RECOMMENDATION FOR AN EMERGENCY USE LISTING OF

COVID-19 VACCINE (VERO CELL), INACTIVATED SUBMITTED BY SINOVAC

Abstract

COVID-19 Vaccine (Vero Cell), Inactivated - CoronaVac™, was submitted to the World Health Organization (WHO) for evaluation under the Emergency Use Listing (EUL) procedure by Sinovac Life Science Co., Ltd., P.R. China (Sinovac). This vaccine is a whole virion vaccine inactivated with Beta-propiolactone (BPL). The purified inactivated SARS-CoV-2 antigen bulk is adsorbed with Aluminum Hydroxide as the adjuvant.

The EUL for CoronaVac™ application has been submitted with two presentations; 0.5mL in Prefilled syringe (PFS) and 0.5mL Vial. However, Sinovac requested on 8 April 2021 that only the Vial presentation will be available for UN agencies/COVAX facilities.

The vaccine received conditional marketing approval by the National Medical Products Administration (NMPA), P.R. China for one year starting 9 February 2021. A list of 21 countries that have been granted an approval for emergency use of the product was provided by Sinovac on 8 March 2021.

Sinovac conducted two phase 1/2 studies in adults 18-59 years of age and 60 years of age and older and one study bridging antibody response of pilot and commercial scale lots. In addition, three phase 3 randomized, placebo-controlled clinical trials in Brazil, Indonesia and Turkey were conducted. The vaccine efficacy estimates in these trials varied substantially from one study to the other, the point estimates being 50.65%, 65.30% and 83.50%, for Brazil, Indonesia and Turkey respectively. Vaccinated participants have been shown to develop binding and neutralizing antibodies 14 days after the second dose. Findings from the phase 1/2 studies indicated that a higher antibody response was observed after a 4-week interval between the two doses. However, Sinovac decided to test a 2-week interval in phase III studies, claiming that this allowed immunization within a shorter period of time. The vaccine was shown to be safe in all the clinical studies. A SARS-CoV-2 challenge study in non-human primates and the available safety evidence from clinical trials and post-emergency use approval do not indicate a risk of vaccine-associated enhanced disease/ vaccine-associated enhanced respiratory disease (VAED/VAERD), however this will need to be monitored further.

The manufacturing site of CoronaVac™ was inspected by the WHO inspection team from 15 to 18 February 2021. The majority of the good manufacturing practices (GMP) issues raised by the WHO and international GMP team inspectors were satisfactorily addressed. The manufacturing site is located in Daxing District, Beijing, P.R. China.

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

1 Introduction

1.1 Background

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.

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).

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.

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint[2] aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

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[3]. Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response

[1] https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research
[2] https://apps.who.int/blueprint-brochure/
[3] 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.

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[4].

The current global COVID-19 public health emergency underscores 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 [5] and the new coronavirus (nCoV) epidemiology is closely monitored. The various technology platforms that are developed based on 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 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 year, 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 ending 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.

1.2.1 The SINOVAC COVID-19 Vaccine

CoronaVac™ vaccine is a whole virion vaccine inactivated with BPL, SARS-CoV-2 virus from the working seed lot is grown in Vero cells. After propagation, the virus is harvested, inactivated, purified and sterile filtered as vaccine bulk. The COVID-19 Vaccine bulk is adsorbed with Aluminum hydroxide, formulated to become final bulk, which is then filled into vials or syringes to become COVID-19 Vaccine.

The finished product vaccine is a single dose with no preservative, 0.5 mL aqueous (milky-white) suspension which can be deposited due to precipitation and can be dispersed by shaking. No clumps/particles shall be found after shaking. The CoronaVac™ vaccine is designed to be stored and transported at 2-8°C, protected from light and freezing must be avoided.

[4] 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.

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

The vaccine is for intramuscular injection and the recommended schedule for immunization is 2 doses with an interval of 2 to 4 weeks. The vaccine is indicated for prevention of symptomatic Covid-19 in individuals 18 years of age and older.

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 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 still expected to complete the development of the product and submit application for licensure and prequalification.

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 sole prerogative to allow the emergency use of a product under EUL within their country.

2 Assessment process

The COVID-19 Vaccine manufactured by SINOVAC, was assessed under the WHO EUL procedure based on the review of data on quality, safety, efficacy, risk management plan (RMP) and programmatic suitability performed by WHO vaccine prequalification experts and evaluators from national regulatory authorities (NRAs) 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 NRA of reference for WHO for CoronaVac™ submission is the NMPA. The information package submitted to WHO followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD).

An international inspection team of experts from WHO, South Africa and observers from the respective medicine regulatory authorities of China i.e. NMPA and BMPA (Beijing Medicinal Product Administration) performed an onsite GMP inspection at Sinovac Life Sciences Co., Ltd., manufacturing facilities in Daxing District, Beijing, P.R. China.

3 Scientific Review

3.1 Quality overview

The development of CoronaVac™ includes the development of starting materials, intermediate bulk, final Bulk, formulation process as well as studies conducted to optimise the adsorption with Aluminum Hydroxide as adjuvant. COVID-19 vaccine (Vero Cell) is a new biological product and there is no specific

international published Pharmacopoeia and no existing reference specifications which could be directly referred to.

Sinovac stated that the development of the manufacturing process of the CoronaVac™ is based on the time-tested vaccine development platform of Sinovac within which a SARS-CoV candidate vaccine proceeded to phase I clinical study developed in the year of 2004. In addition, multiple inactivated vaccines have been developed using the same platform, such as the Hepatitis A vaccine already prequalified by WHO. The manufacturing process of COVID-19 Vaccine Sinovac was established by manufacturing of multiple lab-scale and pilot-scale batches to determine the manufacturing parameters and test the robustness of the process for scale-up. Comparability studies was performed on the process with scale-up from pilot to commercial scales by maintaining the main quality attributes and the process parameters in order to achieve optimal production consistency.

Sinovac adopted the WHO TRS 993 IPV vaccine as a reference along with other Pharmacopeia requirements such as the Chinese Pharmacopoeia, 2015 and 2020 and European Pharmacopeia as guidance for the manufacturing and quality control of this vaccine. The manufacturing process development has been well identified throughout the CTD dossier (Module 3, Section 3.2.S.2.6 and 3.2.P.2.3 and 3.2.A) for manufacturing process of starting materials and intermediates; Cell cultivation, Virus Propagation, Inactivation, and Purification to produce sterile filtered bulk formulation using Aluminum hydroxide as Adjuvant for Antigen adsorption, and filling.

Drug Substance

The Drug Substance/vaccine bulk is manufactured at Sinovac Life Sciences Co., Ltd. (Daxing Site, China).

- The vaccine bulk is derived from inoculation of working seed lot of SARS-CoV-2 virus (strain CZ02 W-202002) into the Vero cells Passage 146.
    - Vero cells are propagated in cell factories (CF) CF10, CF40, and 3 bioreactors
    - Virus propagation in the 3rd bioreactor at 700Kg
- The post-cultivation processes are: virus harvesting, inactivation with BPL 12-24 hours inactivation at 2-8°C and complemented with formaldehyde treatment for 4±0.5 hours at 2-8°C, purification (clarification and concentration by ultrafiltration using 300kDa membrane), two enzymatic cleavage steps with Benzonase to remove host Vero cell DNA, two chromatographic steps for optimal antigen recovery and final filtration with 0.22µm.

SARS-CoV-2 Strain and Seed Lots:

- WXY strain was selected among four candidate strains (China) based on the optimal immunogenicity profile (The immunogenicity is compared by detecting neutralization antibody titre in the sera after immunizing mouse and rat). The CZ02 (Passage 1-P1) strain was developed from the WXY strain. Furthermore, the whole genome sequence of Primary Seed (P2), Master Seed Lot (P3) and Working Seed Lot (P5) CZ02-W-202002-01 and CZ02-W-202003-02 of SARS-CoV-2 was investigated and compared using Geneious 11.1.5 software. The analysis results show that the S protein coding region in the nucleotide sequences of P2, P3 and P5, are 100% identical and completely consistent with the published nucleotide sequence of Spike protein coding region of SARS-CoV-2.
    - The virus characterization tests were fully performed by Sinovac except the adventitious test (in-vivo) that was contract tested by Institute of Laboratory Animal Sciences, China

- The established Vero cell bank was tested by Sinovac and by National Institutes for Food and Drug Control (NIFDC) as per Chinese Pharmacopoeia, 2015 for Cell identification, sterility mycoplasma, endogenous and adventitious viruses.

Bulk size:

- Manufacturing process is developed at pilot scale and verified by production of 9 lots of intermediate/bulk. The pilot batch culturing volume was 30-175 Kg and the batch size of the Bulk was ≤20Kg
- The commercial batch culturing volume is 700 Kg and the batch size of the bulk is ≥100 Kg. Thirty six batches of bulk are produced at commercial scale for Process Validation and consistency, the batch size of these batches is ~ 200Kg. The CQA (Critical Quality Attributes) and CPP (Critical Process Parameters) are evaluated for each of the process (Cell culture, Virus propagation, Virus Harvest, Inactivation and Virus Purification.
- Comparability studies for scale up from pilot scale to commercial scale were carried out (also formulation). Specifications and acceptance criteria for critical steps, intermediates and drug substance have been established for COVID-19 vaccine. Both compendial and non-compendial methods were used
- Container closure system
  - Container for virus working seed lot, the container is 125mL Thermo Fisher bottle, made from PETG.
  - The storage volume of Allegro™ Single Use container used in the storage of COVID-19 Vaccine Bulk is 48.8Kg – 52.6Kg (The storage container used for the subsequent formulation step is 50L).
- Stability and proposed shelf life:
  - Tentative shelf life for COVID-19 vaccine bulk is 6 months when stored at 2-8°C. A study is ongoing:
    - Long-term stability data at 2 – 8 °C for up to 9 months (6 Pilot scale lots); 3 months (3 commercial scale lots) are available and within acceptance criteria, stability is ongoing
    - Stability data at accelerated 25°C is acceptable for up to 42 days
    - Stability data at accelerated 37°C is acceptable up to 21 days.

