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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World Health Organization

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.

Table 3. Neutralizing antibody seropositivity (titre≥1:4) and geometric mean titres (GMTs) in clinical studies with the authorized dose (4 µg) given on the 0/21 or 0/28-day schedule (3, 6-8).

		Adults 18–59 years						Adults ≥60 years	
		COVIV-01 0/28-day schedule	COVIV-01 0/21-day schedule	COVIV-01 0/28-day schedule	COVIV-02 0/21-day schedule	COVIV-05 Pilot lot 0/21-day schedule	COVIV-05 Commercial 0/21-day schedule	COVIV-01 0/28-day schedule	COVIV-02 0/21-day schedule
Time point		**N=24**	**N=42**	**N=84**	**N=838**	**N=585**	**N=589**	**N=24**	**N=42**
Before vaccination	Seropositive % (95%CI)	0	0	0	9 (n.r)	n.r.	n.r.	0	14 (n.r.)
	GMT (95%CI)	2.1 (2.0, 2.3)	n.r.	n.r.	2.3 (2.2, 2.3)	n.r.	n.r.	2.5 (2.1, 2.9)	2.5 (2.1, 3.0)
14 days after second dose	Seropositive % (95%CI)	100 (n.r.)	n.r.	n.r.	100 (99.6,100)	100.0 (99.4,100.0)	99.8 (99.1,100.0)	100 (n.r.)	100 (92, 100)
	GMT (95%CI)	211.2 (159.0, 280.6)	n.r.	n.r.	156.2 (149.8,163.0)	143.4 (136.5,150.7)	141.8 (134.7,149.2)	131.5 (108.2, 159.7)	109.7 (97.4, 123.4)
28 days after second dose	Seropositive % (95%CI)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	GMT (95%CI)	201.2 (149.9,270.0)	233.6 (176.2,309.7)	214.8 (179.2,257.6)	n.r.	n.r.	n.r.	n.r.	n.r.
90 days after second dose	Seropositive % (95%CI)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	GMT (95%CI)	n.r.	285.6 (208.3,391.6)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

n.r. = not reported.

Across studies, neutralizing antibody seroconversion rates were close to 100% by 14 days after the second dose (Table 3)(3, 6-8). GMTs were high at both 14 and 28 days after the second dose in multiple arms. GMTs ranged from 143.4 to 211.2 14 days after the second dose and from 201.2 to 233.6 28 days after the second dose. The one trial arm with 90-day follow up after the second dose maintained a high titre (285, 95%CI 208.3,391.6) with no evidence of waning (8). Other arms with antibody persistence included three doses and not are reviewed. In the phase 1/2 trial, no participants in the placebo group seroconverted (6). Antibody persistence out to 6 months is being generated.

Immunogenicity data from older adults ≥60 years of age are available from the phase 1 study in China and the phase 3 study, with immunogenicity available for a total of 66 participants in this age group (Table 3). Seroconversion reached 100% 14 days after the second dose in both studies. Neutralizing antibody GMTs were high 14 days after the second dose, although they were lower compared to the younger adult age group from the same study. In the phase 1 trial, GMTs in younger adults 18-59 years of age were 211.2 (95%CI 159.0, 280.6) compared with 131.5 (95%CI 108.2, 159.7) in older adults ≥60 years of age.

COVIV-02

COVIV-02 is a multicentre, randomized, double-blind, placebo-controlled, phase 3 clinical trial to evaluate the efficacy, safety and immunogenicity of COVID-19 vaccine BIBP and COVID-19 vaccine WIBP in healthy people aged 18 years and above. The total target sample size was 45 000, for random allocation 1:1:1 to receive COVID-19 vaccine BIBP, COVID-19 vaccine WIBP or placebo. COVID-19 vaccine BIBP is administered on a two-dose (0/21-day) schedule in the deltoid muscle. The study is being conducted in Bahrain, Egypt, Jordan and the United Arab Emirates. The study is ongoing, and was registered at clinicaltrials.gov, NCT04510207.

In COVIV-02, serum samples were collected from all participants 14 days after the second dose. A subset of participants was enrolled into an immunogenicity subgroup (~900 per site) to assess the antibody response on days 14, 28, 90, 180 and 360 after the second dose. Serum samples were tested by cytopathic effect (CPE). The neutralizing antibody was measured based on live virus, with the unit of $lgCCID_{50}$.

Seroconversion 14 days after the second dose was defined as a 4-fold increase in neutralizing antibody titre compared with baseline. Among all trial participants, 99.3% in the COVID-19 vaccine BIBP group seroconverted compared with 2.3% in the placebo group (7). Neutralizing antibody GMTs were 156.0 in the vaccine group compared with 2.7 in the placebo group. The seroconversion rates of total binding antibody (4-fold increase) were 98.1% and 7.7%, respectively, in the vaccine and placebo groups. The total binding antibody GMTs were 1366.1 and 8.9, respectively, in the COVID-19 vaccine BIBP and placebo groups. There were no significant differences when data were stratified by age or sex (7).

The seroconversion rate of neutralizing antibody in the COVID-19 vaccine BIBP group was 99.5% in those aged 18–59 years and 100.0% in those ≥60 years (7). However, GMTs in younger adults 18-59 years of age were 156.2 (95%CI 149.8, 163.0) compared with 109.7 (95%CI 97.4, 123.4). Thus, across both phase 1 and phase 3 studies, neutralizing antibody GMTs were lower in the older adult age group despite high rates of seroconversion.

