Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19

Background document to the WHO Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac

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World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Sinovac-CoronaVac-GRADE-ETR

Contents

Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its meeting on 29 April 2021, which resulted in the issuance of WHO interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac. It is based on published data, data submitted to WHO for Emergency Use listing, and direct information shared by the company. Cut-off date of information included is 29 April 2021.

Recommendations, annexes the background document are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

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

Context

Inactivated viral vaccines have been successfully used in immunization programmes for decades. Since they do not contain replicating virus, they are often a preferred product class for special populations, such as pregnant women and people who are immunocompromised. Inactivated vaccines frequently need to be given in multiple doses and often a booster dose is needed to maintain immunity.

Inactivated vaccines against SARS-CoV-2 are being developed by several vaccine manufacturers (1). The inactivated COVID-19 vaccine Sinovac-CoronaVac was developed by Sinovac. Sinovac-CoronaVac has been authorized as a 2-dose vaccine (3 μ per 0.5ml dose) for individuals aged 18 years and older. The proposed indication for emergency use listing (EUL) is a 2-dose schedule with a preferred interval of 14–28 days between doses. Sinovac-CoronaVac was granted conditional market authorization by the China National Medical Products Administration (NMPA) on 6 February 2021 and has since been granted emergency authorization in 32 countries or jurisdictions (at the time of writing). As of 21 April 2021, more than 260 million doses have been distributed to the public in China and elsewhere, and more than 160 million individuals have been vaccinated. The vaccine is currently being evaluated in several trials and is licensed under emergency use authorizations in several countries and territories (2):

- Conditional approval: China.
- Emergency use: Algeria, Benin, Botswana, Brazil, Cambodia, Chile, China (Hong Kong Special Administrative Region), Colombia, Djibouti, Dominica, Ecuador, El Salvador, Gabon, Georgia, Guinea, Guyana, Indonesia, Malaysia, Mexico, Morocco, Myanmar, Pakistan, Paraguay, Philippines, Thailand, Togo, Tunisia, Turkey, Ukraine, Uruguay, Zimbabwe.

All authorized indications are for individuals 18 years and older, with the exception of Colombia, El Salvador, Thailand and Tunisia (18–59 years), and Uruguay (18–70 years).

The following information is derived from the product information supplied in the context of the WHO Emergency Use Listing Process, Sinovac responses to questions from the SAGE Working Group, published articles and preprints, and other sources. Sinovac has given permission for unpublished data from the EUL process to be made public in this background paper.

Characteristics of Sinovac-CoronaVac vaccine against COVID-19

Sinovac-CoronaVac is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine based on the CZ02 strain. This strain of SARS-CoV-2 was isolated from the bronchoalveolar lavage of a hospitalized patient and is closely related to the 2019-nCoV-BetaCoV Wuhan/WIV04/2019 strain (3).

Composition

The final vaccine product in each 0.5 ml dose is composed of 3 μg of inactivated SARS-CoV-2 virus. The excipients are aluminium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, and water for injection (4). The vaccine does not contain preservatives.

None of the excipients are of animal or human origin. The excipients are well established for use in pharmaceutical products.

Stability

Of the nine finished product batches, three have completed long-term stability observation for six months; no significant change was found in any of the test items (4). The other six batches have completed long-term stability observation for 3 months; the antigen content of each batch of finished product of Sinovac-CoronaVac did not decrease significantly after dissociation.

Shelf-life

In line with the results of an accelerated stability study, the period of validity of the vaccine was tentatively determined by the China National Medical Products Administration (NMPA) to be 2 years at 2–8 °C, and by Agência Nacional de Vigilância Sanitária (ANVISA) to be 1 year at 2–8 °C (4). Each batch of finished product of Sinovac-CoronaVac will continue to be monitored in accordance with the stability study plan.

Drug product description

The dosage form of the vaccine is injectable liquid. Sinovac-CoronaVac is a milky-white suspension. Stratified precipitate may form, which can be dispersed by shaking. No clumps should be found on shaking. The vaccine is available in a single-dose vial or prefilled syringe.

Container

Each vial or prefilled syringe is packed in a single box.

Pharmacokinetics

As neither the delivery system nor the adjuvant used in the development or in the final formulation of Sinovac-CoronaVac is new, human pharmacokinetic studies were not performed.

Preclinical studies

Reproductive and developmental toxicity

The vaccine was injected intramuscularly in 336 Sprague-Dawley rats at doses of 1.5 µg and 6 µg during the period from before mating to the delivery of pup (4). The males were vaccinated before mating on days 1, 8, 15 and 28 and the females were vaccinated before mating on days 1, 8 and 15. Mating occurred one week after the last administration to male rats. Female rats were also vaccinated on gestational day 6 and postnatal day 7. Caesarean sections were performed on half of the pregnant females on gestational day 20 for embryo observation; the other females gave birth and suckled their pups until the end of the lactation period. No significant adverse effect was observed on the growth or fertility of parental female and male rates, or on gestation and lactation in female rats. No developmental toxicity and teratogenicity was seen in the embryos and fetuses, and no effect on the growth and development of F1 pups was observed. The no observed adverse effect level (NOAEL) of the vaccine on the fertility of parental male and female rats, pregnancy, and lactation of parental female rats, embryo-fetal developmental toxicity and teratogenicity, and physical and reflex development of F1 offspring was 6 µg.