Drug Product

- The formulation of final bulk and production of drug product are processed at Sinovac Life Sciences Co., Ltd., Daxing Site, China (commercial lots).
- The manufacturing process of COVID-19 Vaccine Sinovac consisted of three steps; Aluminum adjuvant preparation, formulation of the final bulk and filling.
  The filling validation was completed for 300L of final bulk with approximately 460K vials. Sterile filtered bulk contains the active ingredient of the inactivated SARS-CoV-2 whole virion as antigen and this is adsorbed with Aluminum hydroxide and formulated to become the final bulk. The final bulk is filled in the vial or syringe to become the finished COVID-19 Vaccine.
  One dose of 0.5mL suspension for injection of COVID-19 Vaccine contains 600SU (Spike Unit) (1µg of Antigen equals to 200SU) as the active ingredient of inactivated SARS-CoV-2 antigen along with the excipients; 0.225mg of Aluminum Hydroxide, Sodium chloride 4.5mg and Phosphate buffer solution 0.0025 mmol.

- Based on the release specification, the potency of the final bulk should be ≥0.5 compared with the reference vaccine, and the post-desorption antigen content should be ≥60% of the indicated content in Finished Product.

Control of critical steps:

- The critical step during the formulation process of COVID-19 Vaccine is the adsorption of SARS-CoV-2 antigen with Aluminum Hydroxyde . Sterility, pH, Antigen adsorption rate and potency are tested. Adsorption rate kinetic study was carried out and results revealed that the adsorption rate of antigen in the final bulk is >93.79% (release specification ≥85%)

Process validation:

- Process validation was conducted on three commercial batches of final bulk for formulation and filling steps considering the evaluation of CPPs and CQAs. The 300-400Kg scale was fully validated.

Specifications:

- Specifications and acceptance criteria have been established for COVID-19 vaccine. Both compendial and non-compendial methods were used
- Batch analysis results are provided for multiple batches of Pilot and commercial scale Final Bulk and Finished Product

Impurities:

- The impurity profile for the COVID-19 Vaccine were considered for both process-related and product-related impurities, as per ICH guidelines Q3B and Q6B. Most of the process related impurities were studied at level of bulk and controlled further in the vaccine. For product related impurities, several batches of vaccine were evaluated for impurities sourced from the degradation of active ingredient. No protein degradation product is generated in the Aluminum adsorbed COVID-19 Vaccine. The test results analysis from analytical methods used (Blue staining and mass spectrum) revealed that the protein presented in the three batches of vaccine bulk are SARS-CoV-2 specific S protein, N protein and M protein.
- In-house specifications are established for all process related impurities in the bulk (i.e. Protein impurities, Bovine serum albumin, Vero cell protein, Vero cell DNA, non-restriction endonuclease, β-propiolactone, bacteria endotoxin and free formaldehyde). Impurity removal rate from pilot and commercial scale batches of bulk are well demonstrated with average removal rate exceeding 99.69%.

Container closure system:

- Final bulk: container closure system (PALL or Satorius) with storage capacity 200L
- Finished product: 2-mL vial for single dose of 0.5mL and 0.5mL/PSF (pre-filled syringe)

Stability and proposed shelf life:

- The tentative shelf-life of the Final Bulk is determined as 12 months at 2-8°C. However, the available long-term stability data is 6 months from three commercial lots. The stability is ongoing:

- Accelerated and stress stability study have been completed at 25°C and 37°C for 56 days and 42 days, respectively. Data support 56 days at 25°C and 21 days at 37°C.

- The tentative shelf life of the Drug Product vaccine is 24 months at 2 to 8°C. However, the available stability data at 2 to 8°C submitted so far from Pilot lots and Commercial lots are 12 months and 6 months, respectively.

    - Accelerated and stress stability study have been completed at 25°C and 37°C for 56 days and 42 days, respectively. Data supports 42 days at 25°C and 21 days at 37°C.

3.2 Inspection overview

An international inspection team of experts from WHO, 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: Sinovac Life Sciences Co., Ltd.

Address of manufacturing site: Daxing Biomedicine Industrial Base of Zhongguancun Science Park, Daxing District, Beijing.

Date: 15 to 18 February 2021

Vaccines: The presentation is 1ml pre-filled syringes with 0.5 ml/syringe. A 2ml vial presentation containing 0.5 ml of vaccine is also available. Both presentations are mono dose.

Production Line: The inspection focused on the production and control of COVID-19 vaccine Sinovac in the following buildings:

- COVID-19 vaccine (Vero Cell), inactivated bulk workshop.
- Formulation, filling and packaging workshop.
- Storage area - raw material and excipients warehouse, packaging material warehouse.
- Warehouse area - Cold room of final products.
- QC labs.

The inspection focused on the quality management system of the site and the manufacturing and control of the COVID-19 vaccine Sinovac Life Sciences/CoronaVac 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

- Pharmacovigilance
- Self-inspection
- Quality audits and suppliers' audits and approval
- Personnel
    - Personal hygiene
- Documentation
- Batch Release Process
- Lot Summary Product review

2. Production system
    - The manufacturing process of COVID-19 vaccine
    - Seed lots and Cell banks
    - Drug substance and adjuvant
    - Formulation and Filling
    - Visual inspection, Labelling and Packaging
    - Storage
    - Process validation
    - Sterile filtration
    - Validation of the aseptic processing through media simulations
    - Extractables and Leachables
    - Destruction of rejected or expired products
3. Premises and Equipment system
    - The manufacturing and testing areas associated with COVID-19 vaccine
        - Storage of seeds and cell banks
        - Cell culture area
        - Vaccine bulk workshop
        - Formulation area
        - Filling and packaging for pre-filled syringes presentation
        - Filling and packaging for vials presentation
        - Testing area
        - Warehousing area for final product, raw material and excipient and packaging material
    - Waste management
    - Qualification and validation
    - Water system and pure steam
    - Heating, Ventilation, and Air Conditioning (HVAC) System
    - Steam sterilization by the autoclaves
    - Vial washing machine
    - Depyrogenation Tunnel
    - Filling and stoppering machine
    - Capping machine
    - Visual inspection equipment
    - Cleaning and disinfection
    - Warehouse (temperature and RH mapping and control)
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 in order of severity. Manufacturers are provided with a timeline to respond to the report. During the final review, WHO considered the Corrective and Preventive Actions (CAPA) proposed and undertaken by the manufacturer.

3.3 Non-clinical overview

Eleven non-clinical studies were conducted to assess the efficacy, immunogenicity and safety of COVID-19 Vaccine Sinovac. These were conducted in non-human primates (protective efficacy and safety), mice, rats, rabbits and guinea pigs

EFFICACY: A SARS-CoV-2 challenge study was conducted in 16 NHPs (low and high vaccine dose, 0/14- or 0/7/14-day schedules) plus 8 unvaccinated controls. Reduced or no viral replication was observed in the lungs, with no evidence of enhanced disease.

IMMUNOGENICITY: Neutralizing and binding antibody levels were determined following different COVID-19 Vaccine formulations (with and without adjuvant) were administered intraperitoneally in mice and intramuscularly in rats at different points in time and using different immunization schedules. Alum-adjuvanted formulations were shown to be more immunogenic than non-adjuvanted formulations at the same dosage. Adjuvanted formulations of dosages 300 SU/dose, 600 SU/dose and 1200 SU/dose, and two-dose immunization schedules were chosen to be tested in the phase 1 clinical trial.

SAFETY: No important findings were observed in the safety assessment, which included several toxicology (single- and repeat-dose toxicity, systemic active anaphylaxis, and local tolerance) studies. A reproductive and developmental toxicity study was conducted in Sprague-Dawley (SD) rats. No significant adverse reaction was observed on the fertility of parental female and male rats, and on pregnant and lactating females. No embryo-fetal developmental toxicity, teratogenicity or effect on the growth and development of F1 pups was observed.

3.4 Clinical overview

The evidence to support the CoronaVac™ comes from interim analyses of two phase 1/2 studies conducted in healthy participants aged 18-59 years of age (Corona 01) and 60 years of age and older (Corona 02), both conducted in China, from a bridging study (Corona 05), also conducted in China, and from three phase 3 clinical trials in adults conducted in Brazil (Corona 04), Indonesia (Corona 06) and Turkey (Corona 07). Study Corona 03, conducted in children and adolescents 3-17 years of age, did not provide data for this application.

In the phase 1/2 studies different vaccination schedules and dosages were studied in these clinical trials: the medium or high dosage vaccine were administered at two- or three-dose emergency vaccination schedule (days 0, 14 or days 0, 14, 42), or two- or three-dose routine vaccination schedule (days 0, 28 and days 0, 28, 56) in the study Corona 01; low, medium or high dosages (300 SU/0.5ml, 600 SU/0.5ml and 1200 SU/0.5ml, respectively) of vaccine were administered in a two-dose routine vaccination

schedule (days 0, 28) in the Corona 02 study. Persistence of immune responses at 6-months were provided for the two age groups. The phase 3b bridging clinical trial (Corona 05) was conducted in individuals aged ≥18 years; in this study the dosage and vaccination schedule of the phase 3 efficacy clinical trials were adopted. Corona 04 also assessed immunogenicity in older adults aged 60 years and above, compared to adults 18-59 years of age.

Corona 04 was designed to enroll 13,060 participants, including 11,800 adults aged 18-59 years and 1,260 elderly 60 years and older. Within each age group, subjects were randomly assigned to vaccine or placebo group (Aluminum Hydroxyde, at same concentration as used in the vaccine) in a 1:1 ratio. The participants in the vaccinated arm received two 0.5 mL doses according to a Day 0-Day 14 schedule. All the participants were healthcare workers; the study allowed the inclusion of participants with underlying health conditions that were well controlled comorbidities. The primary endpoint case definition recommended by the NMPA was virologically confirmed (nasopharyngeal swab and/or saliva specimen PCR positive) symptomatic cases of COVID-19.