COVIV-05

COVIV-05 is a randomized, double-blind study to assess the immunogenicity and safety of the COVID-19 vaccine BIBP manufactured by a 300-litre bioreactor process in comparison with that manufactured by a 10-litre bioreactor process, and the lot-to-lot consistency, in adults aged 18–59 years. The vaccine was given on a 2-dose 0/21-day schedule. On day 14 after the second immunization, the neutralizing antibody GMT against SARS-CoV-2 was 141.8 in the group given commercial-scale COVID-19 vaccine BIBP and 143.4 in those given the pilot-scale COVID-19 vaccine BIBP (Table 3); the ratio was 0.99 (95%CI 0.92, 1.06) (3). The SARS-CoV-2 specific IgG antibody GMTs were 617.1 and 671.1, respectively, and the ratio was 0.92 (95%CI 0.80, 1.06). The immunogenicity of the commercial-scale vaccine was determined to have achieved non-inferiority to the pilot vaccine.

Efficacy

Data available at the time of evidence review come from a single multi-country phase 3 efficacy trial, COVIV-02. The primary aim of COVIV-02 is to evaluate the protective efficacy against COVID-19 of two doses of COVID-19 vaccine BIBP and COVID-19 vaccine WIBP in healthy subjects aged 18 years and above, 14 days following the second dose. Secondary aims include evaluation of safety, immunogenicity, and efficacy against severe SARS-CoV-2 infections. Exploratory aims include evaluation of immunological surrogate endpoints and

the occurrence of antibody-dependent enhancement/vaccine-enhanced disease. This interim analysis is based on data as of 31 December 2020 (7, 9).

Exclusion criteria for the study included (but were not limited to) a history of confirmed or suspected COVID-19 disease, a history of severe acute respiratory syndrome (SARS) or Middle East Respiratory Syndrome (MERS) infection, and pregnancy (7). Suspected cases of SARS-CoV-2 infection were identified through passive surveillance using local surveillance networks of medical and health institutions. Participants could also directly contact a hotline or email to notify relevant clinical symptoms. Active surveillance was also conducted through telephone calls once a week and routine surveillance in the individual countries. Suspected cases were evaluated with nasopharyngeal swabs and venous blood taken at the acute and convalescent stages. SARS-CoV-2 nucleic acid was detected by PCR and/or viral gene sequencing, or a SARS-CoV-2-specific antibody test was performed. Subjects with a positive nucleic acid test, positive IgM and IgG antibody and/or a convalescent serum antibody titre 4 or more times higher than the acute phase serum titre were considered confirmed cases of COVID-19. Participants reporting close contact with a suspected case were tested by PCR and serology. Non-hospitalized PCR-positive cases were treated in insolation via telemedicine, with follow-up within 3–5 days to monitor disease progression and severity. Hospitalization was arranged if indicated.

Box 1: Clinical case definition[a]

Generally speaking, a confirmed case required two or more "A symptoms", or with any one or more "B symptoms", or with COVID-19 imaging features and PCR-confirmed SARS-CoV-2 infection. Details may be found in Appendix 2.

Symptoms A (at least 2 days): fever (axillary temperature ≥ 37.5 ºC); chills; sore throat; fatigue; nasal congestion or runny nose; body pain, muscle pain; headache; nausea or vomiting; diarrhoea.

Symptoms B: cough (for at least 2 days); taste or smell disorders (for at least 2 days); shortness of breath or difficulty breathing.

[a] The case definitions used were developed by the manufacturer and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

Box 2: Clinical classification[a]

- **Mild**: the clinical symptoms are mild and there is no sign of pneumonia on imaging.
- **Moderate**: fever and respiratory symptoms with radiological findings of pneumonia.
- **Severe**: confirmed cases that meet any of the following:
  - respiratory distress (respiratory rate ≥30 breaths/min);
  - oxygen saturation ≤93% at rest;
  - arterial partial pressure of oxygen (PaO2) or fraction of inspired oxygen (FiO2) ≤300 mmHg (1 mmHg = 0.133kPa);
  - clinical symptoms progressively worsening, and the chest imaging showing >50% obvious lesion progression within 24-48 hours.
- **Critical**: confirmed cases that meet any of the following:
  - respiratory failure requiring mechanical ventilation;
  - shock;
  - other organ failure that requires treatment in an intensive care unit (ICU);
  - death.

An Endpoint Assessment Committee composed of experts with relevant experience in the field of clinical research, independent of the researcher and the sponsor, reviewed suspect and confirmed COVID-19 cases, without knowledge of group assignment, for final determination.

The per protocol analysis was conducted among participants compliant with the protocol, including all subjects who complied with the inclusion and exclusion criteria and for whom the PCR test was negative during the screening, participated in randomization, received two doses of vaccine, and completed at least one visit 15 days or more after the 2nd dose.

Results – COVID-19 vaccine BIBP only

A total of 41 301 participants were enrolled in the trial, of which over 98% were aged 18–59 years (7). Of the 893 participants aged 60 years or older, 294 were enrolled in the COVID-19 vaccine BIBP group. Approximately 85% of all participants were male, 87% of participants identified as Asian and 13% as Chinese. Of those participants with baseline serostatus, approximately 6% were positive.

