middle-dose and high-dose groups, respectively. Neutralizing antibodies to live SARS-CoV-2 (GMTs after 28 days of vaccination were, respectively, 14.5 (95% CI 9.6 to 21. 8), 16.2 (95% CI 10.4 to 25.2) and 34.0 (95% CI 22.6 to 50.1) for the low-dose, middle-dose and high-dose groups.

ELISpot responses, that were undetectable at baseline, peaked at day 14 after vaccination. The proportions of positive responders ranged from 83 to 97% across the dose groups, with a mean number of spot-forming cells per 100000 cells of 20.8 (95% CI 12.7 to 34.0), 40.8 (95% CI 27.6 to 60.3), and 58.0 (95% CI 39.1 to 85.9) in the low-dose, middle-dose and high-dose groups, respectively. T-cell responses in the high dose group were significantly higher than that in the low-dose group but not when compared to the middle-dose group.

High levels of baseline Ad5 neutralizing antibody titers reduced the peak of post-vaccination T-cell responses in all the dose groups, although positive responders were identified in 75%, 95% and 94% of the participants from low- to high-dose groups. The percentages of the participants with anti-Ad5 neutralizing antibodies ≤200 and >200 was 49.1% and 50.9%, respectively.
IFNγ was detected from CD4+ and CD8+ T cells after 14 and 28 days of vaccination in all dose groups.

Phase II
In the low- and medium- dose groups, the RBD-specific ELISA antibodies peaked at 656.5 (95% CI 575.2–749.2) and 571.0 (467.6–697.3), and the seroconversion rates were 96% (95% CI 93–98) and 97% (92–

99), respectively, at day 28. Both vaccine doses induced significant neutralizing antibody responses to live SARS-CoV-2, with GMTs of 19.5 (95% CI 16.8–22.7) and 18.3 (14.4–23.3) in the low- and medium-dose groups, respectively. Post-vaccination specific interferon γ enzyme-linked immunospot assay responses were observed in 227 (90%, 95% CI 85–93) of 253 participants in the low-dose group, and 113 (88%, 81–92) of 129 participants in the medium-dose group.

Before vaccination, 266 (52%) participants had a high (>200) pre-existing anti-Ad5 neutralizing antibodies. Participants with low pre-existing anti-Ad5 immunity had about twice higher RBD-specific ELISA antibody and neutralizing antibody levels than the participants with high pre-existing anti-Ad5 immunity. Nevertheless, the ELISA antibodies to RBD and neutralizing antibodies at day 28 in vaccinated participants were still significantly higher than those in placebo recipients

Immune persistence data at 6 months post immunization is available for this study. Binding (low-dose group 71.10; 95% CI 57.71 to 87.59; medium-dose group 79.36; 95% CI 57.71 to 87.59) and neutralizing (low-dose group 32.61; 95% CI 26.72 to 39.79; medium-dose group 34.91; 95% CI 29.98 to 40.67) antibody levels (GMTs) at 6 months decreased compared to the levels observed at 28 days post immunization (see above), but in the participants of the Ad5-nCoV vaccine low and medium dose groups they were significantly higher than in the placebo group.

Phase III

The immunogenicity sub cohort of the phase III trial had 538 participants, 271 of whom received the Ad5-nCoV vaccine and 267 received placebo. The participants of the immunogenicity cohort were slightly older, the male to female ratio was more balanced and there were a higher proportion of Hispanic people and a lower proportion of Asian people than in the overall safety cohort. The percentages of pre-existing Ad5 antibody levels >200 in participants of the five countries were very similar, ranging from 32.29% to 34.58%.

Ad5-nCoV vaccine elicited a substantive anti-spike antibody response with a geometric mean antibody titre increase of 32.0-fold from pre-vaccination to 28 days post-vaccination in the Ad5-nCoV group compared with a 1.1-fold increase in the placebo group. Seroconversion was shown in 236 (91.5%) of 258 Ad5-nCoV recipients (GMT 1659.4, 95% CI 1375.9 to 2001.4) compared with 6 (4.7%) of 247 placebo recipients (GMT 53.0, 95% CI 46.4 to 60.7). The neutralizing antibody response after 28 days was higher in the Ad5-nCoV group (GMT 89.6, 95% CI 72.3 to 111.1) than in the placebo group (GMT 8.4, 95% CI 7.2 to 9.8), with a geometric mean fold increase of 11.4 and 1.1, respectively. Seroconversion of neutralizing antibodies was observed in 195 (75.9%) and 8 (3.3%) out of, respectively, 257 Ad5-nCoV vaccine recipients and of 246 participants of the placebo arm.

A phase III study (NCT04540419) was conducted in the Russian Federation, having as sponsor NPO Petrovax and as collaborator CanSinoBIO, having started on 11 September 2020. In this trial, 500 healthy participants aged 18-85 years were enrolled to evaluate the safety and immunogenicity for 6 months after one dose of Ad5-nCoV vaccine. Results showed that the vaccine elicited a specific immune response. The main immunogenicity responses of the Ad5-nCoV vaccine on day 28 post-vaccination were as follows: S-RBD antibody GMT (ELISA) was 405.32 (95% CI 361.58-454.46), the seroconversion rate was 78.5% (95% CL: 73.9-82.6); S-protein antibody GMT 676.86 (95% CI 607.44-754.40), seroconversion rate 90.6% (95% CI 87.2-93.4); SARS-CoV-2 neutralizing antibody GMT 16.73 (95% CI 15.36-18.22), seroconversion rate 59.0% (95% CI 53.3-64.6).

Approximately 600 participants of the phase III trial were included in the immunogenicity sub-cohorts. Ad5 neutralizing antibodies will be determined, that should allow stratified analyses of humoral response by Ad5 antibody level. These data are not yet available.

Cross neutralization

The neutralization activity of sera from Ad5-nCoV vaccine-immunized volunteers against pseudo typed B.1.617.2 (Delta) variant was reduced by 0.9 to 1.4-fold compared with the D614G variant. [REFERENCE: Wang Y, Zhang L, Li Q, *et al*. Infectivity and antigenicity of SARS-CoV-2 B.1.617 variants. *Research Square* preprint. DOI: https://doi.org/10.21203/rs.3.rs-596463/v1 (Posted on June 10, 2021).]

4.2. Risk Management Plan

This assessment is based on the RMP version: 1.2 (25 November 2021).

4.2.1 Product description: Acceptable

4.2.2 Nonclinical information: Acceptable. Preclinical studies have shown that vaccination with the Ad5-nCoV vaccine can introduce both humoral and cellular immune responses in animal models.