Immunogenicity

Following the NMPA guidance for the safety evaluation (non-clinical studies) of pharmaceuticals, the following non-clinical studies of Sinovac-CoronaVac were completed: immunogenicity study and virus challenge studies to determine the possible dosage and schedule of the vaccine, as evidence for clinical application and preliminary evidence of efficacy; general safety evaluation, including single-dose toxicity, repeated-dose toxicity, active systemic anaphylaxis, local tolerance and reproductive toxicity studies, designed to evaluate both the efficacy and safety of the COVID-19 vaccine and to provide supportive evidence for developing clinical studies.

The immunogenicity of Sinovac-CoronaVac was assessed in BALB/c mice given two doses of 0, 1.5, 3 or 6 µg on a 0/7-day schedule (3). No adverse effect or inflammation was observed. Immunogenicity and protective efficacy were assessed in rhesus macaques. The animals were immunized on a 3-dose schedule at 0/7/14 days, with either 3 or 6 µg of vaccine, placebo (adjuvant) or saline. The vaccine was immunogenic at both doses. On day 22 (one week after the third vaccination), 106 $TCID_{50}$ of SARS-CoV-2 CN1 was inoculated intratracheally

into the macaques' lungs. By 3–7 days after inoculation, all control animals exhibited a high load (10^4 to 10^6/ml) of viral genomic RNA in the pharynx, rectum, and lung, as well as severe interstitial pneumonia. All vaccinated animals had mild and focal histopathological changes in a few lobes of lung. Viral RNA was detected in the vaccinated animals, but by day 7 after inoculation all four macaques that received the high dose had no detectable viral load in the pharynx, rectum, or lung. While viral RNA was detected in more animals in the lower-dose group, the load was about 95% lower than that seen in the group given saline. There was no evidence of antibody-dependent enhancement with the limited time interval between vaccination and challenge.

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from several ongoing studies (see Table 1).

Table 1. Overview of clinical studies of Sinovac-CoronaVac (as of 4 March 2021).[a]

Study Name Trial Registration	**Sponsor**	**Phase (primary outcome)**	**Location(s)**	**No. of participants Eligible age groups**	**Dosing regimens**	**Study status**
Corona-01 NCT04352608	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	Phase 1: 144 healthy participants 18–59 years	2 doses, 0/14 or 0/28 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	Complete
				Phase 2: 600 healthy participants 18–59 years	2 or 3 doses, 0/14, 0/28 or 0/28/56 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	
Corona-02 PRO-nCOV-1002 NCT04383574	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	Phase 1: 72 healthy participants ≥60 years	2 doses 0/28 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	Complete
				Phase 2: 350 healthy participants ≥60 years	2 doses, 0/28 day schedule Low dose: 1.5 µg per 0.5-ml dose Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	
Corona-03 PRO-nCOV-1003 NCT04551547	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	522 healthy participants 3–17 years	2 doses, 0/28 day schedule Low dose: 1.5 µg per 0.5-ml dose Medium dose: 3 µg per 0.5-ml dose	Results pending
Corona-04 PRO-nCOV-3001 NCT04617483	Sinovac Research and Development Co., Ltd.	Phase 3 (immunobridge to commercial lot and immunobridge to elderly; single-arm)	China	1040 healthy participants ≥18 years 25% of participants ≥60 years	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Complete
PROFISCOV NCT04456595	Butantan Institute	Phase 3 (vaccine efficacy and safety)	Brazil	12 688 healthy participants ≥18 years, health care workers who treat patients with COVID-19	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Interim results available
CoV2-0320 NCT04508075	PT Bio Farma	Phase 3 (vaccine efficacy and lot-to-lot consistency)	Indonesia	1620 healthy participants 18–59 years	2-doses, 0/14 day schedule 3 µg per 0.5-ml dose	Interim results available
9026-ASI NCT04582344	Health Institutes of Turkey	Phase 3 (vaccine efficacy)	Turkey	13 000 healthy participants 18–59 years First cohort: health care workers in the high-risk group (K-1) Second cohort: people at normal risk (K-2)	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Top line results available