The median duration of follow-up at the time of data lock was 112 days (9). The Clinical Event Committee (CEC) determined that there were 142 confirmed cases of COVID-19 after the second vaccination, of which 26 were in the COVID-19 vaccine WIBP Group, 21 cases in those given COVID-19 vaccine BIBP, and 95 in the placebo group. Most cases occurred in Abu Dhabi, Sharjah, and Bahrain, with fewer in Egypt and Jordan, which began enrolling participants later. For the primary analysis at the data cut-off point, the protective efficacy for COVID-19 vaccine BIBP was 78.1 (95%CI 64.8%, 86.3%) (Table 4) (9). The cumulative incidence curve suggests divergence between the vaccine and placebo groups around three weeks post-first dose (Figure 1).

[a] The case definitions used were developed by the manufacturer and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

Figure 1. Cumulative proportion of participants in COVIV-02 with confirmed COVID-19 in the COVID-19 vaccine BIBP (dotted red line "HB02") and placebo (solid black line) groups.

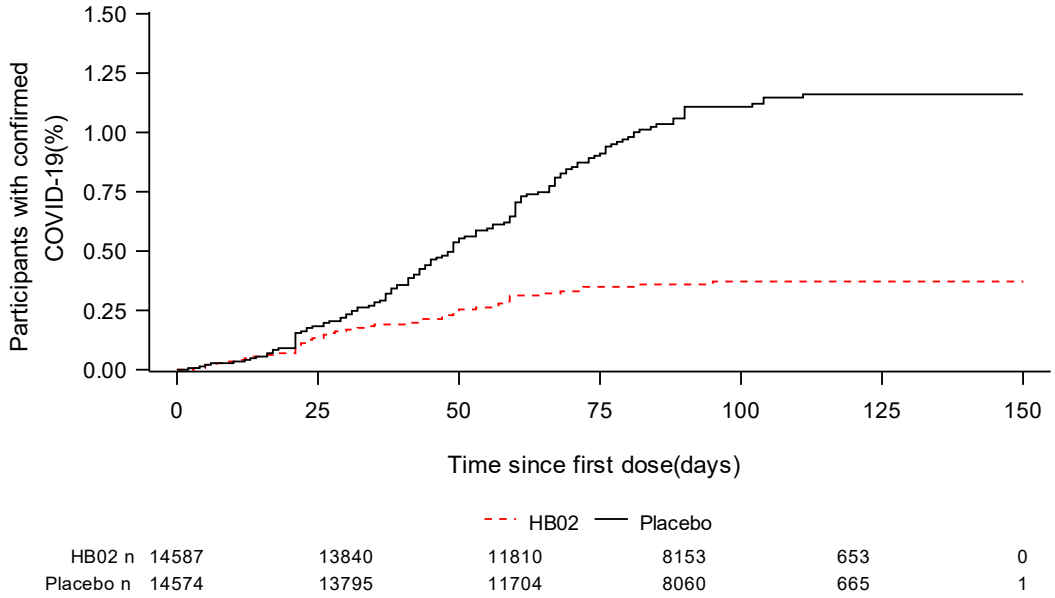


Table 4. Vaccine efficacy per protocol analysis set, COVIV-02, up to data cut-off on 31 December 2020 (9).

	Vaccine Group		Placebo Group		
Group/Subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**VE% (95% CI)**
Overall	13765	21	13765	95	78.1 (64.8, 86.3)
Severe	13765	0	13765	2	n.e.
Sex					
Male	11598	18	11642	83	78.4 (64.1, 87.0)
Female	2167	3	2123	12	75.5 (13.3, 93.1)
Age group					
18-59 years	13556	20	13559	94	78.1 (64.9, 86.3)
≥60 years	209	0	206	0	n.e.
Comorbidities					
Hypertension	374	0	367	4	n.e.
Diabetes	300	2	308	6	63.7 (-79.8, 92.7)
BMI ≥30	3040	7	3080	36	80.7 (56.7, 91.4)
Baseline SARS-CoV-2 status					
Baseline positive	n.r.	0	n.r.	1	n.e.
Baseline negative	n.r.	16	n.r.	83	80.8 (67.2, 88.8)

n.r.=not reported. n.e.=not estimated. VE was not estimated when the number of cases was less than 5.

Efficacy in subpopulations

Adults aged 60 years and above. Clinical efficacy in adults ≥60 years has not been established. The proportion of adults aged 60 or above in the COVIV-02 efficacy study was low (~2%). There were no cases among these participants in any trial arm, and so efficacy in this age group could not be assessed. A second efficacy study in Argentina (COVIV-04), involving 3000 participants, will also include people aged 60 years and over, although it is as yet unclear whether more conclusive results can be obtained from this trial.

Severe disease. Throughout the trial, there were only two cases of severe COVID-19 disease, both of which were in the control group in people aged 18–59 years. Therefore, vaccine efficacy against severe disease has not been demonstrated.

Comorbidities. The trial population in the phase 3 trial was generally healthy; persons with comorbidities, such as uncontrolled hypertension, severe chronic respiratory diseases, and liver and kidney diseases, were excluded from participation. Some subjects with comorbidities were enrolled, and data are available for participants with hypertension, diabetes and BMI ≥30 (Table 4). Vaccine efficacy was demonstrated amongst participants with BMI ≥30 of 80.7% (95%CI 56.7%, 91.4%). For hypertension and diabetes, there were more cases in the placebo group than the COVID-19 vaccine BIBP group, consistent with protection seen in other populations, although the number of participants and cases were small.

Asymptomatic infection. Vaccine efficacy against asymptomatic infection was not an endpoint in the phase 3 trial protocol. Preliminary data on vaccine efficacy against asymptomatic infection was provided (9) but more detail on case ascertainment is needed for interpretation.

