Background document on the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm

Background document to the WHO Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm

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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 29 April 2021, which resulted in the issuance of the WHO Interim recommendations for use of the inactivated COVID-19 vaccine BIBP. Both the recommendations and 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.

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. Because 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 BIBP was developed through a collaboration between the Chinese Center for Disease Control and Prevention (CDC) and the Beijing Institute of Biological Products (BIBP)/China National Biotec Group Company Limited (CNBG). The decision was made to pursue an inactivated vaccine candidate because of the long-history of safe and effective inactivated vaccine use, and the fact that the existing inactivation process platform at BIBP for Sabin-strain inactivated poliovirus vaccine could be used for inactivated COVID-19 vaccine product development and that SARS-CoV-2 virus strains were obtainable in China.

The COVID-19 vaccine BIBP has been authorized as a 2-dose vaccine (6.5 U/dose) given at 0 and 21 days (with flexibility up to an additional 7 days) for the prevention of COVID-19 disease. COVID-19 vaccine BIBP was granted conditional market authorization by the China National Medical Products Administration on 30 December 2020 and has been granted approval or emergency authorization in 57 countries or jurisdictions at the time of writing. Beijing Institute of Biological Products Co., Limited – CNBG, Sinopharm has submitted a dossier to WHO for Emergency Use Listing.

In all countries where it has been authorized, the indication has been for individuals aged 18 years or older. COVID-19 vaccine BIBP is currently under evaluation in five clinical trials, and is licensed under Approved Use or Emergency Use Authorizations in the following countries and territories (2):

- Approved Use (5 jurisdictions): Bahrain, Bolivia, China, Seychelles, United Arab Emirates.
- Emergency Use Authorization (52 jurisdictions): Algeria, Angola, Argentina, Belarus, Bhutan, Bangladesh, Brunei, Cambodia, Cameroon, China (Macao Special Administrative Region), Comoros, Congo, Dominica, Egypt, Ethiopia, Equatorial Guinea, Gabon, Georgia, Guinea, Guyana, Hungary, Indonesia, Iraq, Jordan, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Maldives, Mauritania, Mongolia, Montenegro, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, North Macedonia, Mauritius, Pakistan, Peru, Senegal, Serbia, Sierra Leone, Solomon Islands, Somalia, Sri Lanka, Sudan, Turkmenistan, West Bank and Gaza Strip, Zimbabwe.

CNBG is also developing another inactivated vaccine against SARS-CoV-2, COVID-19 vaccine WIBP, which is being tested as an investigational product in some of the trials that are evaluating COVID-19 vaccine BIBP. Though similarly inactivated with β-propiolactone, the COVID-19 vaccine WIBP is based on a different SARS-CoV-2 strain and is being developed and manufactured by the Wuhan Institute for Biological Products/CNBG. COVID-19 vaccine BIBP and COVID-19 vaccine WIBP are considered different products; the COVID-19 vaccine WIBP is not reviewed in this document.

The information below is derived from the product information supplied in the context of the WHO Emergency Use Listing process, unless otherwise specified. CNBG/BIBP has given permission for these data to be made public in this background paper.

Emergency Use Listing

The COVID-19 vaccine BIBP has obtained emergency use listing on 7 May 2021.

Characteristics of COVID-19 vaccine BIBP

COVID-19 vaccine BIBP is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine based on the 19nCOV-CDC-TAN-HB02 strain (HB02 strain) (3). The original Vero cell line was obtained from WHO, and the original cell bank, master cell bank, and working cell bank were established by BIBP. The cells used for vaccine manufacture are the working Vero cell bank, which is of the 142nd generation.

Composition

The final vaccine product in each 0.5 ml dose is composed of 6.5 U (4 μg) of inactivated SARS-CoV-2 antigens and aluminium hydroxide adjuvant in phosphate-buffered saline (PBS) (3). PBS is composed of disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate, and sodium chloride.

None of the excipients are of animal or human origin (3). The excipients are well established for use in pharmaceutical products.

Stability

The assigned maximum storage time for bulk product is no more than 6 months at 5±3 °C (3). Stability of the bulk product has been tested up to 6 months in long-term real-time, real-temperature studies at 5±3 °C; all specifications were met. Stability testing will continue up to 12, 18, and 24 months. Under accelerated conditions at 25±2 °C, all test results met the specification for 5 weeks (3). At 37±2 °C, the antigen content and protein content met the specification for 1 week. The quality of the bulk product will be continuously monitored in post-approval stability studies, and trend analyses of the testing data will be performed periodically.