Study Name Trial Registration	**Sponsor**	**Phase (primary outcome)**	**Location(s)**	**No. of participants** **Eligible age groups**	**Dosing regimens**	**Study status**
CoronaVac3CL NCT04651790	Pontificia Universidad Catolica de Chile	Phase 3 (safety and immunogenicity, comparing 2 schedules)	Chile	2300 healthy participants ≥18 years 40% of participants ≥60 years	2 doses, 0/14 and 0/28 day schedule 3 µg per 0.5-ml dose	Interim results available
COV-04-IB NCT04747821	Butantan Institute	Phase 4 (stepped-wedge cluster-randomized open-label vaccine effectiveness)	Brazil	30 000 healthy participants ≥18 years	2 doses 0/28 day schedule 3 µg per 0.5-ml dose	Active, not recruiting
NCT04756830	D'Or Institute for Research and Education	Phase 4 (single-group assignment, open label, safety and immunogenicity)	Brazil	1200 healthy participants ≥18 years	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04754698	University of São Paulo General Hospital	Phase 4 (single-group assignment, open label, immunogenicity)	Brazil	2067 participants, persons with rheumatic diseases, persons living with HIV/AIDS and healthy controls ≥18 years	2 doses, 0/21–28 day schedule 3 µg per 0.5-ml dose	Recruiting
CHEMOCOVAC NCT04765215	Namik Kemal University	Phase 4 (single-group assignment, open label, immunogenicity)	Turkey	291 breast or lung cancer patients receiving active chemotherapy and healthy controls 18–90 years	2-doses schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04751721 NCT04751695	Izmir Bakircay University	Phase 4 (single-group assignment, open label, oxidative stress)	Turkey	40 healthy participants 35–65 years (different trials for females and males)	2 doses, 0/24 day schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04775069	Humanity & Health Medical Group Limited	Phase 4 (single-group assignment, open label, Sinovac-CoronaVac, BNT162b2 and AZD1222)	China (Hong Kong SAR)	900 participants with chronic liver disease ≥18 years	2 doses, 0/28 day schedule 3 µg per 0.5-ml dose	Not yet recruiting

[a] Studies were randomized controlled trials unless otherwise indicated.

During early clinical development, work was undertaken to evaluate both a 0/14 day emergency schedule and a 0/28 day routine schedule, the former of which was taken forward in efficacy trials. The clinical data package, available as of 21 April 2021, consists of assessments of safety and immunogenicity in three trials in China (participants ≥18 years of age), safety and efficacy in a phase 3 trial in health care workers treating COVID-19 patients in Brazil (immunogenicity pending), safety, immunogenicity and efficacy in a phase 3 trial in Indonesia, safety and immunogenicity in a phase 3 trial in Chile, and efficacy results from a phase 3 study in Turkey (Table 1, Appendix 1). A paediatric safety and immunogenicity phase 1/2 trial is ongoing in China. Two vaccine effectiveness assessments have been reported from Brazil and Chile, and a large phase 4 vaccine effectiveness stepped wedge study cluster-randomized trial is under way in Brazil. Other ongoing or planned clinical studies are assessing safety and immunogenicity in special populations, such as persons living with HIV/AIDS, rheumatic disease, chronic liver disease, and breast or lung cancer receiving active chemotherapy (Table 1).

The number of trial participants who received at least one dose of Sinovac-CoronaVac and contributed to the safety, immunogenicity, and efficacy analyses are shown in Table 2, stratified by age and whether the vaccine administered was of the authorized dose and schedule (0/14-28 days) or an alternative dose or schedule.

Table 2. Number of trial participants who received at least one dose of Sinovac-CoronaVac and are included in the clinical database available as of 21 April 2021 (from trials in Brazil, Chile, China, Indonesia and Turkey).

	Age group (years)	Authorized dose/schedule	Alternative dose/schedule	Total by age	Total all ages
Safety	18–59	7603	288	7891	8840
	≥60	726	223	949	
Immunogenicity	18–59	1589	288	1987	2608
	≥60	398	223	621	
Efficacy	18–59	12 098	0	12 098	12 310
	≥60	212	0	212	

Immunogenicity studies in humans

Clinical trials demonstrated that Sinovac-CoronaVac is immunogenic both in adults aged 18–59 years and in older adults ≥60 years. Initial indications are that titres decline by 3 months after dose 2. Geometric mean titres (GMTs) in different studies need to be interpreted in the context of the different labs performing the neutralization assays, vaccination schedule (0/14 days or 0/28 days) and the number of days post-vaccination that sera were collected.

Immunogenicity data are available from two clinical studies in China: Corona-01 (4, 5), a phase 1/2 study in individuals aged 18–59 years, and Corona-02 (4, 6), a phase 1/2 study in individuals ≥60 years of age. Data are also available from Corona-04 (4), a phase 3 immunobridging study in younger and older adults, the clinical study report from a phase 3 study in Indonesia (7), and a preliminary analysis from the phase 3 trial in Chile (8). The immunogenicity results, based on neutralizing antibody, are presented here.

Data are available up to 28 days after the second dose for most schedules and age groups, and for 3 months after