Additional efficacy studies

COVIV-03 is a randomized, double-blind, placebo-controlled, phase 3 clinical trial to evaluate the efficacy and safety of inactivated COVID-19 vaccine (Vero cell) in healthy participants aged 18 years and above. It is being conducted in Peru, with 12 000 participants, who are randomly allocated to receive COVID-19 vaccine BIBP, COVID-19 vaccine WIBP or placebo on a 0/21-day two-dose schedule. The study is ongoing, and was registered at clinicaltrials.gov, NCT04612972.

COVIV-04 is a randomized, double-blind, placebo-controlled, phase 3 clinical trial to evaluate the efficacy and safety of COVID-19 vaccine BIBP in healthy participants aged 18 years and above. It is being conducted in Argentina, with 3000 participants, who are randomly allocated to receive COVID-19 vaccine BIBP or placebo on a 0/21 day two-dose schedule. The study is ongoing, and was registered at clinicaltrials.gov, NCT04560881.

Summary

Two doses of COVID-19 vaccine BIBP demonstrated efficacy against non-severe COVID-19 disease in the younger adult population. Data are currently unavailable on protection against severe disease and in older adults ≥60 years of age. Other COVID-19 vaccines have demonstrated higher protection against more severe manifestations of COVID-19, and COVID-19 vaccine BIBP may perform similarly. Two additional vaccine efficacy studies are under way in Argentina and Peru, and data from these studies may help fill some of the current data gaps.

Safety

COVIV-01

In the phase 1/2 trial, COVIV-01 (6), described above, adverse events (AEs) were self-reported by participants, and verified by investigators each day for the first 7 days after each vaccination. In the following 4 weeks, adverse events were recorded by participants on contact cards.

After either vaccination, the most common local adverse reaction was pain, which was reported by 34 (24%) of 144 vaccine recipients, compared with three (6%) of 48 placebo recipients (6). The most commonly reported systemic adverse reaction was fever, which was reported by five (4%) of 144 vaccine recipients, compared with three (6%) of 48 placebo recipients. No serious adverse events were reported within 28 days of vaccination for any group.

In phase 1 (0/28-day schedule), among participants aged 18–59 years, 46% of those given the 2 μg dose experienced an AE within 7 days of vaccination compared with 33% in the 4 μg group, 46% in the 8 μg group, and a total of 25% in all placebo recipients combined. All AEs in days 0–7 were grade 1 or 2 severity (6). The only AE that was statistically significantly higher in the vaccination group was injection site pain, which was reported in 35% of COVID-19 vaccine BIBP vaccinees across all doses compared with 8% in the placebo group. In the 28 days following vaccination, 50% of participants in the 2 μg group experienced an AE, compared with 46% in the 4 μg group, 46% in the 8 μg group, and 29% in the placebo group. All AEs in days 0–28 were grade 1 or grade 2, with the majority being grade 1 (26 grade 1 AEs out of 34 total AEs among 72 vaccinated individuals).

In phase 1 (0/28 day schedule), among participants ≥60 years of age, 4% in the 2 μg group experienced an AE within 7 days of vaccination compared with 25% in the 4 μg group, 21% in the 8 μg group, and a total of 8% in all placebo recipients combined (6). All AEs in days 0–7 were grade 1 or 2 severity. No AEs were statistically significantly higher in the vaccination group than in the placebo group. In the 28 days following vaccination, 8% of participants in the 2 μg group experienced an AE compared with 29% in the 4 μg group, 21% in the 8 μg group and 13% in the placebo group. All AEs on days 0–28 were grade 1 or grade 2, except one grade 3, which occurred in the placebo group. The majority of AEs in the 28 days following vaccination were grade 1 (13 grade 1 AEs out of 14 total AEs among 72 vaccinated individuals).

In phase 2 (8 μg single-dose or 4 μg at 0/14, 0/21 or 0/28 days), at least one AE was reported in 76 vaccine recipients (23%) in the 7 days after any dose, compared with 19 (17%) in the placebo group (6). The AE profile was similar to that in phase 1. Pain was the most common local AE, occurring in 16% of all vaccinees, and 4% of participants in the placebo group (P=0.008). Fever was the most common systemic adverse event, occurring in 7 vaccinees (2%). All AEs on days 0–7 were grade 1 or grade 2, except one grade 3 (self-limiting fever), which occurred in the placebo group. In the 30 days after vaccination, an additional grade 3 AE occurred in the 8 μg single-dose group.

COVIV-02

By the time of the interim analysis for safety (data cut-off 31 December 2020), 14 624 trial participants had received at least one dose of COVID-19 vaccine BIBP (7). The safety follow-up for at least 28 days after vaccination was completed and the long-term safety follow-up is still ongoing. The incidence of solicited adverse events in 18–59-year-olds and in those ≥60 year is summarized in Table 5. The number of participants ≥60 years old was small (294 vaccinated), which limited the ability to detect rare adverse events in this age group. In general, reactogenicity appeared to be lower in the older adult age group.

The most common injection site reaction was pain (18.8% of COVID-19 vaccine BIBP recipients aged 18–59 years and 8.5% of recipients aged ≥60 years) (8). The most common systemic reaction was headache (12.6% of COVID-19 vaccine BIBP recipients aged 18–59 years and 9.2% of recipients aged ≥60 years). Other solicited injection site reactions reported were redness, swelling, and induration, and other common systemic adverse events reported were fever, fatigue, myalgia, arthralgia, cough, dyspnoea, nausea, diarrhoea, and pruritus.