4.2.3 Safety specifications

a. Important identified risks:

CanSinoBIO	WHO	Comments
Anaphylaxis	Anaphylaxis	Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.

b. Important potential risks:

CanSinoBIO	WHO	Comments
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for Ad5-nCoV vaccine, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.
	Programmatic errors	It may be necessary to minimize this situation in advance under real use conditions. This should be monitored via routine pharmacovigilance activities and should be presented in each PBRER/PSUR.
	Thrombosis in combination with thrombocytopenia	A very rare and serious combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed following vaccination with other COVID-19 viral vector-based vaccines during post-marketing use. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia.

c. Missing information:

CanSinoBIO	WHO	Comments
Use in pregnancy and while breast feeding	Use during pregnancy and while breastfeeding	Not included in the pivotal trial and other studies. The document mentioned that the efficacy and safety of candidate vaccine Ad5-nCoV in pregnant women is not studied at present, hence pregnant women shall not use this medicinal product, and women of childbearing age shall be informed on the use of contraceptives for the period of 90 days after vaccination. No data is available on excretion of Ad5-nCoV vaccine in breastmilk. In order to avoid risk associated with Ad5-nCoV vaccine effect on breastfed children, breastfeeding women shall be excluded from trials. However, post-marketing information was not included, such as pregnancy reports, spontaneous abortions, cases of ectopic pregnancy, premature cases, etc. A Local multicenter safety surveillance study of Ad5-nCoV vaccine use in mass population and special population is ongoing only in China; one of the safety concerns are pregnancy and breastfeeding.

		No other additional pharmacovigilance activities are planned.
Use in individuals ≥60 years of age with comorbidities or chronic diseases	Use in individuals ≥60 years of age with comorbidities or chronic diseases	Of the 508 participants in the FAS of the phase II clinical trial (NCT04341389), 65(12.8%) participants were aged ≥ 55 years old. However, in the phase III clinical trial (NCT04526990) the proportion of people aged 60 years and above was low (9.90%), however the efficacy estimates for this age group were very imprecise due to small numbers. Diabetes patients and those with convulsion, epilepsy, encephalopathy or mental disease history or family history were not included or have limited participation in clinical trials and relevant information about them is lacking.
Use in pediatric population <18 years of age	Use in pediatric population <18 years of age	Paediatric patients younger than 18 years will be considered in the Paediatric Investigation Plan. At the time to the data cut-off date, recruitment of patients from children under 18 years old for Ad5-nCoV vaccine trial is on-going (trial registration number – NCT04566770).
Use in immunocompromised	Use in immunocompromised	The safety profile of Ad5-nCoV vaccine is not known in immunocompromised patients, including those receiving immunosuppressant therapy, due to their exclusion from the clinical development program
Use in patients with autoimmune or inflammatory disorders	Use in patients with autoimmune or inflammatory disorders	Not included in the current clinical trials (refer to protocol exclusion criteria). There is limited information on the safety of Ad5-nCoV vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease
Use in frail subjects with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Use in frail subjects with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	No safety data are available for frail individuals with comorbidities. Limited information is available on the safety of Ad5-nCoV vaccine in frail patients with comorbidities. These comorbidities may compromise their immune response and the safety profile of Ad5-nCoV vaccine in this subpopulation could vary from that seen in healthy adults, with a potentially higher risk of severe COVID-19.
Interaction with other vaccines	Interaction with other vaccines	The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g., influenza) has not been evaluated. Therefore, the potential impact on safety and efficacy of Convidecia™ is unknown. Interaction with other vaccines needs to be studied.
Long-term safety data and long-term effectiveness of the vaccine.	Long-term safety data and long-term	Currently limited and further follow-up for all vaccines is required. Additional activities will be needed to obtain such information.

	effectiveness of the vaccine.	
	Impact of the emergence of variants on vaccine efficacy/effectiveness and safety	CanSinoBIO should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases, as soon as available, irrespective of source.
Male HIV+ (MHSM unprotected)		A concern that is specific to Convidecia™ is the risk of facilitating the transmission of HIV to males who have unprotected active anal intercourse with men living with HIV, which was observed in clinical trials with HIV candidate vaccines which used adenovirus type 5 as a vector. Risk minimization activities need to be addressed.

4.2.4 Post-authorization experience

The information presented in this section is limited. The post-authorization experience information needs to be completed in detail, such as fatal cases, seriousness of AEs, pregnancies reports, spontaneous abortions, cases of ectopic pregnancy, premature cases, Guillain Barre cases etc, as it is mentioned in the Appendix 2.3-Clinical independent expert report. The information of this document is not included in the RMP.

4.2.5 Pharmacovigilance Plan

4.2.5.1 Routine Pharmacovigilance activities

The applicant proposed spontaneous reporting and signal detection as part of the routine pharmacovigilance activities. The information for signal detection, such as methodology, resources or timelines needs to be described in detail. CanSinoBIO maintain the global database and conduct the signal detection worldwide. The data sources for signal detection have been specified as the CanSinoBIO's own databases and the publicly available data bases. However, no safety data information is included in the post-authorization section about the data that have been collected, such as pregnancy reports, fatal cases, or potential interactions. The applicant should consider national and international Good Pharmacovigilance (GPV) guidelines for an adequate implementation of these in all WHO regions.

As part of the routine pharmacovigilance activities the monitoring of adverse events (AEs) of interest are listed in annex 1, this list considers facial paralysis, Guillain-Barre Syndrome, and neurological disorders, Transverse myelitis, Encephalitis, Acute disseminated encephalomyelitis (ADEM), Multiple sclerosis, Bell's palsy, Arthritis (rheumatoid, polymyalgia, reactive), Myocarditis/Pericarditis, Thyroiditis, Cerebrovascular events, Immune thrombocytopenia, Thromboembolic events and thrombosis with Thrombocytopenia Syndrome (TTS), anxiety, reactogenicity following vaccination among others, and all serious adverse events.

CanSinoBIO is committed to submit the post-marketing individual case safety reports (ICSRs), the Periodic summary safety reports, safety report in clinical studies and the Monthly Summary Safety Report (MSSR)

to WHO. The MSSR will be compiled to provide timely and continuous benefit risk evaluations. Topics covered by monthly summary safety reports will include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g., pregnant women);
- Interval and cumulative number of reports per High-Level Term (HLT) and System Organ Class (SOC);
- Summary of the designated medical events;
- Exposure data based on distributed doses stratified by global regions;
- Changes to reference safety information and actions in the interval, and current CCDS;
- Ongoing and closed signals in the interval, including a summary of their evaluation; Reviews of signals identified during the period or of safety topics identified by HAs will be addressed in the MSSR;
- AESI reports – summaries of reported cases of all AESI and RMP safety concerns: report numbers and relevant cases. If a disproportionality increased ratio is detected, a further evaluation of the concern will be presented as deemed applicable;
- Fatal reports – numbers and relevant cases (considering co-morbidities and frailty), further evaluation of the concern will be presented as deemed applicable;
- Data on medication errors will be included only if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered warranted (e.g., changes to the PI; DHCP); otherwise, this data will be included with the (six-monthly) periodic safety update report (PSUR).
- Risk/benefit considerations.

MSSR submission complements the submission of 6-monthly PSURs. The need and frequency of submission of such reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6-monthly submissions).

The applicant is requested to implement appropriate methods to ensure adequate traceability. It is not clear whether these traceability enhancements will be applied to shipments through COVAX.