Corona 06 is a phase 3, observer-blind, randomized, placebo- controlled study conducted in 1620 clinically healthy adults aged 18-59 years enrolled at six sites in Indonesia. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness, any confirmed or suspected immunosuppressive or immunodeficient state were exclusion criteria; the study also excluded pregnant and breastfeeding women. Participants were randomly assigned to vaccine or placebo group in 1:1 ratio to either the study vaccine or placebo . Participants of the vaccine group were further randomized in a 1:1:1 ratio to receive three different lots. Immunization regimen included two 0.5 ml doses on Day 0 and Day 14. A total of 1620 participants were enrolled into the study between August and October 2020.

Corona 07 is also a phase 3 randomized placebo-controlled study performed in Turkey. Very little data has been provided about this study in the rolling submission. Additional data about 10214 participants became available by WHO request, and provided as a draft, non-peer reviewed manuscript. Based on this manuscript, there were 6646 and 3568 participants, respectively, in the vaccine and the placebo arm, all aged 18-59 years, with no evidence of current or previous COVID-19, and they were followed up for a median of 43 days. About 10% of the participants were healthcare workers.

3.4.1 Vaccine efficacy

The Corona 04 clinical trial was initiated on July 21, 2020 and the efficacy analysis presented in this report is based on data lock date of December 16th, 2020, when the median follow-up after the second vaccine (or placebo) dose was 73 days. A total of 12,408 subjects were enrolled (vaccine group: 6201; placebo group: 6207) and 9823 subjects were included into the *per protocol* set (PPS) used for the primary efficacy evaluation (vaccine group: 4953; placebo group: 4870). Out of a total of 12,396 subjects included in the ITT analysis set, 11,764 were adults aged 18-59 years and 632 elderly 60+ years and older. There was no significant difference between demographic and other baseline characteristics of study subjects in the vaccine and placebo groups. Mean age of the entire study population was 39.5 years. About 55% presented comorbid conditions (obesity, 22.4%, cardiovascular disease, 12.8%, diabetes, 3.5%).

Out of the 253 confirmed cases accrued among the PPS population (9,823 subjects), 85 cases were reported in the vaccine group (incidence density: 11.03/100 person-years) and 168 cases in the placebo group (incidence density: 22.34/100 person-years). The efficacy of the vaccine was 50.65% (95% CI 35.94-

61.98). Based on the correction of alpha value spent in the interim analysis, the 95.38% CI was 35.66-62.15. This primary analysis of the primary endpoint met the statistical criterion of success as the lower bound of the CI was > 30%. Sensitivity analyses based on three slightly different case definitions generated very similar vaccine estimates ranging from 51.24% (95% CI: 36.92, 62.30) to 54.10% (95% CI: 40.13, 64.81). Only 6 cases were reported among the 419 subjects in the elderly group 60+ years of age, 2 and 4 cases in the vaccine and placebo groups respectively. Subgroup analysis of the primary endpoint in the population with concomitant disease showed efficacy of the vaccine against COVID-19 for subjects with co-morbidities of 48.93% (95% CI: 26.57, 64.49) comparable to that among subjects without concomitant disease 52.40% (95% CI: 30.75, 67.28). However, a VE of 74.9% (95% CI 53.7, 86.4) was estimated for participants with obesity, based on 13 and 50 cases, respectively, and the vaccinated and placebo arms.

As of December 16th 2020, 38 cases with onset 14 days after dose 2 had a WHO score of ≥3, 5 and 30 cases among vaccine and placebo recipients, respectively for a VE estimate of 83.7 (95% CI 58.0, 93.7) . Ten cases with onset 14 days after dose 2 had a WHO score of at ≥4, 0 and 10 cases among vaccine and placebo recipients, respectively for a VE estimate of 100.00% (95% CI: 16.9, 100.00).

The interim efficacy analysis of Corona 06 was conducted on the entire study population (n = 1620) for which detailed demographic and other baseline characteristics of the two entire study groups were not available in the report submitted. By the data cut-off of January 9, 2021, 7 and 18 cases of symptomatic confirmed COVID-19 infection occurring at least 14 days after the second dose were reported among the vaccine and placebo group, respectively. Based on this primary endpoint, vaccine efficacy was estimated as 65.30% (95% CI 18.95, 85.10). There were no severe COVID-19 cases, nor COVID-19 related death.

For Corona 07, as of 23 December 2020 data for a total of 1322 participants who have been followed up from 14 days after having received two doses of vaccine (752) or placebo (570) were available. Three cases of COVID-19 were observed in the vaccine arm and 26 in the placebo arm. Vaccine efficacy was estimated to be 91.25% (95% CI: 71.25, 97.34). Vaccine efficacy at a later stage, when data on 10030 participants (6559 in the vaccine arm and 3471 in the placebo arm) and 41 cases (9 and 32, respectively) were available, was estimated as 83.50% (95% CI 65.42, 92.12). At that point in time, based on 6 hospitalized COVID-19 cases in the placebo group and 0 in the vaccine arm, vaccine efficacy against hospitalized COVID-19 cases was estimated to be 100% (95% CI 20.33, 100). Vaccine efficacy was also shown in participants with obesity; VE was estimated to be 77.3% (95% CI 28.8, 82.7) and 100% (95% CI 40.8, 100.0), respectively, for participants with body mass index (BMI) of 25-29.9 (4 cases in the vaccine arm vs 11 in the placebo arm) and ≥30 (0 vs 8).

Vaccine effectiveness data obtained from independent studies (not sponsored by Sinovac) conducted after vaccine deployment in Chile and Brazil, were provided to the TAG-EUL as pre-print, non-peer-reviewed manuscripts. A prospective national cohort in Chile, including 10.2 million people aged 16 years or more, affiliated with the public national healthcare system, used data linkage to estimate vaccine effectiveness against symptomatic COVID-19, hospitalization, intensive care admission and death by COVID-19. Adjusted vaccine effectiveness estimates (95% confidence intervals in brackets) as of 1st May 2021 for these outcomes were, respectively, 65.90% (65.17, 66.62), 87.47% (86.70, 88.20), 90.30% (89.10, 91.37), and 86.29% (84.53, 87.85). The figures for individuals ≥60 years of age were very similar, respectively 66.63% (65.40, 67.82), 85.34% (84.27, 86.34), 89.19% (87.63, 90.55), and 86.46% (84.64, 88.07).[6]

A matched test-negative case-control study conducted in Brazil in an area of presumed high P.1 (gamma) SARS-CoV-2 variant prevalence, in which 393 pairs of laboratory-confirmed symptomatic COVID-19 cases

[6] Jara A, *et al*. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile (unpublished manuscript)

were compared to test-negative individuals with similar symptoms (controls), vaccine effectiveness of at least one dose of vaccine was estimated to be 49.6% (95% CI 11.3, 71.4)[7]. A test-negative case-control study, also conducted in Brazil in adults ≥70 years of age, from January 17 to 29 April 2021, in a setting of extensive P.1 (gamma) SARS-CoV-2 variant transmission, compared RT-PCR-confirmed COVID-19 cases with controls who had similar symptoms and had a negative RT-PCR for SARS-CoV-2, matched by age category, sex, race, municipality, prior COVID-19 status, and date of RT-PCR testing. A total of 7950 matched pairs, with mean age of 76 years were included. The overall adjusted vaccine effectiveness estimate ≥14 days after the 2nd dose was 41.6% (95% CI, 26.9, 53.3). Stratified analysis revealed adjusted vaccine effectiveness estimates of 61.8% (95% CI 34.8, 77.7), 48.9% (95% CI 23.3, 66.0), and 28.0% (95% CI 0.6, 47.9), respectively, for the 70-74, 75-79, and ≥80 years of age groups.[8]

3.4.2 Vaccine safety

The safety database consisted of 8840 participants who received the Sinovac COVID-19 vaccine, 94% of whom received the approved dose/schedule. The safety database for the ≥60 age group was of 422, 632, 260 and 37, respectively, for the Corona 02, Corona 04, Corona 05, and the Chilean clinical trial).

In the Corona 01 study, conducted in adults aged 18-59 years of age, in the Emergency schedule (D0, D14) the overall rate of adverse event (AEs) was 38.1% in the placebo group. The incidence of vaccine-related AEs (adverse reactions - ARs) was 32.64% (47/144) in the medium dosage group, 35.42% (51/144) in the high dosage group and 17.86% (15/84) in the placebo group, respectively, with no significant difference among the three groups. A large majority of ARs were solicited and all occurred within 7 days after vaccination. The frequencies of AEs related to vaccine were slightly higher after the first dose than after the second dose (21.53%, 24.31% and 14.29%, in the medium dosage, high dosage and placebo, respectively compared to 14.58%, 17.48% and 8.33%, respectively). Most ARs were grade 1 by severity, and only one subject in the high dosage group report one grade 3 hypersensitivity.

The most frequently reported System Organ Class (SOC) class was ”General disorders and administration site conditions”, with frequencies of 27.08% (39/144), 31.94% (46/144) and 15.48% (13/84) in the medium dosage, high dosage and placebo arms respectively. The most frequently reported ARs by PT were pain, followed by fatigue. Pain was reported by 20.14% (29/144), 25.00% (36/144) and 8.33% (7/84) in the medium dosage, high dosage and placebo arms respectively and fatigue by 4.17% (6/144), 6.94% (10/144) and 8.33% (7/84) respectively. All other ARs by PT were reported in less than 5.0% in three groups.

In the participants who received the routine schedule (D0, D28) the overall incidence of AEs was 25.69% (37/144), 27.08% (39/144) and 25.30% in the medium dosage, high dosage and placebo, respectively. The incidence of ARs was 18.06% (26/144), 18.75% (27/144) and 16.87% (14/83), respectively, with no significant difference among the three groups. Most ARs were solicited and all occurred within days after vaccination. ARs were more frequent after the first dose than after the second dose (17.36%, 16.67% and 14.46% post dose 1, respectively compared to 6.38%, 7.75% and 3.57% post dose 2, respectively). All AR were grade 1 and grade 2 by severity. The most frequently reported ARs SOC class was “general disorders and administration site conditions”, reported in 16.67% (24/144), 16.67% (24/144) and 15.66% (13/83)

[7] Hitchings MDT, *et al*. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: a test-negative case-control study. *medRxiv* preprint. DOI: https://doi.org/10.1102/2021.04.07.21255081 (Posted on 7 April 2021).