Table 5. The frequency of solicited adverse events in COVIV-02 phase 3 trial (based on second interim analysis). ADR=Adverse drug reaction.

	18–59 years		≥60 years	
Group	**Vaccine (N =14 338)**	**Placebo（N =14 313)**	**Vaccine (N=294)**	**Placebo (N=292)**
Local ADRs	**2883 (20.11%)**	**4047 (28.27%)**	**28 (9.52%)**	**42 (14.38%)**
Grade 3	3 (0.02%)	7 (0.05%)	0 (0.00%)	0 (0.00%)
Pain	2696 (18.80%)	3887 (27.16%)	25 (8.50%)	39 (13.36%)
Grade 3	1 (0.01%)	6 (0.04%)	0 (0.00%)	0 (0.00%)
Swelling	114 (0.08%)	175 (1.22%)	1 (0.34%)	3 (1.03%)
Grade 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Redness	125 (0.87%)	155 (1.08%)	2 (0.68%)	2 (0.68%)
Grade 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Induration	78 (0.54%)	127 (0.89%)	0 (0.00%)	0 (0.00%)
Grade 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erythema	105 (0.73%)	74 (0.52%)	1 (0.34%)	0 (0.00%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus	69 (0.48%)	64 (0.45%)	1 (0.34%)	1 (0.34%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Systemic ADRs	**3989 (27.82%)**	**3891 (27.19%)**	**54 (18.37%)**	**46 (15.75%)**
Grade 3	76 (0.53%)	78 (0.54%)	0 (0.00%)	0 (0.00%)
Headache	1803 (12.57%)	1722 (12.03%)	27 (9.18%)	24 (8.22%)
Grade 3	14 (0.10%)	10 (0.07%)	0 (0.00%)	0 (0.00%)

	18–59 years		≥60 years	
Group	**Vaccine (N =14 338)**	**Placebo（N =14 313)**	**Vaccine (N=294)**	**Placebo (N=292)**
Muscle pain	749 (5.22%)	737 (5.15%)	5(1.70%)	3 (1.03%)
Grade 3	8 (0.06%)	4 (0.03%)	0 (0.00%)	0 (0.00%)
Diarrhoea	506 (3.53%)	569 (3.98%)	7 (2.38%)	5 (1.71%)
Grade 3	8 (0.06%)	9 (0.06%)	0 (0.00%)	0 (0.00%)
Cough	479 (3.34%)	504 (3.52%)	6 (2.04%)	5 (1.71%)
Grade 3	4 (0.03%)	2 (0.01%)	0 (0.00%)	0 (0.00%)
Fever	375 (2.62%)	337 (2.35%)	8 (2.72%)	3 (1.03%)
Grade 3	24 (0.17%)	37 (0.26%)	0 (0.00%)	0 (0.00%)
Fatigue	1577 (11.00%)	1480 (10.34%)	16 (5.44%)	12 (4.11%)
Grade 3	18 (0.13%)	8 (0.06%)	0 (0.00%)	0 (0.00%)
Dyspnoea	157 (1.09%)	172 (1.20%)	0 (0.00%)	1 (0.34%)
Grade 3	6 (0.04%)	2 (0.01%)	0 (0.00%)	0 (0.00%)
Arthralgia	186 (1.30%)	178 (1.24%)	2 (0.68%)	4 (1.37%)
Grade 3	2 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	163 (1.14%)	144 (1.01%)	7 (2.38%)	3 (1.03%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus(no skin lesion)	194 (1.35%)	185 (1.29%)	6 (2.04%)	3 (1.03%)
Grade 3	1 (0.01%)	2 (0.01%)	0 (0.00%)	0 (0.00%)
Constipation	107 (0.75%)	112 (0.78%)	1 (0.34%)	2 (0.68%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting	85 (0.59%)	84 (0.59%)	1 (0.34%)	0 (0.00%)
Grade 3	3 (0.02%)	5 (0.03%)	0 (0.00%)	0 (0.00%)
Dysphagia	59 (0.41%)	63 (0.44%)	0 (0.00%)	0 (0.00%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anorexia	36 (0.25%)	28 (0.20%)	0 (0.00%)	0 (0.00%)
Grade 3	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abnormal skin mucosa	24 (0.17%)	36 (0.24%)	0 (0.00%)	0 (0.00%)
Grade 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Acute hypersensitive reaction	38 (0.27%)	38 (0.27%)	0 (0.00%)	1 (0.34%)
Grade 3	0 (0.00%)	1 (0.01%)	0 (0.00%)	0 (0.00%)

Adverse events of grade 3 and above

There were 113 participants (0.77%) in the placebo group who experienced 133 AEs rated as grade 3 and 104 participants (0.40%) in the COVID-19 vaccine BIBP group who experienced 137 AEs rated as grade 3 (10). The incidence rates of AEs of grade 3 and above assessed to be related to the placebo and COVID-19 vaccine BIBP were 0.66% and 0.66%, respectively. There were no Grade 4 adverse events in the trial.

Grade 3 adverse events at the injection site reported in clinical trials included pain, erythema and pruritus; the grade 3 systemic adverse events reported included fever, fatigue, headache, myalgia, arthralgia, cough, dyspnoea, nausea, vomiting, diarrhoea, and dysphagia (Table 5) (8).