The applicant is considering only China and one study in Argentina to collect AEs in low- and middle-income countries (LMICs), even when the vaccine has been deployed in other countries or regions. Adequate pharmacovigilance activities and data collection are important, especially as limited data is available from clinical trials and post-authorization information collected to date.

The applicant did not mention how to monitor and evaluate the impact of emerging SARS-CoV-2 variants (such as Delta, Omicron, or others that may appear in the future) on the effectiveness of Convidecia™, nor their intention to discuss with WHO in case changes are planned to the vaccine to address this issue.

4.2.5.2 Additional pharmacovigilance activities

In the previous RMP version 1.1, CanSinoBIO considered additional pharmacovigilance activities, four interventional and one non-interventional studies are planned or ongoing to address the following:

- Global multicenter randomized double-blind placebo-controlled trial of Ad5-nCoV vaccine with an adaptive design (NCT04526990). Safety concern: Anaphylaxis, elderly, ADE (Antibody dependent enhancement), long-term safety data and effectiveness. Ongoing.

- Randomized double-blind placebo-controlled trial of Ad5-nCoV vaccine. Safety concern: safety in children under 18 years old. China. Ongoing.

- Local single center trial of lot-to-lot consistency of Ad5-nCoV in adults. Safety concern: Anaphylaxis, elderly and long-term safety data. China. Ongoing.

- Local single center trial of immune-bridging and lot-to-lot consistency of Ad5-nCoV in different age groups. Safety concern: Children and adolescents long-term safety data. China. Ongoing.

- Local multicenter safety surveillance study of Ad5-nCoV vaccine use in mass population and special population. Safety concern: Anaphylaxis, pregnant and breastfeeding women, elderly patients with immunocompromised patients with autoimmune or inflammatory disorders, patients with other significant concomitant diseases. China. Planned.

Non-interventional studies are planned to evaluate effectiveness and safety in LMIC. The study NCT04526990, *Global multicenter randomized double-blind p*lacebo-controlled trial of Ad5-nCoV vaccine with an adaptive design, is the pivotal phase 3 trial. The objectives of this study are: efficacy, safety and immunogenicity (mentioned in the document Appendix 2.3-Clinical independent expert report). However, in the RMP is also included long-term safety and effectiveness in addition to the objectives mentioned above, which is not adequate with the current protocol. CanSinoBIO is requested to design a different protocol to evaluate effectiveness and long-term safety, it is possible that this new proposal could include thrombosis events.

In the RMP version 1.2 CanSinoBIO considered additional pharmacovigilance activities, interventional and non-interventional studies are planned or ongoing to address as the following:

- Global multi-center randomized double-blind placebo-controlled trial of Ad5-nCoV vaccine with an adaptive design. Phase III. Safety concern addressed: Anaphylaxis, pregnancy, patients with comorbidities, ≥60 years of age, vaccine-associated enhanced disease (VAED), long-term safety data and effectiveness. Ongoing. Global, including Russia, Pakistan, Argentina, Chile, and Mexico.

- Phase IIb trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older, living with HIV. Phase IIb. Safety concern addressed: In immunocompromised population living with HIV. Ongoing. Argentina.

- Randomized double-blind placebo-controlled trial of Ad5-nCoV vaccine. Phase IIb. Safety concern addressed: Use in pediatric population <18 years of age Ongoing. China.

- Randomized double-blind trial to study the lot-to-lot consistency of Ad5-nCoV vaccine. Phase III. Safety concern addressed: Anaphylaxis and long-term safety data. Ongoing. China.

- Clinical Trial of Immunobridging and lot-to-lot Consistency of COVID-19 Vaccine (Ad5-nCoV) in Different Age Groups. Phase III. Safety concern addressed: Long-term safety data. Ongoing. China.

- A Phase IV Non-Interventional Enhanced Active Surveillance Study of adults (age 18 and above) vaccinated with COVID-19 Vaccine (Ad5-nCoV) CTR20212335. Phase IV. Safety concern addressed: Anaphylaxis, use during pregnancy and while breastfeeding, use in individuals ≥60 years of age with comorbidities or chronic diseases, use in patients with comorbidities (e.g., hypertension, diabetes, chronic neurological disease, cardiovascular disorders). long-term safety, impact of the emergence of variants on vaccine efficacy/effectiveness and safety. Ongoing. China.

- The Single-center, Open-label Phase I Clinical Trial of Booster Vaccination of Adenovirus Type-5 Vectored COVID-19 Vaccine in Healthy Adults Aged 18-60 Years. Phase I. Safety concern addressed: Long-term safety and interaction with other vaccines or drugs (Interchangeability or sequential use with other vaccines). Ongoing. China.

- Study on Sequential Immunization of Inactivated SARS-CoV-2 Vaccine and Recombinant SARS-CoV-2 Vaccine (Ad5 Vector) Phase IV. Safety concern addressed: Interaction with other vaccines or drugs (Interchangeability or sequential use with other vaccines). Ongoing. China.

- Study on Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (Ad5 Vector) in Elderly Adults. Phase IV. Safety concern addressed: Use in individuals ≥60 years of age Interaction with other vaccines or drugs (Interchangeability or sequential use with other vaccines). Ongoing. China.

- Study of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults aged 18 years and above previously received one dose of Sputnik V. Phase IV. Safety concern addressed: Interaction with other vaccines or drugs (Interchangeability or sequential use with other vaccines). Ongoing. Argentina.

The objective of the study CTR20212335 is *To evaluate the incidence and relative risk of safety concerns and AESIs.* However, it is addressed effectiveness as part of the safety concerns and the protocol was not submitted therefore it is not clear the design or methods. CanSinoBIO is requested to submit a proposal to evaluate effectiveness in different WHO regions and the protocol to evaluate long-term safety, that also include thrombosis events.

4.2.6 Risk minimization activities

In general, the routine risk minimization activities are sufficient to manage the safety concerns of the vaccine. The applicant is encouraged to consider developing educational materials aimed at minimizing

the risk of immunization errors, such as printed posters or guides, in addition to providing information with the Summary of Product Characteristics (SmPC) in all WHO regions.

Although other vaccines using human type 5 adenovirus showed inconsistent results regarding a potential increased risk of acquisition of HIV infection in men who practice active anal intercourse with men living with HIV, there is currently no evidence that Convidecia is related to that risk. Notwithstanding that, the applicant is requested to mention in the SmPC this potential risk, and to recommend the use of condoms in vaccinated individuals.

4.2.7 Conclusion

The risk benefit assessment is favourable. The applicant was requested to include additional activities to monitor and collect information of AEs, in low- and middle-income countries (LMICs) of certain regions. The applicant includes Argentina as part of the additional pharmacovigilance activities. A global pregnancy registry needs to be considered to collect the information in this population.

The post-authorization experience information needs to be included in detail, such as fatal cases, seriousness of AEs, pregnancies reports, spontaneous abortions, cases of ectopic pregnancy, premature cases, Guillain Barre cases etcetera, as it is mentioned in the Appendix 2.3-Clinical independent expert report.