[8] Ranzani OT, *et al*. Effectiveness of the CoronaVac vaccine in the elderly population during a P.1 variant-associated epidemic of COVID-19 in Brazil: a test-negative case-control study. *medRxiv* preprint. DOI: https://doi.org/10.1101/2021.05.19.21257472. (Posted on 21 May 2021]

of the medium dosage, high dosage and placebo group, respectively. The most frequently reported PT were pain, followed by fatigue. The incidences of pain were 10.42% (15/144), 11.11% (16/144) and 10.84% (9/83), respectively, and fatigue were 6.94% (10/144), 2.78% (4/144) and 2.41% (2/83), respectively. All other adverse reactions by PT were reported in less than 5.0% in three groups.

Three serious adverse events (SAE) were reported by 3 subjects, all in the emergency schedule group during the phase 2; they include one case of hemorrhoids, one non-infectious cystitis and one soft tissue injury of left leg. All were considered as not related to vaccination by investigators. There was no case of ADE.

In the Corona 02 study (elderly ≥60 years of age), only the routine schedule was evaluated. The overall incidence of AEs was 31.00% (31/100), 30.40% (38/125), 35.77% (44/124) and 32.88% (24/73) in low dosage, medium dosage, high dosage and placebo groups, respectively. ARs were reported in 20.00% (20/100), 20.00% (25/125), 21.95% (27/124) and 20.55% (15/73) respectively, with no significant difference among the four groups. The large majority of the ARs were solicited and occurred within 7 days after vaccination. All ARs were grade 1 and grade 2 by severity. There was no difference in the AEs between the three vaccine dosage groups. No dose related increase in the frequency of AEs was noted between the first and the second dose.

The most frequently reported ARs categorized by SOC was “general disorders and administration site conditions”, with the incidences of 18.00% (18/100), 17.60% (22/125), 17.07% (21/123) and 8.22% (6/73) in the four groups, respectively. The most frequently reported PT of AR was local pain which was reported in 11.00% (11/100), 11.20% (14/125), 8.94% (11/123) and 4.11% (3/73) of the low dosage, medium dosage, high dosage and placebo group, respectively. All other ARs by PT were reported in less than 5.0% of subjects. Headache and mucocutaneous eruption were slightly higher in high dosage group than in the other groups.

In the Corona 02 study eight SAEs were reported by 7 subjects. They include 4 SAEs in the low dosage group (cholangiocarcinoma (1), liver cancer (1), kidney cyst (1) and hypoxic ischemic encephalopathy (1), 1 SAE in medium dosage group (pancreatitis) and 3SAEs in high dosage group including one subject with artery disease and one with coronary atherosclerosis and hypertension. None of these 8 SAEs was assessed by the investigators to be causally related to vaccination. There was no case of ADE

In the Corona 04, a total of 12,396 subjects were included in the first dose safety set (SS1), 6196 and 6200 in the vaccine and placebo group, respectively, and 10,934 subjects in the second dose safety set, 5481 and 5453, respectively. There was no significant difference in demographic and other baseline characteristics between the vaccine and placebo group.

AEs related to vaccination were more frequently reported among vaccine recipients, 77.1% versus 66.37 % ($p<0.0001$) and were predominantly solicited AEs. Unsolicited ARs were reported among 36.83% and 35.76% of the vaccine and placebo groups, respectively ($p=0.2177$). There was no difference in the frequency of immediate AEs noted in 7.42% and 6.67%, respectively. The majority of ARs occurring within 7 days after vaccination and AEs within 7 days of vaccination were noted in 74.38% and 61.72%, of the vaccine and placebo group, respectively ($p<0.0001$). The most common local AE was vaccination site pain reported in 60.93% and 33.02% of vaccine and placebo recipients, respectively ($p<0.0001$), followed by local swelling in 5.87% and 2.13%, respectively ($p<0.0001$). Most common systemic AEs were headache (50.11% and 51.36%, respectively), fatigue (18.83% and 17.32%, respectively) and myalgias (14.19% and 12.61%, respectively). There was no significant difference in systemic AEs between the groups. There were no significant differences in the frequency of Grade 2 and Grade 3 ARs between the groups. Grade 4 ARs were noted in 0.05% and 0.03% in the vaccine and placebo group, respectively.

ARs after the first dose were noted in 65.49% and 55.45%, in the vaccine and placebo group, (p<0.0001) and after the second dose in 60.10% and 44.34%, respectively (p<0.0001) indicating that there was no dose related increase in reactogenicity. ARs among the age group 18-59 years were 78.25% and 67.28%, in the vaccine and placebo group, respectively (p<0.0001); among the age group 60+ years the incidence rates were 63.61% and 59.49%, respectively, suggesting a lower reactogenicity among the elderly. There was no difference in the rates of AEs related to vaccination between vaccine recipients with co-morbidities (78.36%) and those without co-morbidities (75.54%).

As to SAEs, two deaths, one in each study group, were reported, one due to cardiopulmonary arrest, the other to suicide. Both deaths were considered not related to the vaccination. A total of 64 subjects reported 67 SAEs, 34 and 33 events in the vaccine and placebo group, respectively. The overall incidence of SAEs was 0.52% (64/12,396). There was no notable imbalance in the incidence of SAEs by SOC except for that of COVID-19 in the placebo group (0.15%) and vaccine group (0.03%) (p = 0.0384). All SAEs were not considered related to vaccination. No case of VAERD was reported among the vaccine group.

In the Corona 06 study the incidence rate of AEs within 28 days post dose 2 were 71.6% and 71.1% in vaccine and placebo group, respectively (p=0.912). The incidence rates of solicited AEs were 63.0% and 54.0%, in the vaccine and placebo group, respectively and the rates of unsolicited AEs were 45.0% and 43.7%, respectively. There was no significant difference in the solicited local AEs (50.9% vs 43.7%) between the treatment groups, while solicited systemic AEs were more frequently reported among the vaccine group, 41.9% vs 25.2% (p<0.001). Among the vaccine group the most frequently reported local and systemic AEs were local pain in injection site (33.3% and 30.5% of subjects after first and second injection, respectively) and myalgia (25.2% subjects and 19.6% subjects after first and second injection, respectively). In the placebo group, local pain was reported by 22.2% subjects and 30.1% subjects after first and second injection, respectively and myalgia was reported by 12.6% subjects and 9.0% subjects after first and second injection, respectively. Most AEs were mild in both vaccine and placebo groups. Only one subject had Grade 3 hypersensitivity (urticaria) which occurred at Day 2 after vaccination and recovered at Day 6 after treatment. There was no significant difference in the incidence and intensity of ARs between the participants who received vaccines from the three different vaccine batches.

In the Corona 07 study, safety data of 10214 participants were available for analysis. A total of 3845 AEs, which were short-lived (median 1 day), were observed in 1862 participants. Overall AE incidence was 18.9% and 16.9% in the vaccine and placebo arms, respectively. The majority of the AEs (90.2%) were grade 1 and 87.5% were observed within 7 days of the vaccine administration. Pain at the injection site was the most common local AE (2.4% of the participants of the vaccine arm). Among the systemic AEs, fatigue (8.2%) and myalgia (4.0%) were reported more frequently in the vaccine arm. Eleven SAEs were reported, six of them in the vaccine arm, one of them (grade 3 allergic reaction that resolved uneventfully within 24 hours) considered as possibly related to the vaccine.

Post-authorization passive surveillance data from China (35.8 million vaccine doses distributed), and from Brazil, Indonesia and Chile (about 20 million vaccine doses distributed) have indicated no unexpected safety signals.

3.4.3 Immunogenicity

Corona 01 and 02 studies have shown that this vaccine induces neutralizing antibody after the second dose. However, vaccine induced antibody levels were not compared to a panel of human convalescent sera and these relevant comparative data are missing. Given an acceptable reactogenicity and safety profile, Sinovac decided to conduct phase III studies with the medium dosage, 600SU per 0.5mL dose given according to the emergency schedule, two doses at Day 0 and 14 rather than according to the

routine schedule that was shown to evoke a higher antibody response. In the immune persistence evaluation of Corona 02 study the level of neutralizing antibodies declined significantly after 6 months of follow-up. Seropositive rates and GMTs of the low-dosage, medium-dosage, high-dosage and placebo groups were 12.63%, 17.35%, 22.58% and 2.13%, and 3.1, 3.4, 4.1 and 2.1, respectively, 6 months after whole-schedule vaccination, suggesting that a booster dose may be necessary.

In the Corona 04 study a low seroconversion rate for the N protein was observed, with higher anti-RBD antibody responses in the 18-59 year age group (median of 64.4 BAU/mL vs 0.4 in the placebo arm), compared to those ≥60 years age group (26.0 BAU/mL vs 0.4). Out of a sample of 109 participants tested for neutralizing antibodies, 50% had ≥4-fold increase for all tested SARS-CoV-2 variants (B.1.1.28, P.1 – now called gamma and considered a variant of concern, and P.2, now called zeta and considered a variant of interest, all circulating in Brazil at the time). Thirty-two (71.1%; GMT 64.4) out of 45 participants in the vaccine group were seroconverted to B.1.1.28, 31 (68.9%; GMT 46.8) to gamma, and 36 (80.0%; GMT 45.8) to zeta. The three variants used in the neutralization assays are distinct from the strain which the vaccine originates from.