The frequency of unsolicited adverse events in phase 3 clinical trials was 19.2%, and the incidence of grade 3 and above unsolicited adverse events was 0.2%. Unsolicited adverse events of grade 3 severity were oropharyngeal soreness (0.01%), non-injection site rash (0.01%), lymphadenopathy (0.01%) and hypersensitivity (0.01%).

Serious AEs

Eighty participants (0.6%) in the placebo group reported 114 serious AEs, and 59 participants (0.4%) in the COVID-19 vaccine BIBP group reported 129 serious AEs (7). Those from all but two participants were assessed

not to be related to the vaccine. The two participants with serious AEs thought to be related to the vaccine are described below (7).

One subject had serious nausea, vomiting and other symptoms that were confirmed to be related to vaccination; the subject was hospitalized and recovered. A second subject was reported as having "right upper limb weakness" and being unable to speak clearly; this subject was diagnosed as having "inflammatory demyelination syndrome, multiple sclerosis (excluded upon further investigation), clinical isolated syndrome, and acute disseminated encephalomyelitis" by the hospital. It has not been possible to determine whether this case was related to the vaccination.

Adverse events of special interest

As per the Brighton Collaboration guidance of March 2020 (11), the adverse reactions affecting the nervous system were prespecified as adverse events of special interest (AESIs). In the placebo and COVID-19 vaccine BIBP groups, 3.71% and 3.81% of participants experienced an AE of the nervous system (8). The severity of most unsolicited adverse events related to vaccines was grade 1. Headache was common, mostly at grade 1. There was no difference in incidence of neurological unsolicited adverse events when stratified by younger and older adults (data not shown). There were two cases of Bell's palsy in the trial, one in the placebo group and one in the COVID-19 vaccine BIBP group (4).

Table 6. Occurrence of unsolicited adverse events of special interest (neurological symptoms) in the 28 days after vaccination (COVIV-02 phase 3 trial) (8).

Adverse events	Placebo (N=14 606)			COVID-19 vaccine BIBP (N=14 634)		
	No. of occurrences	No. of participants	Incidence (%)	No. of occurrences	No. of participants	Incidence (%)
Neurological symptoms	599	542	3.71	618	558	3.81
Headache	291	278	1.9	279	268	1.83
Dizziness	146	137	0.94	151	142	0.97
Lethargy	78	77	0.53	99	93	0.64
Hypoesthesia	20	19	0.13	25	25	0.17
Loss of taste	20	18	0.12	17	17	0.12
Loss of smell	10	10	0.07	15	13	0.09
Drowsiness	7	7	0.05	6	6	0.04
Paraesthesia	7	7	0.05	5	5	0.03
Hypersomnia	4	4	0.03	3	3	0.02
Dysgeusia	4	4	0.03	4	4	0.03
Parageusia	5	5	0.03	2	2	0.01
Tremor	1	1	0.01	3	3	0.02
Lack of sleep	0	0	0	3	3	0.02
Head discomfort	2	2	0.01	0	0	0

To date, one thrombotic event has been identified among the 29 240 subjects in the phase 3 clinical trial; the person was in the COVID-19 vaccine BIBP group (2). The subject was male, 50 years old, and received one dose of COVID-19 vaccine BIBP. The medical record showed that the subject had suffered from hepatitis C 10 years previously, and had received a full course of treatment for hepatitis C. The details provided by the investigators show that the subject had a history of blood clots before vaccination. This information was not provided initially His current medication was low-dose aspirin. Mild palpitations (grade 2) occurred two days after vaccination and

were not treated; seven days after vaccination, the subject suffered from abdominal pain and was examined using Doppler ultrasound. Thrombus was diagnosed, though details on which vessel and platelet count were not provided. The investigators rated the event as grade 1 and unrelated to the vaccine. This participant did not receive the second dose.

Special considerations

Pregnancy and lactation

The available data on COVID-19 vaccine-BIBP in pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. Based on data provided to date, no pregnancies have been reported during post-authorization rollout of COVID-19 vaccine BIBP. In phase 3 clinical trials, eight pregnancies were reported in the placebo group and five in the COVID-19 vaccine BIBP group, all of which occurred following vaccination (10). There has been no inadvertent vaccination during pregnancy. Pregnancies and birth outcomes will be monitored during the existing trials. No specific studies in pregnant women are currently planned.

Paediatric population

Results are not yet available in subjects less than 18 years of age. Safety and immunogenicity data from a 3-dose 0/28/56-day schedule of 2 µg, 4 µg, and 8 µg per dose will be available through COVIV-01 (Table 2). The number of participants in each age group (13–17, 6–12, and 3–5 years of age) was 96 in phase 1 and 240 in phase 2.

Immunosuppression

Combination use with immunosuppressive drugs, such as immunosuppressive agents, chemotherapy drugs, antimetabolic drugs, alkylating agents, cytotoxic drugs and corticosteroids, may reduce the immune response to this product.

