FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF ZIFIVAX

Badan POM, the Indonesia Food and Drug Administration, has issued **an Emergency Use Authorization (EUA)** to permit the emergency use of Zifivax. Zifivax is a vaccine which may prevent individuals from getting COVID-19. Read this Fact Sheet for information about Zifivax prior to providing vaccination.

The Emergency Use Authorization of Zifivax is to induce immune response to SARS-CoV-2 for the prevention of COVID-19 in individuals 18 years of age and above

Zifivax is contraindicated in person who is

1. hypersensitive to any component of this vaccine, or
2. suffers from Primary Immunodeficiency.

ADMINISTRATION

The recommended route of administration is intramuscular injection in deltoid muscle in the upper arm. Shake well before injection.

The Zifivax vaccination series is 3 doses given at 1-month intervals (months 0, 1, and 2), 0.5 mL per dose.

In recent studies, Zifivax can be used as heterologous booster dose in people who have received two doses of inactivated COVID-19 Vaccine (Sinovac or Sinopharm) 6-8 months prior in people aged 18 years and above.

Zifivax is available as a suspension for injection packed in 0,5 mL (1 dose) and 1,0 mL (2 doses) vial. This product contains no preservative.

See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** related to Zifivax.

This Fact Sheet may have been updated. For more recent Fact Sheet see www.pom.go.id

For more information on clinical trials that are testing the use of Zifivax, please see www.clinicaltrials.gov

INSTRUCTIONS FOR ADMINISTRATION

This section provides essential information on the use of Zifivax which is to induce immune response against SARS-CoV-2 for the prevention of COVID-19 in individuals aged 18 years and above.

Please refer to this fact sheet for information on use of Zifivax under the EUA.

Composition

Each dose (0.5 mL) contains Recombinant Novel Coronavirus Vaccine (CHO cell) 25 μg NCP-RBD*/dose
*protein from receptor-binding domain of SARS-CoV-2 spike glycoprotein, expressed in recombinant CHO cells
Two doses (1.0 mL) contain Recombinant Novel Coronavirus Vaccine (CHO cell) 50 μg NCP-RBD.

The vaccine is a milky-white suspension, stratified precipitate may form which can be dispersed by shaking.

Excipients: aluminum hydroxide, sodium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate, and Histidine.
This product contains no preservative.

Indication

This vaccine stimulates the body to induce immune response to SARS-CoV-2 for the prevention of COVID-19 in individuals 18 years of age and above.

Contraindications

This product is contraindicated in person who is hypersensitive to any component of this vaccine or suffers from Primary Immunodeficiency

Dosage and Administration

The recommended route of administration is intramuscular injection in deltoid muscle in the upper arm. Shake well before injection.

The Zifivax vaccination series is 3 doses given at 1-month intervals (months 0, 1, and 2), 0.5 mL per dose.

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<u>Special Populations</u>

Paediatric population

The safety and efficacy of Zifivax in children under 18 years of age have not yet been established. No data is available.