5. Outcome of review

5.1. Quality

The PEG concludes that the EUL application contains the essential information required for the listing, in compliance with the granularity required for an EUL dossier. As a result of rounds of questions and answers, the applicant produced additional technical details, especially in the control of the drug substance and the drug product.

Manufacturing sites have been inspected and were found GMP-compliant, a decision that was communicated to the EUL applicant in an inspection closing letter dated 1 March 2022. The process, materials, containers, standards, and control tests have been described in detail. The product has been characterised and stability studies have already been initiated. In general, the overall level of regulatory compliance is deemed acceptable. The applicant has adequately addressed the issues raised in two rounds of questions (30 November 2021 and 7 February 2022) and through communications with the applicant via email when further clarification was needed.

Raw materials are sufficiently described and controlled. The cell bank system and virus bank system were extensively tested and qualified. Critical process parameters were identified, and the drug substance and drug product processes were appropriately validated. Comparability analyses were performed at the two manufacturing scales (perfusion at 50L and 800L) of the drug substance and the drug product batches used in confirmatory clinical trials.

The drug substance and drug product manufacturing processes and process controls are described in detail. The manufacturing site have passed the GMP compliance inspection by the regulatory authority (NMPA) of the producing country.

The drug substance and drug substance specifications proposed by the applicant are deemed acceptable. Analytical methods for release and stability testing were described in detail. Non-compendial methods were properly validated. Reference standards have been described.

Container closure systems of drug substance and drug product are properly qualified (including extractables / leachable testing).

The lot-to-lot consistency was evaluated by using batches of drug product manufactured at 800L commercial scale perfusion process.

The currently proposed shelf lives for the drug substance (6 months, 2 - 8°C) and drug product (12 months, 2 - 8°C) are supported by real time/real conditions stability studies. The proposed shelf-lives are deemed acceptable under the EUL procedure. Studies are on-going and any extension of the shelf-life for the drug substance and the drug product should be justified by the corresponding real time data and submitted to WHO through a variation procedure. The occurrence of an out of specification (OOS) during these studies should be investigated and communicated to WHO.

A quality related complaint should trigger an immediate and thoroughly investigation, and any required action should be communicated to the WHO.

As a result of the evaluation of the EUL application, a series of recommendations are issued. These recommendations must be addressed by the applicant in correspondence with the timeline provided each case. In the event that the final recommendation is to list the vaccine under the conditions of the EUL procedure, these recommendations would constitute post EUL commitments, which will be followed by the PEG.

5.2. Inspection

The site inspection was carried out at CanSinoBIO and deficiencies of varying severity were identified, documented and categorized according to criticality and impact on GMP compliance.

The inspection revealed no critical deficiency, 9 major deficiencies and 14 other deficiencies. These non-compliances included but were not limited to the major deficiencies presented below:

Major deficiencies identified during the inspection.

1. The sterile filtration of the drug substance
2. The design of the filling line for the aseptic filling of the vaccine
3. The air flow pattern studies
4. The setup of the filling machine
    - The gowning of the aseptic operators
    - Aseptic practices and procedures
    - The visibility of the critical aseptic operations in some aseptic rooms

5. The connections to ensure the sterility of the products
    - The validation and controls of the aseptic connection by welding
6. The environmental monitoring program
7. The validations and qualifications
    - Vials washing machine
    - PW system and WFI system
8. The process of reviewing and approving the essential document produced for validation and qualification purposes
9. Pharmaceutical quality system

The manufacturer was provided with a detailed inspection report listing the non-compliances with a request to propose and undertake corrective and preventative action (CAPA) to address these deficiencies.

Subsequently, CanSinoBIO has undertaken remedial actions to address the issues listed in the inspection report. The actions taken and proposed to be taken to correct the deficiencies have been reviewed by the WHO PQT Inspection Team and found satisfactory. Following the review, the PQT Inspection Team recommended that the site can be considered to be compliant with the standards of GMP published by the WHO.

The CanSinoBIO was officially informed on 1 March 2022 by WHO on its GMP compliance status and acceptance for the following activities:

- Manufacture of drug substances and finished bulk vaccines.
- Aseptic filling and packaging into small volume containers of axenic vaccine.
- Analytical, biological, microbiological and animal testing of drug substance and other raw materials associated with intermediates and finished vaccines.

5.3. Clinical

This clinical assessment raised a series of queries and comments from the reviewers on different aspects of the nonclinical and clinical submitted evidence, as well as on issues related to the RMP. Two rounds of nonclinical and clinical questions were submitted to CanSinoBIO, and the clarifications and additional information required were provided.

From the clinical point of view the PEG recommends that an EUL may be granted by WHO to Convidecia™ for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals from 18 to 59 years of age. As with other COVID-19 vaccines, protection is higher against severe forms of COVID-19. Vaccine efficacy for individuals 60 years and over is very imprecise and not convincing from the available clinical trial data. Vaccine efficacy was shown for individuals with “any comorbidity” and for those with hypertension. There is no clinical evidence of efficacy against variants of concern (VOCs) of the SARS-CoV-2. Regarding VOCs, CanSinoBIO claims that a study conducted by the National Institutes for Food and Drug Control (NIFDC), which is a WHO Collaborating Centre for Drug Quality Assurance showed that

Convidecia™ neutralized VOCs, including the Delta variant, whereas no data was still available regarding the Omicron variant.

Duration of protection has so far been demonstrated only for a few weeks, however, 6-month follow-up data of an extension of the phase III clinical trial, in which the former placebo group received one dose of Ad5-nCoV vaccine will only be available after this EUL meeting. The Ad5-nCoV vaccine was shown to be effective against symptomatic COVID-19 and COVID-19 pneumonia in a case-control study conducted in China after an outbreak caused by the Delta variant.
Changes in the RMP and in the product, as pointed out in this report, need to be made.

The following commitments should be agreed upon by CanSinoBIO as a necessary condition for the granting of an EUL for Convidecia™.

1. The applicant should submit to WHO the final reports of the ongoing and already completed clinical trials (that were not yet submitted), once they become available. These reports should include long-term immunogenicity data whenever available. (The WHO International Standard for the evaluation of neutralizing and binding antibody responses should be used).
2. The applicant should agree with changes in the package insert as addressed in section 6. Technical considerations" of this document.
3. The applicant should present a plan to assess whether Convidecia™ could also be indicated for use in individuals 60 years of age and older, individuals with comorbidities, immunocompromised individuals (including people living with HIV), and in pregnant/lactating women. This can be done by interventional and/or observational studies, conducted by CanSinoBIO and/or (independently or associated) by other institutions such as universities and Ministries of Health. The presentation by the applicant of draft protocols with information about when, where and how this information is expected to be obtained, and with clear timelines for their execution, is required.
4. The RMP should also include/address the following:
   - Safety specifications:
     - Potential risks: text should be aligned with the table in section 3.4.3, and *programmatic errors* should be added.
     - Missing information: text should be aligned with the table in section 3.4.3, and *Interchangeability or sequential use with other vaccines* and *impact of the emergence of variants on vaccine efficacy/effectiveness and safety, and* Male HIV+ (MHSM unprotected) should be added.
   - Pharmacovigilance plan.
   - The applicant is requested to present the proposal for additional pharmacovigilance activities for vaccine safety and for effectiveness in different WHO regions. A global pregnancy registry needs to be considered to collect the information in this population.
   - Risk minimization activities.
   - The applicant should implement educational support measures to be implemented at country level in all WHO regions.