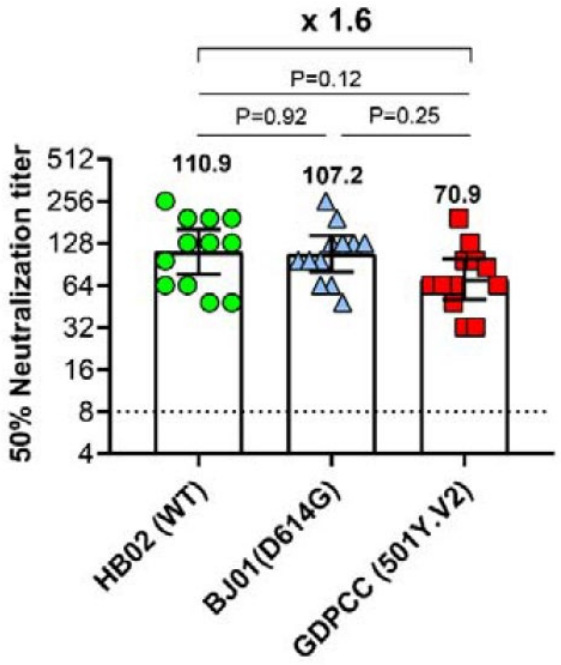
Safety related to vaccine interactions

A phase 4 immunogenicity and safety trial of COVID-19 vaccine BIBP coadministration with the 23-valent pneumococcal polysaccharide vaccine (PPV23) or quadrivalent inactivated influenza vaccine (IIV4) is under way. Results are expected soon.

Emerging virus variants of concern

Estimates of clinical protection against variants of concern (VOC) are not yet available for COVID-19 vaccine BIBP. A recent preprint evaluated neutralization of 12 serum samples from the COVIV-02 phase 3 trial, taken 28 days after the second vaccine dose, against the COVID-19 vaccine BIBP parent strain HB02 and SARS-CoV-2 VOC 501Y.V2 (12). Sera came from participants with a range of neutralization titres. Neutralization of live SARS-CoV-2 strains GDPCC (501Y.V2) was measured by the microcytopathogenic effect assay. All 12 serum samples from COVID-19 vaccine BIBP recipients were able to neutralize 501Y.V2, although the GMT was 1.6-fold lower than against HB02 (110.9 (95%CI, 76.7–160.2%) against HB02 and 70.9 (95%CI, 50.8–98.8%) against 501Y.V2 (Figure 2).

Figure 2. Neutralization titres of 12 antisera from recipients of COVID-19 vaccine BIBP against canonical SARS-CoV-2 and its variants, D614G and 501Y.V2. Taken from (12).



Booster doses

Vaccine efficacy results are based on median follow up of 112 days after the first dose. Booster doses are not yet included in any clinical trial, although BIBP are in discussions with the phase 3 trial investigators about the feasibility and implementation plans for adding a booster dose to the existing study. No decision has yet been made on the necessity of a booster dose. (13).

BIBP is sponsoring a phase 4 clinical study in China to evaluate the safety, immunogenicity, and immune persistence among people aged ≥3 years. The schedules evaluated will be 0, 21, 42 days; 0, 21, 111 days; and 0, 21, 171 days. The study has been approved by the Ethics Committee and will be implemented in May 2021 (13).

Post-licensure experience

More than 65 million doses of COVID-19 vaccine BIBP have been used in emergency programmes (9). Post-licensure safety, evaluated through routine passive surveillance, is available from China, though data are not yet shared from other settings. Post-licensure safety remains limited and both routine pharmacovigilance as well as supplementary phase 4 studies are ongoing or planned.

Risk management plan

The following studies are ongoing or planned as part of the clinical development program and the Risk Management Plan (13, 14):

- Follow up of existing clinical trial participants (Phase 3: 12 months follow up)
- Vaccine efficacy in Peru and Argentina
- Vaccine effectiveness in United Arab Emirates (amongst vaccinees ≥60 years of age), Bahrain, and Pakistan
- Paediatric immunogenicity and safety trial in China
- Safety, immunogenicity, and immune persistence among people aged ≥3 years with variable booster dose schedules (booster at day 42, 111, or 171)
- Vaccine co-administration (23-valent pneumococcal polysaccharide vaccine or quadrivalent inactivated influenza vaccine) study in China

- Active safety monitoring cohort (N>100,000) in China, including monitoring for anaphylaxis, 40% adults ≥60 years of age, and adults with comorbidities (6 months follow up)
- Active safety monitoring cohort (N=1,000) in China, including special populations such as immunocompromised and elderly patients with chronic bronchitis, thrombocytopenia, or vital organ damage (6 months follow up)
- Passive safety monitoring (N=1,000,000) in China through China's National AEFI system

As listed above, BIBP has developed a protocol to conduct active safety studies in 100 000 vaccine recipients from between 6 and 19 provinces in China. It is planned that at least 40% of participants will be adults over 60 years of age and 5% will have comorbidities, including chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, and cardiovascular disorders. A second post-licensure active safety surveillance study with 1 000 participants will also include people with comorbidities and special groups, such as people with immunodeficiency or immunocompromising conditions (acquired immunodeficiency syndrome (AIDS), malignant tumour, nephrotic syndrome), and elderly patients with chronic bronchitis, thrombocytopenia or vital organ damage. The occurrence of abnormal laboratory indicators, such as platelet count, will be monitored. Relevant data from these post-licensure safety studies are expected to be provided by the end of 2021.

Post-licensure safety monitoring

Safety data among people vaccinated in China with COVID-19 vaccine BIBP have been generated through post-authorization use and monitoring by the passive AEFI monitoring system of China CDC. A report of post-licensure safety was provided based on data as of 30 December 2020 (10). Approximately 5.9 million people in China had been vaccinated with COVID-19 vaccine BIBP; the number of reported adverse events was 1453, including 1 120 general reactions (expected reactogenicity) and 333 other adverse reactions. The total incidence of adverse events was 24.6 per 100 000 doses, with 19.0 general reactions per 100 000 doses and 5.6 other adverse reactions per 100,000 doses. Complete stratification by severity has not been provided.