In Corona 06 (Indonesia) blood samples were taken from a randomly selected immunogenicity subset of 540 participants at Day 0, Day 28 and Day 104 to measure ELISA IgG antibody responses to RBD and neutralizing antibody responses. IgG seroconversion rate at Day 28, i.e. 14 days after the second injection, was 97.48% among vaccine recipients, compared to 5.3% in placebo recipients. IgG antibody GMCs were 220.27, 5181.19 and 1605.90 on day 0, 28 and 104, respectively, compared to 220.37, 223.61, and 229.17 respectively among placebo recipients. Neutralizing antibody seroconversion rate at Day 28, i.e. 14 days after the second injection, was 87.15% among vaccine recipients, compared to 0.0% in placebo recipients. Neutralizing antibody GMTs were 2.00, 15.76 and 7.12 on day 0, 28 and 104, respectively, compared to 2.00, 2.02, and 2.19, respectively among placebo recipients.

Immunogenicity data was available for 1413 participants of the Corona 07 study (981 of them from the vaccine arm); 89.7% of the vaccine arm developed RBD antibodies, compared to 4.4% of the placebo arm. There was a trend of decreasing antibody positivity rate with increasing age. Neutralizing antibodies were determined in 387 participants who had positive RBD antibodies; mean antibody titers ≥1/15 were observed in 356 (92%) of them.

Regarding the lot-to-lot consistency assessment within Corona 06, IgG seroconversion rates at Day 28 were 96.18%, 97.76%, and 98.48% for the three different batches, and IgG antibody GMC were 5093.78, 5421.63 and 5032.34. Neutralizing antibody seroconversion rate at Day 28 was 90.08%, 88.81%, and 82.58% whereas neutralizing antibody GMTs were 15.97, 16.59 and 14.75. Lot-to-lot consistency was considered to be demonstrated.

Corona 05 was divided in two stages. Stage 1 involved 520 healthy adults aged 26-45 years randomized in a 1:1 ratio to receive the medium dosage vaccine (600 SU/0.5 mL) of vaccine either from a commercial scale lot or from a pilot scale lot. In stage 2 a total of 780 participants, including 260 who were 60 years of age or older received two doses of the medium-dosage vaccine at days 0 and 14. Lot-to-lot consistency was demonstrated whereas the neutralizing antibody response was significantly lower in the elderly compared to the other adults. Two weeks after the second dose neutralizing antibody seroconversion rate in the elderly and adult groups were 82.47% and 91.58%, respectively; neutralizing antibody GMT were 11.82 and 18.21, respectively.
Regarding the new SARS-CoV-2 variants of concern, Sinovac conducted a cross-neutralization evaluation of the South African (B.1.351, beta) and the Brazilian (P.1, gamma) variants, which were compared to the

vaccine. The neutralization ability of the serum from individuals vaccinated with COVID-19 Vaccine Sinovac was decreased for both variants compared to the CZ01 strain (1/5.27 for B.1.351 and 1/4.73 for P.1).

3.4.4 Special populations

Results in the elderly and in participants with comorbidities (taken together) are described in the subsections above.

3.5 Risk Management Plan

The RMP submitted by the applicant describes the safety and effectiveness for the purpose of EUL to monitor the vaccine in the different WHO regions.

3.5.1 Product description

Acceptable

3.5.2 Nonclinical information

Acceptable

3.5.3 Clinical information

The clinical information is incomplete. The RMP presented by the applicant doesn't include the summary of the efficacy and safety information with the most relevant findings. Therefore, this section needs to be completed by the applicant and it should include the description of the AEs and the serious cases, that is also missing in the document.

a. Important identified risks:

Sinovac	WHO	Comments
None	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:

Sinovac	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 Sinovac COVID-19 Vaccine (Vero Cell), Inactivated, 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. It will be monitored via routine pharmacovigilance activities and will be presented in each PBRER/PSUR

c. Missing information:

Sinovac	WHO	Comments
Use in pregnancy and lactating women	Use during pregnancy and while breastfeeding	Pregnant and lactating women not included in the clinical trials
Use in immunocompromised patients	Use in immunocompromised patients, including HIV.	This population was excluded from the clinical trials.
Use in elderly ≥60 with uncontrolled chronic diseases	Use in elderly ≥60	Clinical trials in the elderly are on-going at this moment, sufficient safety and efficacy data have not yet been obtained.
Use in patients with important organ impairment	Use in patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Diabetes patients and those with convulsion, epilepsy, encephalopathy or mental disease history or family history are not included in clinical trials and lack relevant information.
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.
	Interchangeability or sequential use with other vaccines	The evidence to support interchangeability or sequential use of Sinovac COVID-19 Vaccine (Vero Cell), Inactivated with other COVID-19 vaccines is still not available.
Use in pediatric population aged from 3 to 17 Years	Use in pediatric population <18 years of age	No efficacy data are available from participants ages <18 years and younger. Phase 1/2 trial is ongoing in China.

Use in patients with autoimmune or inflammatory disorders	Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of Sinovac COVID-19 Vaccine (Vero Cell), Inactivated in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.
Long-term safety	Long-term safety	Long-term safety profile of Sinovac COVID-19 Vaccine (Vero Cell), Inactivated is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information.
	Impact of the emergence of variants on vaccine efficacy/effectiveness and safety	Sinovac should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source.

3.4.4 Pharmacovigilance Plan

The Applicant provides in the RMP a nominal list with the routine pharmacovigilance activities. a detailed description of methods, periodicity, and sources should be included for:

- Monitor of AEs and AEFI (spontaneous reporting)
- Signal detection
- Cold-chain monitoring
- Traceability
- Global ICSR reconciliations

Regional differences for implementation of all those activities should be considered. Also, a monthly safety report should be submitted to WHO with the following information:

1. Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women);
2. Total number of adverse event reports by country, WHO regions and globally;
3. Exposure data stratified by country including any available data on age groups, race, ethnicity, on indigenous populations and remote communities;
4. Changes to reference safety information in the interval;
5. Ongoing and closed signals in the interval;
6. List of adverse events of special interest including the Safety Platform for Emergency vaccines (SPEAC) list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and observed/expected analyses;
7. Fatal reports – numbers and relevant cases, including observed/expected analyses;
8. Vaccination failure / lack of efficacy (including confirmed and suspected cases) reports and vaccination errors (categories according to preferred terms);
9. Potential interaction with other vaccines/concomitant treatments-number and relevant cases;
10. Summary outcomes of some of the routine pharmacovigilance activities for the purpose of rapid signal detection and communication activities. Summary of all ongoing registries and studies in

the six-month scheduled PBRERs, unless a safety signal is identified that requires immediate regulatory action; and

11. Overall risk/benefit assessment.

The spontaneous reporting should be harmonized in most of the countries with the Vigibase platform.

The monitoring of adverse events (AEs) of interest should consider neurological disorders, reactogenicity following vaccination and all serious adverse events, as included in routine pharmacovigilance in the submitted RMP.

Additionally, for traceability, the applicant should describe shipping conditions including automated temperature and location logging; labelling and barcoding (if applicable); and vaccination cards / stickers. The applicant should also describe the appropriate methods to ensure adequate traceability, so that each batch delivered through COVAX can always be traced to COVAX.

Sinovac is considering observational and interventional studies as additional pharmacovigilance activities:

1. Large scale safety observation based on target population (only China)
2. Safety observation based on special population
3. Retrospective study based on pregnant and lactating women
4. Case control study based on sentinel hospitals
5. Study on the safety and immunogenicity of COVID-19 vaccine in HIV-infected people
6. Combined Immunization Research

The applicant is requested to submit a proposal for effectiveness and safety in different WHO regions, including in detail the protocols or detailed protocol synopses. It is necessary to clarify the end point, safety concerns addressed, study design, when those studies are planned, and which sites and countries will be selected.

In addition, the applicant is requested to monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as alpha, beta, gamma and delta, formerly known, respectively, as B.1.1.7, B.1.351, P.1, and B.1.617.2, according to their Pango nomenclature, and others that may appear in the future) on the effectiveness of Sinovac COVID-19 Vaccine (Vero Cell), Inactivated and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

Conclusion:

The applicant is requested to submit an RMP that addresses specific considerations related to LMIC. The applicant is therefore requested to generate the necessary information about safety and effectiveness in the different WHO regions for the purpose of EUL. These recommendations should be integrated in an updated version of the RMP specifically for WHO.

3.4.5 Risk minimization activities

The routine risk minimization activities should be according to the safety profile specifications and the applicant should ensure the feasibility to measure these activities that should be implemented in all WHO regions.

The applicant could consider, to minimize the risk of immunization errors, educational support (for example printed posters / guides / instructional material), establish adequate communication with vaccine responsible programs in the country or any other initiative that could be helpful to avoid or minimize this potential risk.

4 Outcome of review

4.1 Quality

The company provided satisfactory responses to the majority of CMC related recommendations raised from the first round of the CMC assessment. Sinovac provided satisfactory responses to the CMC related issues raised through the rounds of assessment. Sinovac committed to address a few remaining CMC related recommendations. These should be resolved as part of the post-EUL approval, including pending studies identified during the review of dossier. The proposed shelf-life of 24 months is not supported by the available stability data. The stability studies are still ongoing. Only 12 months data at 2 to 8°C are available. Sinovac agreed that additional stability data will be submitted to WHO in timely manner to obtain extension to the shelf life of the Final Product

4.2 GMP Inspection

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

The inspection revealed no critical deficiency, 5 major deficiencies grouping 48 issues, along with 8 other deficiencies grouping 14 minor issues. These non-compliances included but were not limited to the major deficiencies presented below.

Major deficiencies identified during the inspection.

1. The extent and level of validations as well as the controls in place for critical manufacturing processes of sterile filtration were incomplete.
2. The control strategy and control points during the manufacturing process were insufficiently implemented.
3. The qualification, the validation and the management of the media simulations of the aseptic processes were found incomplete.
4. The quality management system was found deficient for the elements below:
    - Quality risk management
    - Change controls
    - Management review (MR)

- Deviation management
- Complaints
- CAPA management
- Self-inspection
- Product recall

5. Poor documentation and record management practices.

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

The Sinovac Life Sciences was officially informed on 28th April 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.