In addition, in light of the evidence of vaccine escape of emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of Omicron and other variants of concern (VOCs) that may appear in the future, on the effectiveness of Convidecia™ and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

6. Technical considerations

6.1. Vaccine characteristics

Pharmaceutical form

Convidecia™ (Ad5-nCoV-S recombinant) is a solution for injection.

Description

One dose of Ad5-nCoV vaccine contains 3.5 $\times 10^{10}$ VP - 6.0 $\times 10^{10}$ VP Ad5-nCoV as active ingredient.

The product is colourless or slightly white sterile liquid for injection which is filled in 2 ml glass vials. A single dose vial contains 0.5 mL Ad5-nCoV vaccine in a 2 mL glass vial, while a three-dose presentation contains 1.5 mL (three doses, 3 × 0.5 mL) of Ad5-nCoV vaccine in a 2 mL glass vial.

The vaccine does not contain components of animal or human origin.

Qualitative and quantitative composition

The active ingredient of Convidecia™ is the replication-defective recombinant human type 5 Adenovirus expressing S protein of SARS-CoV-2.

The formulation of the vaccine includes excipients like mannitol, sucrose, polysorbate 80, sodium chloride, magnesium chloride, N-(2-Hydroxyethyl) Piperazine-N'-(2-ethanesulfonic acid) (HEPES), glycerin and water for injection.

Please, refer to section 1.2.1 of this report.

6.2. Special precautions for storage and handling

Convidecia™ does not contain any preservatives therefore vaccine vials should be used immediately after opening or as soon as practically possible, always within 6 hours or at the end of the immunization session, whichever comes first. The vaccine should be stored at 2℃ to 8℃, even after the opening of the vaccine vial. Any unused vaccine at the end of the immunization session should discarded. Where a full 0.5 mL dose cannot be extracted, the remaining volume should be discarded. Pooling of excess vaccine from multiple vials is contraindicated.

Before use, health care provider must check whether the packaging container, label, appearance, and expiration date meet the requirements. A vaccine vial should not be used if damage or crack is observed, foreign particulate matter, spots, stains, scratches on the outer surface of the vaccine container, unclear label, expired vaccine, or abnormal appearance.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. Use a separate 23G or 25G, 1.5-inch needle and syringe to extract the liquid from the vial for administration for each person.

6.3. Indication, warnings and contraindications

[**4.1 Therapeutic indications]**
This Ad5-nCoV vaccine is indicated for active immunization of individuals aged 18 years and older for the prevention of the coronavirus disease, COVID-19, caused by SARS-CoV-2.
The use of the vaccine should be in accordance with the local official recommendations.
Comments
1. Only the first sentence should be kept but the indication should be limited for individuals from 18 to 59 years of age.
2. Refer to the "Ad5-nCoV vaccine" as Convidecia™.

[**4.3 Contraindications]**
(1) Allergic reaction to any active ingredient, inactive ingredient and substances used in the manufacturing process of Ad5-nCoV vaccine or similar vaccines.
(2) Severe allergic reactions to vaccines in the past (such as acute allergic reactions, angioedema, dyspnea, etc.).
(3) Uncontrolled epilepsy and other progressive neurological diseases, and history of Guillain-Barré syndrome.
(4) Pregnant and lactating women.
Comments
1. Refer to the "Ad5-nCoV vaccine" as Convidecia™.
2. There is no basis to contraindicate this vaccine for individuals with previous severe allergic reactions to vaccines in general.
3. Pregnancy and lactation should not be an absolute contraindication. See [4.6 Fertility, pregnancy and lactation]

[**4.4 Special warnings and precautions for use]**
(1) The protection persistency of the Ad5-nCoV vaccine has not yet been established. Necessary self-protection measures against COVID-19 still should be taken after vaccination.
(2) People suffering from acute diseases, acute-outbreak period of chronic diseases, severe chronic diseases, allergies and fever should take precautionary measures. If necessary, vaccination of Ad5-nCoV should be postponed after doctor's evaluation.
(3) Cautionary use for diabetic patients and those with history of convulsions, epilepsy, encephalopathy or mental illness or family history.
(4) Cautionary use for those with a history of asthma.
(5) As with other intramuscular injection, Ad5-nCoV vaccine should be given with caution to individuals with thrombocytopenia or any coagulation dysfunction or to persons on anticoagulation therapy, since intramuscular injection may cause bleeding or bruising.
(6) The safety and efficacy data for people with impaired immune function (such as malignant tumors, nephrotic syndrome and acquired immune deficiency syndrome, AIDS) are limited. Those people should be vaccinated based on individualized considerations.
(7) Those who received immune globulin injection should be vaccinated at an interval of more than 1 month.
(8) Given that the relationship between the vaccination of human type 5 adenoviral vector and the risk of HIV infection is not yet clear, Ad5-nCoV should be used with caution in people with high HIV exposure.
(9) No data are available on the efficacy of the Ad5-nCoV vaccine in people with SARS-CoV-2 infection history at this point.
(10) Same as other vaccines, this Ad5-nCoV vaccine may not produce 100% efficacy in the vaccinated population.
Comments

1. Refer to the "Ad5-nCoV vaccine" as Convidecia™.
2. Regarding point (8), suggested text: "Given the evidence from studies with other vaccines using the human type 5 adenovirus vectors of increased risk of acquisition of HIV infection in men who practiced active anal intercourse with men living with HIV, use of condoms is strongly recommended for these individuals to be vaccinated with Convidecia ™.
3. Point (9) should be deleted, as it might induce individuals with previous SARS-CoV-2 infection to consider vaccination unnecessary.

6.4. Posology and method of administration

[**4.2 Posology and method of administration]**
This Ad5-nCoV vaccine should be administered by trained healthcare professional.
Posology
Individuals 18 years of age and older
The vaccine course of the Ad5-nCoV vaccine consists of single dose of 0.5ml for one person.
Elderly population
The safety and efficacy data in people aged 60 years and above are limited.
Pediatrics population
The data in pediatric population are limited.
Method of administration
Ad5-nCoV vaccine is for intramuscular injection in the deltoid muscle of the upper arm.
For instructions of administration, see section 6.6.
Comments
1. Refer to the "Ad5-NCoV vaccine" as Convidecia™.
2. In "Posology" the text should read "Convidecia™ is administered as a single-dose of 0.5 mL by intramuscular injection only".
3. In "Elderly population" the text should read "Vaccine efficacy in people aged 60 years and above have not yet been established"
4. In "Pediatric population" the text should read "Vaccine safety and efficacy in children and adolescents have not yet been established".