Included in the 1120 general adverse reactions reported were 108 local reactions and 1051 systemic reactions. Among the local reactions, there were 39 reports of induration at the injection site, of which 26 were mild (≤2.5 cm), 11 moderate (2.6–5.0 cm), and 2 severe (>5.0 cm). A total of 69 cases of redness and swelling at the injection site were reported, of which 38 were mild (≤2.5 cm), 25 moderate (2.6–5.0 cm) and 6 severe (>5.0 cm). Among the systemic reactions, there were 292 reports of fever, of which 78 were mild (37.1–37.5 ºC), 128 moderate (37.6–38.5 ºC) and 86 severe (≥ 38.6 ºC). All the above AEs resolved or improved.

Most of the 333 reports of other adverse reactions after COVID-19 vaccine BIBP were local reactions, such as allergic rash (2.9%), maculopapular rash (0.2%) and urticaria (0.6%). Eleven cases of facial paralysis were reported, all of which were assessed to be related to vaccination. Of the 11, eight have improved and three are undergoing treatment. There were 26 coincidental events after injection with COVID-19 vaccine BIBP, giving an incidence rate of 0.44 per 100 000 doses, mainly caused by various infections, such as upper respiratory tract infection, acute gastroenteritis, and diarrhoea.

An updated summary was provided on the safety of COVID-19 vaccine BIBP in older adults through programmatic use (14). Based on 1.1 million doses of COVID-19 vaccine BIBP- administered to people 60 years of age or older in China, AEFIs were reported 79 individuals, with 45 adverse reactions considered related to vaccination. Most common reports were dizziness (n=23), headache (n=9), fatigue (n=9), nausea (n=7), fever (n=6), vomiting (n=6), allergic dermatitis (n=6).

A formal comprehensive report of post-licensure safety data from China is not yet available, nor are post-licensure safety data from outside China.

Vaccine effectiveness

Vaccine effectiveness assessments are limited. A preliminary, high-level, unpublished summary report of a vaccine effectiveness study in the context of routine rollout in Bahrain was shared (15). The study used a test-negative design and national surveillance and vaccination databases. Vaccine effectiveness was high, including across age groups and gender. Additional methodologic details will be important to appropriately assess and interpret vaccine effectiveness.

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Appendix 1. Number of participants who received at last one dose of COVID-19 vaccine BIBP and were included in safety, immunogenicity, and efficacy analyses.

Table A1. Number of trial participants who received at least one dose of COVID-19 vaccine BIBP and were included in the safety clinical database reviewed by SAGE

Age group	Study	Number who received authorized 4 µg dose	Number who received alternative dose/schedule
18–59 years	COVIV-01 phase 1	24	48
	COVIV-01 phase 2	228	288
	COVIV-02	14 338	N/A
	COVIV-05	1199	N/A
	Total	**15 789**	**336**
≥60 years	COVIV-01 phase 1	24	48
	COVIV-01 phase 2	60	120
	COVIV-02	294	N/A
	Total	**378**	**168**

Table A2. Number of trial participants who received at least one dose of COVID-19 vaccine BIBP and were included in the immunogenicity clinical database reviewed by SAGE

Age group	Study	Number who received authorized 4 µg dose	Number who received alternative dose/schedule
18–59 years	COVIV-01 phase 1	24	48
	COVIV-01 phase 2	228	287
	COVIV-02	834	N/A
	COVIV-05	1181	N/A
	Total	**2267**	**335**
≥60 years	COVIV-01 phase 1	24	48
	COVIV-01 phase 2	59	116
	COVIV-02	42	N/A
	Total	**125**	**164**

Table A3. Number of trial participants who received at least one dose of COVID-19 vaccine BIBP and were included in the efficacy clinical database reviewed by SAGE

Age group	Study	Number who received authorized 4 µg dose	Number who received alternative dose/schedule
18–59 years	COVIV-02	13 556	N/A
≥60 years	COVIV-02	209	N/A

Appendix 2. Primary case definition for confirmed COVID-19

The primary case definition criteria varies based on whether an epidemiologic history (defined below) was present.

Epidemiological History

A. Long-term residence or stay in the epidemic area for more than 7 days is deemed to have an epidemiological history.
B. Or any subject has a history of travel or residence in the community where the case appeared within 14 days before the onset of symptom.
C. Or any subject in contact with SARS-CoV-2 infected or asymptomatic infected persons within 14 days before the onset of symptoms.
D. Or any subject of community clustered cases (2 or more cases of fever and/or respiratory symptoms developed in a small area such as home, office, school, etc. within 2 weeks).

Epidemiologic history present: Two or more A symptoms, or with any one or more B symptoms, or with COVID-19 imaging features and PCR-confirmed SARS-CoV-2 infection.

No epidemiologic history present: Two or more A symptoms or one or more B symptoms and detectable SARS-CoV-2 IgM, or with two or more A symptoms and one or more B symptoms, or with imaging features of COVID-19 and PCR-confirmed SARS-CoV-2 infection.

Clinical Symptoms

- A Symptoms (presence for at least 2 days): fever (axillary temperature ≥37.5℃), chills, sore throat. fatigue, nasal congestion or runny nose, body pain, myalgia. headache, nausea or vomiting, diarrhoea.
- B Symptoms: Cough (presence for at least 2 days), new taste or smell disorders (presence for at least 2 days), shortness of breath or difficulty breath.

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/BIBP/background/2021.1