Shelf-life

The proposed shelf-life on the label is 24 months (3). The product should be stored and transported refrigerated (2–8 °C) and protected from light. It should not be frozen. Stability testing will continue up to 18, 24, and 36 months.

Drug product description

The dosage form of the vaccine is injectable liquid. The product is a semi-transparent suspension, slightly white in colour (after shaking), in a single-dose vial or prefilled syringe. The vial (2 ml) is composed of middle borosilicate glass, with an aluminium foil cap and a film-coated rubber stopper. The prefilled syringe (1 ml) is composed of the needle cover, needle-bearing glass tube, plunger rubber cap and plunger stick.

Upon storage, precipitation can be observed, which is easily dispersed by shaking. The product should be stored and transported at 2–8 °C.

Container

Prefilled syringes are available in boxes of 300 as follows: one syringe and the product leaflet are packed in a carton, ten cartons are wrapped with polyethylene film, and 30 of these carton wraps are packed in an outer box.

Single-dose vials are available in boxes of 400 as follows: one vial and the product leaflet are packed in a carton, ten cartons are wrapped with polyethylene film, and 40 of these carton wraps are packed in an outer box. A larger box, containing 600 vials, is also available, packaged as follows: three vials and the product leaflet are packed in a carton, ten cartons are wrapped with polyethylene film, and twenty of these carton wraps are packed into an outer box.

Pharmacokinetics

As neither the delivery system nor the adjuvant used in the development or in the final formulation of COVID-19 vaccine BIBP is new, human pharmacokinetic studies were not performed.

Preclinical studies

Reproductive and developmental toxicology

BIBP contracted JOINN Laboratories to conduct reproductive toxicology studies using standardized methodologies (4). The vaccine was repeatedly injected intramuscularly in 336 Sprague-Dawley (SD) rats at doses of 0.5 or 1.5 ml and compared with a negative control group (received sodium chloride) and an adjuvant control group during the period from before mating to implantation and delivery of the pup. Males were vaccinated before mating on days 1, 15, 29 and 43, females were vaccinated before mating on days 1, 15, and 29, respectively. Mating occurred one week after the last administration to male rats. Female rats were also vaccinated on gestational day 6 and postnatal day 7. Male rats were euthanized 3 weeks after the mating period ended. 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 young until the end of the lactation period (postnatal day 21).

There were no clinically observed vaccine-associated adverse reactions in the animals in the different dose groups; there were also no abortions, premature deliveries, dystocia, late deliveries or incomplete deliveries. There were no changes in body weight or food intake, and no statistical differences in the fertility indicators, days of cohabitation, days of mating, or irregularity rate of estrous cycle of female rats in the adjuvant control group and the test group compared to the negative control group (P>0.05). There were no toxicologically significant differences in sperm motility, sperm count, sperm morphology, weight and organ coefficient of the testes, epididymis, prostate, seminal vesicle and coagulating glandular organs of the male rats in the adjuvant control group and the test groups compared with the negative control group. There were no statistical differences in the average number of corpora lutea during pregnancy, the number of implantation sites, number and rate of live births, number and rate of absorbed births (early and late stage), number of stillbirths, number of abnormal placentas, stillbirth rate, loss rate before or after implantation, rate of abnormal placenta and uterus, or fetal weight (P>0.05). There were no statistical differences in the body weight, placental weight, body length, tail length, sex ratio, and appearance malformation rate of fetal rats in the adjuvant control group and the test groups compared with the negative control group, or in the bone variation and abnormality rates and visceral variation and abnormality rate of fetal rats in the high-dose group (P>0.05).

There were no toxicologically significant changes in the live birth index, lactation survival rate, body weight, gender ratio, appearance malformation rate, and age of reaching the physical development indexes and reflex development indexes of F1 offspring rats in the adjuvant control group and the test groups compared with the negative control group.

No vaccine-associated pathological differences were found on gross inspection and microscopic observation of the reproductive organs (testis, epididymis, prostate, seminal vesicle with coagulating gland, ovary and uterus) of parental male and female rats in the adjuvant control group and the low- and high-dose groups compared with the negative control group. No obvious abnormal changes were observed in the gross autopsy of F1 offspring rats.

No obvious adverse effects were observed on the fertility of parental male and female rats, and pregnant/lactating female rats; no embryo-fetal developmental toxicity or teratogenicity were observed; and no effects on the growth and development of F1 offspring rats were observed.

The no observed adverse effect level of the COVID-19 vaccine BIBP, for the fertility of parental male and female rats, the gestation and lactation of parental female rats, embryo-fetal developmental toxicity and teratogenicity, and the growth and development of F1 offspring rats was 1.5 mL (3 doses).