6.5. Fertility, pregnancy and lactation

[**4.6 Fertility, pregnancy and lactation]**
(1) Women of childbearing age: The data collected in clinical trials for women who have unintended pregnancy after Ad5-nCoV vaccination is very limited. The available data are not sufficient to assess the risk of adverse pregnancy outcomes (including spontaneous abortion) after vaccination with Ad5-nCoV.
(2) Pregnant or lactating women: The clinical data of Ad5-nCoV vaccine in pregnant and lactating women are limited.
(3) Fertility
No direct or indirect harmful effects have been found based on the reproductive toxicity study in animals.
Comment
Suggested text, aiming at standardizing information among listed COVID-19 vaccines:
Pregnancy
Limited experience exists with use of Convidecia™ in pregnant women. There is currently no evidence available of direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of Convidecia™ in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
Breastfeeding
Unknown is whether Convidecia™ is excreted in human milk.

Fertility

There is currently no evidence available from animal studies of direct or indirect harmful effects with respect to reproductive toxicity.

6.6. Interaction with other medicinal products and other forms of interaction

[4.5 Interaction with other medicinal products and other forms of interaction]

(1) Simultaneous vaccination with other vaccines: No clinical trial performed for simultaneous vaccination with other vaccines.

(2) Concomitant use with other drugs: No data are available on the effect of other drugs on the immune response of Ad5-nCoV, such as immunosuppressants, chemotherapeutics, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, etc.

For people who received or are receiving drug therapy or other vaccines, professional physician consultation is required to avoid possible drug interactions.

Comment

1. Refer to the "Ad5-nCoV vaccine" as Convidecia™.

6.7. Safety profile

[4.8 Undesirable effects]

CanSinoBIO's proposed package insert provides (in section 4.8) the safety information for Convidecia™ split into two subsections: 'Summary of adverse reactions in clinical trials of Ad5-nCoV vaccine' (4.8.1) and 'Detailed adverse reactions in clinical trials of Ad5-nCoV vaccine' (4.8.2), the latter split into 'Phase I and II clinical trials in China' and 'International phase III clinical trial'. The text is long and it is not copied in this report.

Comments

1. Refer to the "Ad5-NCoV vaccine" as Convidecia™.
2. A 'Post-marketing experience' subsection should be included focusing on adverse events not observed in the clinical trials and/or observed with different frequency. This should be based both on the Chinese and in the international experience, although such distinction should only be stated if relevant (e.g., if indicative of relative to ethnicity).

This subsection should mention the suspected cases of thrombosis and thrombocytopenia syndrome (including the case of immune thrombocytopenia considered as possibly related to the vaccine in the causality assessment), Guillain Barre syndrome and anaphylaxis,

7. Monitoring of performance of the vaccine in the field

7.1. Vaccine efficacy/effectiveness and safety Monitoring

CanSinoBIO relies on a passive adverse event following immunization (AEFI) surveillance system carried out in China and in countries where Convidecia™ has been approved and started to be distributed to obtain post-authorization information about this vaccine. This AEFI surveillance covers a large number of individuals, and so far about 25% of the reports come from China. CanSinoBIO needs to conduct observational and interventional studies as additional pharmacovigilance activities in order to obtain additional vaccine effectiveness and safety data, particularly for individuals 60 years of age and older, and those with comorbidities, given that such evidence will not come from the clinical trials that were part of the clinical development program of this vaccine. These activities should not be limited to China and need to be obtained from low- and middle-income countries (LMICs) from different regions.

Evidence of vaccine efficacy or effectiveness needs to be produced from interventional or observational studies to support the indication of Convidecia™ in individuals with different comorbidities and

immunocompromised individuals (including people living with HIV), and its safety in pregnant/lactating women.

Additional information, on the co-administration of Convidecia™ and other vaccines, particularly influenza vaccine (given that both vaccines are administered in campaigns) will be welcome. CanSinoBIO also needs to clearly explain how they are going to monitor and evaluate the effect of emerging SARS-CoV-2 variants on the effectiveness of Convidecia™. A clear commitment from CanSinoBIO to conduct such monitoring and evaluation is expected.

Given the low neutralizing antibody levels observed after primary immunization with Convidecia™ it is likely that homologous or heterologous boosters will be necessary over time, what should be demonstrated by clinical data.

7.2. Programmatic aspects

Programmatic suitability incl. MDVP and VVM

The vaccine does not bear a VVM. It complies with WHO Multidose Vial Policy, as stated in the proposed WHO Product Information.

The vaccine contains no preservative. Therefore, after first puncture store at 2°C to 8°C and use within 6 hours or at the end of the immunization session, whichever comes first.

International shipping

At the time of producing this report, the validation of the packaging configuration intended for international shipping (post EUL commitment) – as per the new WHO shipping guidance - was not yet concluded. The cold chain monitoring device (Libero CS) that will be used for international shipping (COVAX supply) is a WHO prequalified device.

The proposed packaging configuration for international shipping has the following characteristics:

Number of doses	Vials in secondary box	Doses in secondary box	Secondary box dimensions (cm)			Secondary box volume (cm^3)	Volume per dose
			H	L	W		
1	40	40	4.4	15.6	9.5	652.08	16.30
3	40	120	4.4	15.6	9.5	652.08	5.43

8. SAGE recommendations

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by

SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

SAGE issued interim recommendations on the use of the CanSinoBIO Ad5-nCoV-S vaccine (Convidecia™) at its plenary meeting on 4-7 April 2022, which were subsequently endorsed by the Director-General of WHO, and published https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad5-nCoV-Convidecia) on 19 May 2022. The recommendations are based on a double-blind, randomised, international, placebo-controlled phase 3, clinical trial (NCT04526990) in adults aged 18 years and older was conducted in Argentina, Chile, Mexico, Pakistan, and Russia. The study involved 18 363 vaccinated and 18 354 unvaccinated participants and took place from September 2020, and the endpoint of 150 COVID-19 cases was reached in January 2021, i.e., before the emergence of Delta and Omicron variants. The study included adults above 60 years of age and persons with co-morbidities. In addition, immunopersistence and booster data were analysed (NCT04568811), as well as a homologous vs heterologous booster study (NCT04892459).

The intended use of the vaccine is in persons aged 18 years and above, without an upper age limit, using a one-dose schedule. Booster vaccinations should be considered 4-6 months after completion of the primary immunization, in accordance with WHO's prioritization of highest and high-risk populations. Ad5-nCoV vaccine may be used as a booster dose following a completed primary series using any other EUL COVID-19 vaccine. The Ad5-nCoV booster following a primary series with the inactivated COVID-19 vaccine developed by Sinovac (CoronaVac) was associated with higher vaccine effectiveness compared to a homologous CoronaVac booster.

A very rare syndrome of blood clotting combined with low platelet counts, described as thrombosis with thrombocytopenia syndrome (TTS) has been reported around 3 to 30 days following vaccination with Ad5-nCoV. In countries with ongoing SARS-CoV-2 transmission, the benefit of vaccination in protecting against COVID-19 far outweighs the risks of TTS.