Of importance to note that since several major deficiencies were made during the inspection, WHO wishes to remind the company that the improvements outlined in the corrective measures must robustly be implemented and the improved level of GMP compliance sustained. WHO will therefore verify the effective implementation of the improvements by performing the next inspection of Sinovac Life Sciences operations within 12 months.

4.3 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 Sinovac and most of the clarifications and additional information required were provided.

From the clinical point of view the PEG/TAG recommend that an EUL be granted by WHO to CoronaVac™ for “active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 18 to 59 years of age”. The evidence to support the use of this vaccine comes from the results of the clinical trials and have been confirmed by independent (not sponsored by Sinovac) observational effectiveness studies conducted after emergency use approval of this vaccine.

Additional evidence should be obtained from interventional or observational studies to assess whether CoronaVac™ could also be indicated in individuals 60 years of age and over, those with different

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

Changes in the RMP and product insert, as pointed out in this report, need to be made.

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

1. To provide the final clinical study reports of the ongoing studies (CORONA 01, CORONA 02, CORONA 04, CORONA 06, and CORONA 07) whose interim analyses have been presented as part of the application, as well as of the ongoing clinical trial conducted in Chile that was not included in this application, once they become available.
2. To provide the interim and full reports of the ongoing and planned effectiveness (cohort and test-negative design case-control) studies conducted in Chile, Brazil, Dominican Republic and other countries, independent or Sinovac-sponsored, as they become available.
3. Whenever possible and considered ethical, to encourage participants to remain in the ongoing phase 3 as originally randomized for as long as possible, in order to accumulate long term safety follow-up data after dose 2 of the vaccine.
4. To send WHO monthly safety reports, and Periodic Benefit Risk Evaluation Reports (PBRER) every 6 months in the first year post-EUL, followed by annual reports thereafter.
5. To report the outcome of the cases of pregnancy observed in the clinical studies as part of the PBRER.
6. To investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy/effectiveness of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as alpha, beta, gamma and delta, formerly known as B.1.1.7, B.1.351, P.1, B.1.617.2, according to the Pango nomenclature, and others). This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.
7. To make the changes in the product insert as addressed in section “5 Technical considerations” of the TAG report, including but not limited to: the vaccine indication limited to adults from 18 to 59 years of age; exclusion of pregnant and lactating women as vaccine contraindications; change of the “observation time after vaccination" for “at least 15 minutes” instead of “at least 30 minutes”; change of the text about vaccine use in pregnancy and breastfeeding. The product insert should be revised for technical terminology adequacy.
8. To conduct, within the estimated timelines, or follow up closely (in case of independent studies) studies that aim at providing: a) vaccine effectiveness estimates in people 60+ years of age and with comorbidities (including the S project, in the town of Serrana, Brazil; a study in kidney transplant recipients in Brazil, whose interim report is expected for March 2022; the ongoing Ministry of Health cohort study conducted in Chile); b) vaccine effectiveness and safety study in people living with HIV, currently planned for South Africa; c) safety study in pregnant and lactating women, planned to be conducted in Brazil; d) prevention of severe and fatal cases of COVID-19 (to be addressed by the Chilean cohort study and a test-negative case control study to be conducted in the Dominican Republic; e) vaccine co-administration (with influenza vaccine, in a study in the Zhejiang province, and with influenza and polysaccharide pneumococcal vaccines, to be conducted in the Guangdong province); f) cross-neutralization studies to investigate breakthrough COVID-19 cases in China and overseas. The Sinovac-sponsored studies are

considered additional pharmacovigilance activities. Periodic follow-up reports on these studies should be sent to WHO as part of the PBRER or earlier, whenever appropriate.

9. Regarding the Risk Management Plan, under "safety specifications": a) the text of "identified risks" should be aligned with the table in section 3.4.3, and "anaphylaxis" should be added; b) the text of "potential risks" should be aligned with the table in section 3.4.3, and "programmatic error" should be added; c) the text of "missing information" 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 should be added.
10. Regarding the Risk Management Plan, under "Pharmacovigilance Plan": a) as part of the routine activities, "Traceability and Vaccination Reminder cards" should consider differences between regions or countries and the applicant should submit the tools and process to implement this; b) the manufacturer should clarify how adverse events / safety information will be collected as this may vary depending on different health and pharmacovigilance systems; the clarification must address how the quality of the information will be warranted wherever the vaccine is used; c) the protocols of the studies considered as additional pharmacovigilance activities should be included in the Pharmacovigilance Plan and shared with WHO.
11. Regarding the Risk Management Plan, under "Risk minimization activities", the company should present regional annexes that ensure the correct implementation of risk minimization activities given the differences between regions or countries. These should include: a) guidance on the requirements of the dosing station or facilities, the equipment needed and the training of the dosing staff, specially to attend cases of anaphylactic shock; b) a minimum period of 15-minute of observation after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.
12. In addition to the above, the company is required to: a) report serious adverse events following immunization (within 15 days of receipt of the report); b) report quality complaints from the field for batches supplied; c) report any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA of reference (NMPA); d) report any problems/constraints in production or quality control which might affect the emergency use condition granted to this product.

Sinovac may consider submitting the results of ongoing observational effectiveness studies or any additional supportive clinical evidence, once they are available, to support the extension of the indication of CoronaVac™ for the prevention of COVID-19 in individuals 60 years of age and older.

5 Technical considerations

The technical considerations included in this section are those proposed by the applicant. The TAG and the PEG's considerations are made in the "Comments" after each subsection.

5.1 Vaccine characteristics

CoronaVac™ is an Adjuvanted, Inactivated SARS-CoV-2 whole virion vaccine produced from the inoculation of working seed lot of SARS-CoV-2 virus (strain CZ02 W-202002) into Vero cells. Post inoculation, the harvested virus antigen undergoes inactivation step with BPL and complemented with formaldehyde treatment, purification (clarification and concentration by ultrafiltration), enzymatic

cleavage (Benzonase) and chromatography for optimal antigen recovery and finally sterile filtration to obtain Drug Substance Bulk. The bulk is diluted and adsorbed with Aluminum hydroxide to become the Final Bulk, the Final bulk is filled into vials or syringes as a final container of COVID-19 Vaccine (Vero Cell), Inactivated Vaccine. The vaccine is free of antibiotics and preservatives.

Each vial (or pre-filled syringe) contains 0.5mL of product for intramuscular injection, each dose containing 600SU of inactivated SARS-CoV-2 antigen and 0.225 mg of Aluminum hydroxide adjuvant.

5.2 Special precautions for storage and handling

This product is a single dose vaccine packaged into a vial, 40 vials per box. Store and transport between 2 to 8℃ and protect from light and Do Not Freeze.
The shelf life of the vaccine is tentatively scheduled as 24 months.

Comment:
Available data does not support 24 months shelf life. The approved product shelf life is of the vaccine is 12 months"

5.3 Indication, warnings and contraindications

Indication
CoronaVac is indicated for active immunization against diseases caused by SARS-CoV-2 virus.

Comment
The indication should be for " active immunization to prevent COVID-19 caused by SARS-CoV-2 virus in individuals from 18 to 59 years of age".

Warnings
[Precautions]

1. Due to the insufficient data of protection persistence, necessary protective measures should be taken in line with the COVID-19 epidemic.
2. Due to the insufficient data of efficacy in people aged 60 and above, when use CoronaVac among people aged 60 and above by relevant institutions, the health status and exposure risk of people aged 60 and above shall be considered.
3. This vaccine is strictly prohibited for intravenous injection. There is no safety and efficacy data of subcutaneous or intradermal injection.
4. Before use, check whether the packaging container, label, appearance and validity period meet the requirements or not. Do not use if there are cracks in the glass needle tube, spots, stains and scratches on the outer surface of the glass needle tube, label is not clear or more than the expiration date and abnormal appearance.
5. Avoid expose CoronaVac to the disinfectant during use.
6. This product should be stored at places out of reach of children.
7. Adequate treatment provisions, including epinephrine injection and emergency treatment, should be available for immediate use. Individuals should be observed for at least 30 minutes on site after vaccination.
8. Do not mix with other vaccines in the same syringe.

9. Do not freeze. It shall be administered immediately after open.
10. Patients with acute diseases, acute exacerbation of chronic diseases, severe chronic diseases, atopy and fever should be used with caution; if necessary, delay vaccination after doctor's evaluation.
11. Patients with diabetes, or history of convulsions, epilepsy, encephalopathy or mental illness, or family history of those diseases should be used with caution.
12. Patients with thrombocytopenia or hemorrhagic diseases, intramuscular injection of this product may cause bleeding, so it should be used with caution.
13. The safety and efficacy data of this product on people with impaired immune function (such as malignant tumor, nephrotic syndrome, AIDS patients) have not been obtained, and the vaccination of this product should be based on individual considerations.
14. The injection of human immunoglobulin should be given at least one month interval to avoid affecting the immune effect.
15. No clinical study has been carried out on the evaluation of immune response with other vaccines on the immunogenicity at the same time (before, after or at the same time). Professionals should be consulted when concomitant use.
16. Do not use if there is any adverse reaction of nervous system after inoculation.
17. Like other vaccines, the protective effect may not reach 100% for all recipients.

Comment

Item 7) Observation time after vaccination should be "at least 15 minutes" instead of "at least 30 minutes" in line with SAGE recommendations.

English should be revised for use of adequate terminology.

Contraindications

1. People with history of an allergic reaction to CoronaVac or other inactivated vaccine, or any component of CoronaVac (active or inactive ingredients, or any material used in the process);
2. Previous severe allergic reactions to the vaccine (eg, acute anaphylaxis, angioedema, dyspnea, etc.);
3. People with severe neurological conditions (eg, transverse myelitis, Guillain-Barré syndrome, demyelinating diseases, etc.);
4. Patients with uncontrolled severe chronic diseases;
5. Pregnant and lactating women.

Comments

There is no reason why allergy to other inactivated vaccines (indicated to prevent other diseases) should be a contraindication for the use of Sinovac COVID-19 vaccine. Allergy to other inactivated COVID-19 vaccines may be a contraindication.