Immunogenicity and safety

The immunogenicity of COVID-19 vaccine BIBP was assessed in BALB/c mice given one, two or three high, medium or low doses at varying time points (5). The vaccine was immunogenic at all doses and schedules. For all two-dose schedules (0/7, 0/14 and 0/21 days), neutralizing antibody titres were higher than with a one-dose schedule; the highest level of neutralizing antibodies was reached with the 0/21 days schedule. A three-dose schedule (0/7/14 days) was assessed and was more immunogenic than the one- and two-dose schedules at each dose. Immunogenicity was also assessed in rabbits, guinea pigs, rats, and mice, using one- and three-dose schedules (0/7/14 days) and low, medium and high doses. All animals were seropositive across all schedules and doses 21 days after the first immunization. Neutralizing antibodies were higher on the three-dose schedule than the one-dose schedule in rabbits and guinea pigs.

Preclinical safety studies did not identify any concerns with COVID-19 vaccine BIBP (5). Acute toxicity was studied in SD rats, which were observed for 14 days post-immunization before being euthanized. There were no deaths, clinical signs, differences in weight or feeding state, or histopathological changes between the vaccine and placebo groups. The maximum tolerated dose (MTD) was 24 μg per rat, which is equivalent to 900 times the dose

approved for emergency use in humans. Anaphylaxis studies in guinea pigs did not identify any increased symptoms of allergic reactions in the vaccinated group compared with the control group. To assess long-term toxicity, 20 male and 20 female cynomolgus monkeys were divided into 4 groups containing 5 monkeys of each sex. The groups received placebo, 2, 4, or 8 µg of COVID-19 vaccine BIBP once a week for a total of 4 injections. Three-fifths of animals were euthanized and dissected on day 25, and the rest on day 36. No deaths occurred and no significant abnormalities in clinical, physiological and pathological indicators or gross anatomy were detected. Granulomatous inflammation due to injection was observed in the vaccinated groups. The no observed adverse effect level was 8µ g, the highest dose tested.

The efficacy of COVID-19 vaccine BIBP was assessed in rhesus macaques (5). Ten macaques were immunized using a two-dose schedule at 0 and 14 days: 4 were given COVID-19 vaccine BIBP at low dose (2 µg), 4 at high dose (8 µg), and 2 were given placebo (physiological saline). Neutralizing antibody titres on the day of challenge reached 215 in the low-dose group and 256 in the high-dose group.

The animals were challenged on day 24 (10 days after the second dose) through direct inoculation of 10^6 $TCID_{50}$ of SARS-CoV-2 virus (SARS-CoV-2/WH-09/human/2020/CHN) via the intratracheal route under anaesthesia. Viral load was assessed on throat and anal swabs by real-time polymerase chain reaction (PCR) on days 3, 5, and 7 post-challenge. Macaques in the placebo group maintained a high viral load throughout the evaluation period on both throat and anal swabs. Viral RNA was detected in both the low- and high-dose group. In the high-dose group, viral load was statistically significantly lower than in the placebo group at all time points for both throat and anal swabs. On day 7, no animals in the high-dose group had detectable virus by throat swab and 2 of the 4 animals had detectable virus on anal swab. In the low-dose group, viral load was statistically significantly lower than in the placebo group on days 3 and 7 by throat swab, but was not different from the placebo group by anal swab.

On day 7 post-challenge, the animals were euthanized. In the placebo group, a high viral load was detected in the 3 of 7 lung lobes, while no virus was detected in any lung lobe in either the low- or high-dose group.

Histopathological examination showed that macaques in the placebo group had severe interstitial pneumonia, while those in the low- and high-dose groups had normal lungs with focal mild changes in a few lobes. There was no evidence of antibody-dependent enhancement of infection among vaccinated macaques 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 three ongoing studies, with total numbers of participants contributing to the clinical database at the time of review in Table 1.

- COVIV-01, a phase 1/2 trial conducted in China;
- COVIV-02, a phase 3 efficacy trial conducted in Bahrain, Egypt, Jordan and the United Arab Emirates;
- COVIV-05, a phase 3 commercial immuno-bridging and lot-to-lot consistency study conducted in China.

Table 1. Number of trial participants who received at least one dose of COVID-19 vaccine BIBP and are included in the clinical database as of 20 April 2021 (2).

	Age group (years)	Authorized dose/schedule	Alternative dose/schedule	Total by age	Total all ages
Safety	18–59	15 789	336	16 125	16 671
	≥60	378	168	546	
Immunogenicity	18–59	2 267	334	2 601	2 890
	≥60	125	164	289	
Efficacy	18–59	13 556	0	13 556	13 765
	≥60	209	0	209	

Other studies are ongoing but have not yet reported results:

- COVIV-03, a phase 3 trial in Peru;
- COVIV-04, a phase 3 trial in Argentina;
- COVIV-PPV23-IIV4-Combine, a pneumococcal polysaccharide and inactivated influenza vaccine coadministration phase 4 trial.