While developmental and reproductive toxicology studies had been conducted, insufficient data are available from clinical trials to assess the safety in pregnant women.

Increased risk of HIV acquisition has previously been observed with some Ad5 vectored HIV vaccines. Noting that not all Ad5 platforms are the same, among approximately 58 million persons vaccinated with Ad5-nCOV globally, no safety signal was identified in terms of HIV acquisition, however, surveillance was not set up to detect HIV infections. A possible association between Ad5 vectored COVID-19 vaccines and increased susceptibility to HIV acquisition is currently of a theoretical nature and is unproven.

9. Regulatory oversight

The regulatory oversight of Convidecia™ will be carried out by the NMPA the national regulatory authority of the People's Republic of China. The batch release of the vaccine will be performed by National Institutes for Food and Drug Control (NIFDC) of the NMPA.

The NMPA is categorized by WHO as a functional regulatory authority and will be the regulatory authority of reference for the WHO EUL of this vaccine.

10. Benefit/Risk Assessment

According to the WHO Coronavirus (COVID-19) Dashboard (https://covid19.who.int/), the COVID-19 pandemic has caused, as of 29 April 2022, over 510 million confirmed cases of the disease and over 6.2 million deaths. COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population, has become a major cause of morbidity and mortality while vaccines were not available and in the absence of proven specific treatment. In the relatively few countries where COVID-19 vaccines have been administered in large scale and a large proportion of their population have been vaccinated, the occurrence of hospitalizations and deaths by COVID-19 have decreased substantially, particularly in vaccinated individuals. This success has not been observed worldwide, however, given that vaccine coverage has been low or very low in many countries. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility has caused concern. There is also concern about the efficacy of already approved vaccines against future VOCs. The development and availability of effective and safe vaccines may decrease the spread of COVID-19 and its morbidity and mortality.

The vaccine vector is a replication defective Ad5 vector with genetically engineered deletions of the Early (E1 and E3) genes. The vector can only replicate in engineered cells that express the deleted E1 and E3 genes. During abortive replication of Ad5-nCoV in non-complementing cells the inserted SARS-CoV-2 S protein is expressed, secreted from the cell to elicit neutralizing and binding antibodies and cellular responses in vaccinees. The Ad5 vector is derived from a human adenovirus that is known to cause mild disease. As the vector cannot replicate, the risks of infection and vector shedding are minimal. The vector is translated in the cell nucleus so that there is a small, theoretical possibility that DNA may become integrated into the cell chromosomes, with unknown effect. The theoretical risk to a vaccinee attributable to the vector is very small. The SARS-CoV-2 S protein expressed from the insert is non-functional and constitutes no risk to the vaccinee.

The formulation and excipients are generally regarded as safe for vaccine use. The vaccine has been shown to be safe, immunogenic, and protective in multiple animal models. Available data do not indicate a propensity for Convidecia™ to induce ADE in animal models. A concern that is specific to Convidecia™ is the risk of facilitating the transmission of HIV for males who have unprotected active anal intercourse with men living with HIV, which was observed in clinical trials with HIV candidate vaccines which used adenovirus type 5 as a vector [REFERENCE 5]. According to CanSinoBIO, in the Ad5-EBOV [a candidate Ebola vaccine] phase II clinical trial in Sierra Leone (Pan African Clinical Trials Registry, number PACTR201509001259869), in which a total of 500 West African subjects were enrolled, the infection rate of HIV in the participants was not increased when the trial was completed. CanSinoBIO claims that this finding is reassuring regarding the use of Ad5-vectored vaccines in populations with high prevalence of HIV infection.[11] The issue of the use of Convidecia™ in men living with HIV will continue to be followed up as part of the RMP.

[11] Buchbinder SP, McElrath MJ, Dieffenbach C, Corey L. Use of adenovirus type-5 vectored vaccines: a cautionary tale. Lancet 2020; 296: E68-E69. https://doi.org/10.1016/S0140-6736(20)32156-5. (Published online October 19, 2020).

This vaccine can be compared with the only other COVID-19 vaccine listed for emergency use by WHO that requires a single dose, which is also from a non-replicating virus platform, but that uses Adenovirus 26. The vaccine efficacy estimates for adults and the safety profile of both vaccines are similar, although the concern about HIV transmission in males seems specific for vaccines which use adenovirus 5 as vector. Regarding the increased risk of TTS, only suspected but no confirmed cases of thrombosis with thrombocytopenia, a rare condition associated with COVID-19 vaccines with non-replicating adenoviruses, have been observed so far to be associated with the use of Convidecia™.
Continuous monitoring of Convidecia™ for this adverse reaction is needed.

Immunogenicity evaluation showed relatively high seroconversion rates for neutralizing and virus-binding antibodies, although with very low titers. There is little data on persistence of antibody levels, although it is likely that they would decrease over time as observed with the other listed COVID-19 vaccines. Immunogenicity is shown to be reduced but still higher than after placebo in individuals with baseline Ad5-specific antibodies. Efficacy data from the phase III study conducted in countries with Ad5 seroprevalence above 30% suggests that this does not affect efficacy of the vaccine, especially again severe disease. It will be however important to monitor vaccine efficacy in countries with high Ad5 seroprevalence. There is also little data on the immunogenicity and efficacy against VOCs. Data from a case-control study in China conducted after an outbreak of COVID-19 caused by the Delta variant indicate that Convidecia™ is moderately protective against symptomatic COVID-19 and COVID-19 pneumonia. No evidence from clinical trials exists for protection in immunocompromised individuals (including people living with HIV). No safety data is available for pregnant women and for comorbidities, especially in older or frail individuals, who may be more at risk of severe COVID-19. The need for homologous or heterologous boosting should be studied given the expected decrease in neutralizing antibodies in vaccinated individuals over time that have been observed with the already authorized COVID-19 vaccines.

11. Conclusion

Considering the public health need to halt COVID-19 morbidity and mortality and to continue immunizing the world's population to the largest extent possible, the introduction of new vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on the available evidence assessed, the PEG considers that sufficient data is available on Convidecia™ to be used during the current pandemic, subject to post-listing commitments as indicated in the below sections

The current clinical evidence supports that the benefits of Convidecia™ in preventing symptomatic COVID-19 outweigh its risks in adults from 18 to 59 years of age. Convidecia™ use in pregnant women should only be indicated where and for whom the risk of COVID-19 clearly outweighs the potential risk associated with the vaccine (e.g., for female health professionals who are likely to have occupational exposure to SARS-CoV-2).

11.1. Quality (CMC) perspective

Level of regulatory compliance

The PEG concludes that the Modules 1, 2 and 3 of the WHO EUL submission contain the essential information to support the EUL application. These modules have been updated as per the responses to the PEG list of questions (2). Manufacturing sites have been inspected and were found GMP-compliant. The process, materials, containers, standards, and control tests have been described in detail. The product has been characterized and stability studies have been initiated. In general, the overall level of regulatory compliance is deemed acceptable. The applicant has adequately addressed the issues raised in the different round of questions.