"Pregnant and lactating women" should be excluded from the contraindications. (See section on "Fertility, pregnancy and lactation")

5.4 Posology and method of administration

[Administration and Schedule]

Two doses should be administered for primary immunization. The second dose is preferably given 14-28 days after the first dose. 0.5 mL per dose.
CoronaVac should be administered by intramuscular injection in the deltoid region of the upper arm. Shake well before use.
It has not been determined whether this product requires booster immunization.

Comment
No comment.

5.5 Fertility, pregnancy and lactation

[Special Population Medication]

1. Women of childbearing age: the data collected of women with unexpected pregnancy after vaccination from clinical trials are very limited, which is not enough to decide the risk of adverse pregnancy outcomes after vaccination.
2. Pregnant or lactating women: the clinical data of pregnant and lactating women are not available at present.
3. People aged 60 and above: the immunogenicity and safety data from conducted clinical trials have been obtained, while the efficacy data from phase III clinical trial is insufficient.

Comment
Suggested text:
Pregnancy
Limited experience exists with use of Sinovac COVID-19 Vaccine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of Sinovac COVID-19 Vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
Breastfeeding
It is unknown whether Sinovac COVID-19 Vaccine is excreted in human milk.
Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity

"People aged 60 and above" should not be part of this section.

5.6 Interaction with other medicinal products and other forms of interaction

1. Concomitant use with other vaccines: no clinical study has been carried out with other vaccines administered at the same time (before, after or at the same time), on the immune response.
2. Concomitant use with other drugs: immunosuppressive drugs, such as immunosuppressive drugs, chemotherapy drugs, antimetabolic drugs, alkylating agents, cytotoxic drugs, corticosteroid drugs, etc., may reduce the immune response to this product.
3. Patients undergoing treatment: for patients undergoing treatment, please consult the professional doctors before use CoronaVac to avoid possible drug interactions.

Comment
No comment.

5.7 Safety profile

[Adverse Reactions]

The safety of CoronaVac was evaluated in 4 clinical trials conducted domestic and overseas, including randomized, double-blind, placebo-controlled phase I/II clinical trials in people aged 18-59 years and in elderly aged 60 years and above, a phase III clinical efficacy trial in Brazilian health professionals aged 18 years and above, and a phase IIIb bridging trial in different production scales and different populations. Systematic safety observation was carried out within 7 days after each vaccination, and adverse events were collected by voluntary report of subjects and regular follow-up of investigators on 8-14/28 days, long-term of serious adverse events within 12 months after the full vaccination is still ongoing.

1. General description of adverse reactions in clinical trials of this product

A total of 14,572 subjects aged 18 and above were enrolled in a series of clinical trials conducted domestic and overseas, of which 7,658 subjects received at least one dose. All subjects have completed at least 28 days follow-up after full immunization, and long-term safety visits are ongoing.

According to the grading standard of adverse reaction incidence from Council for International Organizations of Medical Sciences (CIOMS), i.e. very common (≥10%), common (1%-10%, 1% was inclusive), uncommon (0.1%-1%, 0.1% was inclusive), rare (0.01%-0.11%, 0.01% was inclusive) and very rare (<0.01%), all adverse reactions were summarized and described as follows.

i) Adverse reactions at injection site

Very common: pain

Common: swelling, pruritus, erythema, induration

Uncommon: burn at injection site

ii) Systemic adverse reactions

Very common: headache, fatigue

Common: myalgia, nausea, diarrhea, arthralgia, cough, chills, pruritus, loss of appetite, rhinorrhea, sore throat, nasal congestion, abdominal pain

Uncommon: vomit, hypersensitivity, abnormal skin and mucosa, fever, tremor, flushing, edema, dizziness, drowsiness

Rare: muscle spasms, eyelid edema, nose bleeds/epistaxis, abdominal distension, constipation, hyposmia, ocular congestion, hot flashes, hiccup, conjunctival congestion

iii) Severity of adverse reactions

The severity of adverse reactions observed in these clinical trials is mainly Grade 1 (mild), the incidence rate of adverse reactions for Grade 3 and the above was 1.31%.

Grade 3 and above adverse reactions includes pain at injection site, cough, fever, headache, sore throat, abdominal pain, dizziness and drowsiness.

iv) Serious adverse event (SAE)

No serious adverse event related to vaccination was identified up to February 3, 2021.

2. Adverse reactions in clinical trials conducted domestic and overseas

i) Domestic clinical trials

A total of 2203 subjects aged 18 years and above were enrolled into phase I/II and phase IIIb bridging clinical trials, of which 1452 subjects received at least one dose of vaccination (medium

dosage in phase I/II), including 1067 subjects aged 18-59 years (73.48%) and 385 subjects aged 60 years and above (26.52%). All subjects have completed at least 28 days of follow-up after whole immunization, and long-term safety monitoring is ongoing.

Solicited adverse reactions were mainly reported within 28 days after immunization. The incidence rates of unsolicited adverse reactions in adults and elderly subjects were 1.50% and 1.30%, respectively. Grade 3 adverse reactions occurred in 2 subjects aged 18-59 years. The incidence of Grade 3 adverse reactions was 0.14%, and the symptoms were fever and headache.

The safety results for phase I/II and phase IIIb bridging trials are shown in Table 1.

Table 1 Incidence of Adverse Reactions in domestic Phase I/II and Phase IIIb Bridging Clinical Trials n (%)

[Not copied here]

ii) Brazil clinical trial

A total of 12,396 subjects aged 18 years and above were enrolled in phase III clinical trials, of which 6202 subjects received at least one dose, including 316 subjects aged 60 years and above (5.10%). All subjects have completed at least 28 days of follow-up after whole immunization, and long-term safety monitoring is ongoing.

The results of solicited adverse reactions in phase III clinical trial are shown in Table 2. The incidence rate of unsolicited adverse reactions was 36.83%, the symptoms were mainly runny nose (7.01%), sore throat (6.93%), nasal congestion (2.74%), abdominal pain (1.34%) and dizziness (0.66%).

The severity of adverse reactions were mainly Grade 1 and Grade 2, the incidence of Grade 3 adverse reactions was 1.58%. Among the unsolicited adverse reactions, the Grade 3 symptoms compared with solicited adverse reactions were sore throat (0.03%), abdominal pain (0.03%), dizziness (0.02%) and drowsiness (0.02%).

Table 2 Incidence of Solicited Adverse Reactions in Phase III Clinical Trials in Brazil n (%)

[Not copied here]

Comment

No comment.

6 Monitoring of performance of the vaccine in the field

6.1 Vaccine efficacy/effectiveness and safety Monitoring

Sinovac is still following up on the participants of studies Corona 01 and Corona 02 (conducted in China), Corona 04 (conducted in Brazil), Corona 06 (conducted in Indonesia) and Corona 07 (conducted in Turkey), whose complete results are yet to be presented. A preprint has been posted recently presenting immunogenicity data from a study conducted in Chile that was not mentioned in the application. The final results of these studies, or the results of interim analyses should be shared in due time with WHO. The same is applicable to other ongoing and future Sinovac-sponsored or independent observational studies.

Sinovac relies on a passive adverse event following immunization (AEFI) surveillance system carried out by the Chinese Centre for Disease Control (CDC) to obtain post-marketing information about its vaccines. The same is already applicable to the Sinovac COVID-19 vaccine, which has already received post-Emergency Use Approval in China. This AEFI surveillance, although covering a huge number of individuals, is limited to China. Sinovac has proposed to conduct observational and interventional studies as additional pharmacovigilance activities in order to obtain additional vaccine effectiveness and safety data. It is important that these activities are not limited to China and are 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 extend the indication of Sinovac COVID-19 vaccine in individuals 60 years of age and older. Sinovac should also assess the effectiveness and safety of Sinovac COVID-19 Vaccine in individuals with different comorbidities and immunocompromised individuals (including people living with HIV), and its safety in pregnant/lactating women. SARS-CoV-2 variants of concern are now prevalent in many countries and spreading rapidly, which makes the monitoring and evaluation of vaccine effectiveness against them important.

By WHO request Sinovac explained how such assessments will be conducted in practice, stating the study design and/or surveillance system, the likely place(s) where they will be conducted, the sponsor(s) (either Sinovac and/or other institutions such as universities and Ministries of Health), and timelines. Additional information has also been provided on the coadministration of Sinovac COVID-19 vaccine and influenza vaccine and polysacharide pneumococcal vaccines.

6.2 Programmatic aspects

This product is a single dose vaccine packaged into a vial. The Company has not provided self-assessment against programmatic suitability. The CoronaVac™ vaccine EUL application has been submitted with two presentations; 0.5mL in Prefilled syringe and 0.5mL Vial. *However, on 8 April 2021 Sinovac requested to exclude the PFS presentation and only the Vial presentation be available for UN agencies/COVAX facilities*.

Programmatic suitability

The proposed non-auto-disabling pre-filled syringes are not compliant with WHO requirements WHO/IVB/14.10 on programmatic suitability of candidate vaccines for WHO prequalification. The presentation has some programmatic disadvantages in developing country settings:

- Absence of an auto-disable (AD) feature to prevent re-use of the device and thus, reduce the possible spread of blood borne diseases;
- Supplied with a separate needle, so an imbalance of numbers of distributed needles and syringes could prompt re-use of needles, with risk of blood borne diseases;
- Safe disposal of the used syringes (containing glass, rubber and metal) is more difficult than disposal of the AD plastic syringes used to deliver vaccines from a vial presentation and countries may not have the required infrastructure (e.g., high temperature incineration);
- The cold chain volume per dose is larger than a single-dose vial presentation which could challenge a country's cold chain capacity.

The pre-filled syringe presentation meets the same quality standards as the vial presentations and can be used under pandemic situation if Health Authorities in a recipient country consider that they have the ability to satisfactorily deal with such issues.

- No Vaccine Vial Monitor (VVM) is proposed with this Sinovac EUL application. The Company have not indicated any plan to include a VVM with this vaccine.
- Packaging procedures supported by validation for international shipping are provided to meet the requirements of WHO guidelines on packaging and shipment.