Table 2. Overview of clinical studies of COVID-19 vaccine BIBP (as of 20 April 2021)

Study name Trial registration	**Sponsor**	**Phase** **(primary outcome)**	**Location(s)**	**No. of participants** **Eligible age groups**	**Investigational products**	**Dosing regimens**	**Study status**
COVIV-01 ChiCTR2000032459	Beijing Institute of Biological Products Co., Ltd	Phase 1/2 (safety)	China	2128 healthy subjects ≥3 years	COVID-19 vaccine BIBP	Multiple[a]	Interim results available for participants aged ≥18 years
COVIV-02 NCT04510207	China National Biotec Group Company Limited	Phase 3 (efficacy)	Bahrain, Egypt, Jordan, United Arab Emirates	45 000 healthy subjects ≥18 years	COVID-19 vaccine BIBP COVID-19 vaccine WIBP	2-dose regimen, 4 µg dose, 0/21 day schedule	Interim results available
COVIV-03 NCT04612972	Universidad Peruana Cayetano Heredia	Phase 3 (efficacy)	Peru	12 000 healthy subjects ≥18 years	COVID-19 vaccine BIBP COVID-19 vaccine WIBP	2-dose regimen, 4 µg/ dose, 0/21 day schedule	Recruiting
COVIV-04 NCT04560881	Laboratorio Elea Phoenix S.A.	Phase 3 (efficacy)	Argentina	3000 healthy subjects ≥18 years	COVID-19 vaccine BIBP	2-dose regimen, 4 µg dose, 0/21 day schedule	Recruiting
COVIV-05 CTR20201998	Beijing Institute of Biological Products Co., Ltd	Phase 3 (immuno-bridging and lot-to-lot consistency of commercial product)	China	2100 healthy subjects aged 18–59 years	COVID-19 vaccine BIBP	2-dose regimen, 4 µg dose, 0/21 day schedule	Interim results available
COVIV-PPV23-IIV4-Combine NCT04790851	CNBG	Phase 4 coadministration study	China	1152 healthy subjects	COVID-19 vaccine BIBP	2-dose regimen, 4 µg dose	Recruiting

[a] Multiple dosing, schedule, and age group combinations using low dosage (2 µg), medium dosage (4 µg) and high dosage (8 µg); 3-dose schedule (28 days apart), 2-dose schedule (14, 21, or 28 days apart), and 1-dose schedule; age groups 18–59 years, ≥60 years, 13–17 years, 6–12 years, and 3–5 years.

Immunogenicity studies in humans

COVIV-01

COVIV-01 was a randomized, double-blind placebo-controlled phase 1/2 safety and immunogenicity study with dose-finding and dose escalation (6). Seroconversion at day 14 was defined as a 4-fold increase in neutralizing antibody titre. Serum samples from participants were tested by cytopathic effect (CPE). The neutralizing antibody was measured based on live virus, with the unit of log 50% cell culture infectious dose ($lgCCID_{50}$).

COVIV-01 was a 34-arm study (not including placebo groups), with a combination of dosing levels, dosing schedules, and age groups (3). Safety and immunogenicity results from the two-dose schedules have been published (6). The dose and schedule most analogous to the authorized schedule was a 2-dose schedule of 4 µg per dose administered at 0 and 28 days; these results are given below.

In phase 1, 192 healthy participants aged 18–80 years, who were seronegative for SARS-CoV-2, non-pregnant and non-lactating, were divided into two groups by age (with equal numbers of participants in the 18–59 and ≥60 years groups) (6). Participants were randomly assigned 1:1:1:1 to receive vaccine in a two-dose schedule of 2 µg, 4 µg (licensed dose), or 8 µg or placebo (saline-containing aluminium hydroxide adjuvant) on days 0 and 28. Blood samples were taken on days 4, 14, 28, 32, and 42 after the first dose. Neutralizing antibody titres were assessed on all blood samples using SARS-CoV-2 virus strain 19nCoV-CDC-Tan-Strain05,QD01. In phase 2, healthy adults (aged 18–59 years) were randomly assigned (1:1:1:1) to receive one of three different vaccine/schedule combinations or placebo on a single-dose schedule. Vaccine schedules evaluated were a single-dose of 8 µg on day 0 or on a two-dose schedule of 4 µg on days 0 and 14, 0 and 21, or 0 and 28.