Overall conclusion

The DS and DP manufacturing processes and process controls are described in detail. The manufacturing site for production of the drug substance and drug product at CanSinoBIO with address in 185 South Avenue, TEDA West District, 300462 Tianjin, China have valid GMP certificates.

Raw materials are sufficiently described and controlled. The cell bank system and virus bank system were extensively tested and qualified. Critical process parameters were identified, drug substance and drug product processes are validated. Batch and comparability analyses were performed and submitted which indicated that the product from commercial scale is comparable to the batches used in clinical trials.

The drug substance and drug product specifications proposed by the applicant are deemed acceptable, and the analytical methods for release and stability testing were described. Non-compendial methods were properly validated. Reference standards have been described.

Container closure systems of drug substance and drug product were properly qualified (including extractables / leachable testing).

The currently proposed shelf lives for the DS (6 months, 2 - 8°C) and DP (12 months, 2 - 8°C) are supported by real time/real conditions stability studies of batches manufactured at different scales. The proposed shelf lives are deemed acceptable.

In conclusion, based on the review of the quality data provided by the applicant, PEG has a positive opinion for the listing of Convidecia™ (Ad5-nCoV-S recombinant) under the EUL procedure.

Perspective

Because of the available limited data at accelerated and stressed storage conditions, the EUL holder is asked to provide complementary stability data, as this becomes available. Any extension of the shelf-life for the drug substance and drug product should be justified by the corresponding real time data and submitted to WHO through a variation procedure.

As for any variation altering the conditions for which this EUL is granted, vaccine batches will not be procured by UN procuring agencies or by COVAX if variations are not previously assessed and approved by both, the National Regulatory Authority of the vaccine producing country (NMPA) and by WHO.

In the event of any out of specifications (OOS) and quality related complaints, a thoroughly investigation should be triggered immediately, and any required action should be communicated to the WHO.

The EUL applicant should addressed the following recommendations:

1. A 40-vials packaging configuration is proposed to further optimize the packaging for international shipment. The shipping validation protocol (File No.: TRV-001-P01, Approved date, 2021.11.30) is prepared for COVAX supply with 40-vial packaging box. Since at the time of the EUL no vaccine was supplied with the 40-vial packaging box, the validation plan for 40 vials has not yet been performed. The EUL applicant is preparing the validation internally and commits to complete this before the end of May 2022. WHO expects receiving the validation report after the TAG EUL meeting (Q9 and Q10 of the assessment report).
2. An updated international shipping validation protocol was submitted on 12 March 2022 for a packaging plan of 1200 vials and the insulated aircraft box. The EUL applicant will conduct the shipping validation according to a new designed protocol and submit the results to WHO as soon as this is executed.
3. CanSinoBIO should start working on the introduction and implementation GS1 standards. In this regard, liaising with UN supply agencies such as UNICEF is highly recommended.
4. The EUL applicant refers studies on biophysical characteristics of Ad5-nCoV Drug Substance under stress conditions, e.g., at 37℃, are currently on-going. Various analytical techniques, including SDS-PAGE, LC-MS, Dynamic Light Scattering (DLS), Transmission Electron Microscope (TEM), Size Exclusion Chromatography- HPLC (SEC-HPLC) are used to evaluate the relationship of structure and function. CanSinoBIO commits to complete the studies and submit the final report to WHO after the TAG EUL meeting (Q29).
5. Considering the limited data, some specifications were calculated and set by mean ± 2.58 SD method, based on available batch data at the time of the EUL submission. The applicant agrees to assess the specification of aggregation in 6 months' time, with more batches, and calculate the data with defined tolerance intervals (e.g., Q33, Q38). In this regard, the company is asked to provide as a formal Post EUL commitment, a number of batches rather than a timeframe (half-year), to establish tolerance intervals for specifications.
6. In order to ensure consistent quality over the product life cycle, the EUL holder should adequately monitor and review the finished product potency specifications as additional data become available. Specification updates should be communicated and submitted via a variation procedure. In any case, firmly link the potencies of finished product with batches used in confirmatory phase 3 clinical studies.
7. Out of specifications (OOS) during the stability programme should be communicated expeditiously.
8. The EUL applicant commits to revise the expression of Residual Host Cell DNA together with Residual Host Cell Protein from ng/VP to ng/dose. The internal documents revision will be completed after the TAG EUL meeting (Q50).
9. Stability studies updates, including results of characterization tests, should be provided post-EUL for drug product lots that are being included in the stability programme, upon availability of data for 12, 18 and 24 months and completion of the study. Interim updates every 6 months should be provided beginning the date of the listing of the Convidecia™.
10. Considering that stability studies of the reference standards are in progress in line with the stability protocols, the EUL applicant is committed to keep WHO informed of the stability of the reference standards in accordance with the defined timeline of the protocol.

11. The EUL applicant is asked to compile and submit a complete new EUL dossier, considering the different sections that were updated due to the evaluation process. Updated sections must be properly identified and cross-referenced to the corresponding list of questions.

11.2. Clinical perspective

The following commitments should be agreed upon by CanSinoBIO as a necessary condition for the granting of an EUL for Convidecia™.

1. The applicant should submit to WHO the final report of the ongoing and already completed clinical trials (that were not yet submitted), once they become available. These reports should include long-term immunogenicity data whenever available, including against VOCs. The WHO International Standard for the evaluation of neutralizing and binding antibody responses should be used).
2. The applicant should agree with changes in the package insert as addressed in section "6 Technical considerations" of this document.
3. The applicant should present a plan to assess whether Convidecia™ could also be indicated for use in individuals 60 years of age and older, individuals with comorbidities, immunocompromised individuals (including people living with HIV), and in pregnant/lactating women. This can be done by interventional and/or observational studies, conducted by CanSinoBIO and/or (independently or associated) by other institutions such as universities and Ministries of Health. The presentation by the applicant of draft protocols with information about when, where and how this information is expected to be obtained, and with clear timelines for their execution, is required.
4. The RMP should also include/address the following:
    - Safety specifications:
        - Potential risks: text should be aligned with the table in section 3.4.3, and *programmatic errors* should be added.
        - Missing information: text should be aligned with the table in section 3.4.3, and *Interchangeability or sequential use with other vaccines* and *impact of the emergence of variants on vaccine efficacy/effectiveness and safety,* Male HIV+ (MHSM unprotected) should be added.
    - Pharmacovigilance plan.
    - The applicant is requested to present the proposal for additional pharmacovigilance activities for vaccine safety and for effectiveness in different WHO regions. A global pregnancy registry needs to be considered to collect the information in this population.
    - Risk minimization activities.

In addition, in light of the evidence of vaccine escape of emerging SARS-CoV-2 variants, the applicant is requested to closely monitor and evaluate the impact of Omicron and other variants of concern (VOCs) that may appear in the future, on the effectiveness of Convidecia™ and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.