7 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 made its interim recommendations on the use of CoronaVac™ at its plenary meeting on 29 April 2021, which were subsequently endorsed by the Director-General of WHO. The recommendations are based on randomized clinical trial (RCT) data reported until the meeting data, and a post-introduction cohort study in Chile. The intended use of the vaccine is in persons aged 18 years and above, without an upper age limit. Recognizing the very limited data in older adults from the RCT, immunogenicity and in particular post-introduction observational data were considered for the recommendation. To make this recommendation more robust and evidence based, additional data should be generated on the safety and effectiveness of the vaccine in this age group. The recommended schedule is two doses with an interval of 2-4 weeks. The need for booster doses needs further studies. The vaccine showed a satisfactory safety profile and no severe hypersensitivity and anaphylaxis reactions have been recorded in clinical trials. So far, limited data are available on vaccine effectiveness against variants of concern. A post-introduction cohort study was conducted in context of circulating B.1.1.7 and P.1 and demonstrated high vaccine effectiveness against hospitalizations and deaths. No effectiveness information yet available regarding B.1.617.

Recommendations on addressing current knowledge gaps through further post-authorization studies have been made.

8 Regulatory oversight

Sinovac life Sciences Co., Ltd., is the Marketing Authorization Holder. The vaccine received conditional marketing approval by the NMPA, P.R. China for one year starting from 9 February 2021. The vaccine has been authorized in 21 countries (Benin, Brazil, Cambodia, Chile, Columbia, Djibouti, Dominica, Ecuador, Gabon, Malaysia, Mexico, Myanmar, Philippines, Thailand, Tunisia, Turkey, Uruguay, Zimbabwe).

9 Benefit/Risk Assessment

According to WHO, the COVID-19 pandemic has caused, as of 23 June, over 178 million cases of the disease and over 3.09 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 proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they are susceptible to the virus. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility has caused concern. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

As with any other vaccine, adverse events following immunization can be expected. This can occur immediately following injection, caused by the reactogenicity of the vaccine materials or through allergy to some components of the vaccine. In addition, long-term ill-effects may be detected months or years following vaccination. Of concern for inactivated vaccines, by analogy with past experience with other vaccines and with other coronaviruses candidate vaccines, is vaccine ADE or VAERD. Limited data do not indicate a propensity for the Sinovac COVID-19 vaccine to induce VAERD in animal models and suspected cases have not been reported after the roll out of this vaccine in several countries.

This vaccine may, theoretically, have an advantage over other vaccines that target only the spike protein. Naturally evolving SARS-CoV-2 variants of concern with mutations in the spike protein may render spike protein vaccines less effective, while the immune responses raised by the whole inactivated virus Sinovac vaccine may continue to provide protection. However, the immune response to the spike protein antigen may be generally lower in inactivated vaccines compared to vaccines from other technological platforms and may not generate strong cellular response. Therefore, the effectiveness of Sinovac COVID-19 vaccine against emerging SARS-CoV-2 variants must be monitored and evaluated and genetic sequence of viruses causing breakthrough infections characterised.

Ongoing clinical trials in China, Brazil, Indonesia, Turkey and Chile have demonstrated safety and tolerability of the Sinovac COVID-19 vaccine, similar to other approved adjuvanted inactivated viral vaccines. Post-Emergency Use Approval (EUA) safety data from China, obtained from safety surveillance, suggest that Sinovac COVID-19 vaccine is safe for the use in adults 18 years of age and above.

Protective efficacy has been demonstrated in interim analyses of three trials, although the vaccine efficacy estimates (compared to placebo) have varied substantially , from just over 50% to over 80%, for unclear reasons. The evidence of vaccine efficacy in people 60 years of age and older is very limited from the clinical trial data because of the limited sample size, but recently reported data from in dependent studies conducted in Chile and Brazil suggests that Sinovac COVID-19 vaccine may be effective in this age group, in particular in protecting against severe disease Limited immunogenicity data are available for all age groups, but there is evidence of a notable decrease of neutralizing antibodies in the ≥60y age group, hence the need to generate additional data in this population. No evidence from clinical trials exists for individuals with comorbidities and immunocompromised individuals (including people living with HIV). Safety data are also not available for these groups and for pregnant and breastfeeding women.

The current clinical evidence supports that the benefits of Sinovac COVID-19 vaccine in preventing symptomatic COVID-19 outweigh their risks in adults from 18 to 59 years of age. This vaccine has been deployed in several countries, where it has been often used in the elderly, who are usually seen as a priority group for vaccination, but efficacy could not be assessed in randomized clinical studies in this population Early evidence of vaccine effectiveness in this age group has been provided from an independent study from Chile, although vaccine effectiveness of the same magnitude has not been supported by independent studies conducted in Brazil. Therefore, additional evidence to support an indication in this age group is needed.

In addition, no evidence of vaccine efficacy from clinical trials exists for individuals with co-morbidities (except for obesity) and immunocompromised individuals (including people living with HIV). Safety data are also not available for these groups and for pregnant and breastfeeding women. It is likely that the benefit/risk is also positive for the use of Sinovac COVID-19 vaccine in pregnant and lactating women, but such evidence is currently not available and should be produced by Sinovac, perhaps in partnership with other stakeholders. Sinovac has provided information on ongoing and planned studies that they have committed to conduct. There is currently limited evidence for duration of protection and the need for a boosting dose, in light of early evidence of declining immunity 6 months post vaccination, will need to be promptly investigated, especially in older individuals. This hat is going to be addressed in a study to be conducted in Chile

10 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 is needed.

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

Should new evidence become available that change the benefit-risk assessment (e.g. as a result of the new variants) the EUL recommendation could be reconsidered

10.1 Quality (CMC) perspective

1. The majority of the CMC issues LoQ round 1 of EUL application raised by the TAG were addressed by the company including responses to LoQ round 2 and no major issue is pending.
2. The stability studies are still ongoing. The proposed shelf-life of 24 months is not supported by the available stability data. Only 12 months data at 2 to 8°C are available from pilot scale lots and 6 months from commercial scale. Sinovac agreed that additional stability data will be submitted to WHO in timely manner to obtain extension to the shelf life of Final Product.
3. A shelf life of 12 months can be considered
4. Sinovac is committed to continue generating data to ensure the vaccine is meeting the global standards of quality, safety and efficacy. The following are to be provided in a timely agreed manner:

- Stability data of Master and Working Seed Lots from ongoing stability studies when it becomes available.
- The protocol of establishing, Standard Operating Procedures and testing report of In-house reference standard for Titration test method.
- Photostability study protocol and Test report
- The validation for robustness of the identification/Antigen content/Post dissociated Antigen Content methods along with report.
- Establishing a trend analysis based on the lower and upper limits of currently established specifications and also to improve and tightening the release specification as more data from commercial batches produced in 2021.
- The extractability and leachability studies on product of final bulk COVID-19 Vaccine with direct contact with containers.

10.2 Clinical perspective

The following commitments were agreed upon by Sinovac as a necessary condition for the granting of an EUL for CoronaVac™:

From the clinical perspective, the company commits :

1. To provide the final clinical study reports of the ongoing studies (CORONA 01, CORONA 02, CORONA 04, CORONA 06, and CORONA 07) whose interim analyses have been presented as part of the application, as well as of the ongoing clinical trial conducted in Chile that was not included in this application, once they become available.
2. To provide the interim and full reports of the ongoing and planned effectiveness (cohort and test-negative design case-control) studies conducted in Chile, Brazil, Dominican Republic and other countries, independent or Sinovac-sponsored, as they become available.
3. Whenever possible and considered ethical, to encourage participants to remain in the ongoing phase 3 as originally randomized for as long as possible, in order to accumulate long term safety follow-up data after dose 2 of the vaccine.
4. To send WHO monthly safety reports, and Periodic Benefit Risk Evaluation Reports (PBRER) every 6 months in the first year post-EUL, followed by annual reports thereafter.
5. To report the outcome of the cases of pregnancy observed in the clinical studies as part of the PBRER.
6. To investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy/effectiveness of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as alpha, beta, gamma and delta, formerly known as B.1.1.7, B.1.351, P.1, B.1.617.2, according to the Pango nomenclature, and others). This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.
7. To make the changes in the product insert as addressed in section “5 Technical considerations” of the TAG report, including but not limited to: the vaccine indication limited to adults from 18 to 59 years of age; exclusion of pregnant and lactating women as vaccine contraindications; change of the “observation time after vaccination" for “at least 15 minutes” instead of “at least

30 minutes"; change of the text about vaccine use in pregnancy and breastfeeding. The product insert should be revised for technical terminology adequacy.

8. To conduct, within the estimated timelines, or follow up closely (in case of independent studies) studies that aim at providing: a) vaccine effectiveness estimates in people 60+ years of age and with comorbidities (including the S project, in the town of Serrana, Brazil; a study in kidney transplant recipients in Brazil, whose interim report is expected for March 2022; the ongoing Ministry of Health cohort study conducted in Chile); b) vaccine effectiveness and safety study in people living with HIV, currently planned for South Africa; c) safety study in pregnant and lactating women, planned to be conducted in Brazil; d) prevention of severe and fatal cases of COVID-19 (to be addressed by the Chilean cohort study and a test-negative case control study to be conducted in the Dominican Republic; e) vaccine co-administration (with influenza vaccine, in a study in the Zhejiang province, and with influenza and polysaccharide pneumococcal vaccines, to be conducted in the Guangdong province); f) cross-neutralization studies to investigate breakthrough COVID-19 cases in China and overseas. The Sinovac-sponsored studies are considered additional pharmacovigilance activities. Periodic follow-up reports on these studies should be sent to WHO as part of the PBRER or earlier, whenever appropriate.
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12. In addition to the above, the company is required to: a) report serious adverse events following immunization (within 15 days of receipt of the report); b) report quality complaints from the field for batches supplied; c) report any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA of reference (NMPA); d) report any problems/constraints in production or quality control which might affect the emergency use condition granted to this product.

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