WARNINGS

1. Shake well before use. Do not use the vaccine if the vial shows abnormities such as crack, foreign matters, clumps that can't disperse after shaking, or illegible label.
2. The vaccine shall be administered immediately after the vial is opened.
3. Adrenaline should be available for first aid in case of severe anaphylactic reactions. The recipients should be observed for at least 30 minutes on site after injection.
4. Freezing is strictly prohibited.
5. For individuals under the following circumstances, the use of this vaccine should be with caution:
    a. Have allergies, including allergies to ingredients in the Zifivax vaccine
    b. Experiencing a high fever
    c. Have acute illness and/or acute attacks of chronic disease. If this condition is present, vaccination is postponed
    d. Have coagulation/bleeding disorder or thrombocytopenia.
    e. Suspected or confirmed immunodeficiency or currently receiving immunosuppressive therapy such as IV immunoglobulins, blood products, long-term corticosteroids, as they may lower the efficacy of the vaccine
    f. Have epilepsy or other uncontrolled neurological disorders, such as Guillain-Barre Syndrome.
    g. Has autoimmune disease.
    h. Have a history of severe asthma or other severe adverse reactions to vaccines, such as urticaria, dyspnea, dan angioneurotic edema.
    i. Have serious chronic illness (serious heart problems, uncontrolled hypertension, uncontrolled diabetes, liver/kidney disease, kidney disease, tumors and cancer)
    j. For the elderly, when experiencing the following signs:
        i. Difficulty climbing 10 steps of stairs
        ii. Decreased physical activity (often experiencing fatigue)
        iii. Have 4 of 11 diseases (hypertension, diabetes, cancer (other than minor skin cancer), chronic lung disease, heart attack, congestive heart failure, chest pain, asthma, joint pain, stroke, kidney disease)
        iv. Difficulty walking about 100 to 200 meters.
        v. Significant weight loss in a year.
    k. Are pregnant or planning a pregnancy
    l. Breastfeeding
    m. Previously/currently suffering from COVID-19. If you are suffering from COVID-19, vaccination can be postponed

DRUG INTERACTIONS

Concomitant administration of other vaccines: there has been no clinical studies on the effect of concomitant (pre, post or simultaneous) administration of other vaccines on the immunogenicity of this vaccine. There is no data available to assess the effect of simultaneous administration of this product with other vaccines.

For patients currently receiving immunosuppressive therapy such as IV immunoglobulins, blood products, long-term corticosteroids, it is recommended that they consult a professional physician before receiving the vaccine as these may lower the efficacy of the vaccine and to avoid any possible drug interaction.

FERTILITY, PREGNANCY AND LACTATION

There is no safety and efficacy data available for the use of Zifivax in pregnant and breastfeeding women.

ADVERSE REACTIONS

The frequencies of adverse events are defined as follows: very common (≥ 10%), common (≥ 1% and < 10%), uncommon (infrequent) (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), and very rare (< 0.01%).

According to the clinical trials conducted in China, Indonesia, Uzbekistan, Ecuador, and Pakistan, most of the adverse events reported in these studies were mild to moderate.

The safety of Zifivax Vaccine was evaluated in participants 18-59 years of age in one phase 1 study in China, one phase 2 study in China, and one phase 3 study conducted in China, Indonesia, Uzbekistan, Ecuador, and Pakistan. The safety in elderly participants 60 years of age and above was evaluated in one phase 1 clinical study in China and the same phase 3 global clinical study.

Phase 1 Clinical Study in China

Phase 1 clinical trial of Zifivax in China involved 50 participants 18 to 59 years of age which are included in the safety analysis that consists of 20 in high-dose group (50 µg/0.5 mL), 20 in low-dose group (25 µg/0.5 mL), and 10 in placebo group with vaccination schedule month 0, 1 , 2. The incidences of adverse events related to the vaccination were 85.00% in high-dose group, 65.00% in low-dose group, and 70.00% in placebo group. The most common adverse events were pain and itching at injection site. Most of the adverse events were reported as mild (Grade 1 or 2), only 1 case was grade 3 (flush and swelling). No serious adverse event occurred in the trial.

Phase 2 Clinical Study in China

Phase 2 clinical trial of Zifivax in China involved 900 participants 18 to 59 years of age. The incidences of adverse events related to the vaccination were 20.00%, 24.00%, 14.67%, 39.33%, 32.00% and 20.67% in the low-dose 2 vaccinations group, high-dose 2 vaccinations group, placebo 2 vaccinations group, low-dose 3 vaccinations group, high-dose 3 vaccinations group and placebo 3 vaccinations group, respectively. Most of the adverse reactions fell into Grade 1 and Grade 2 in severity. The adverse reactions with statistical differences between the groups included fatigue/asthenia, pain, swelling, induration, flush and itching. The incidence of adverse reactions ⩾ Grade 3 after vaccination was 1.33%, 0.67%, 1.33%, 3.33% and 1.33%, respectively. The incidences of serious adverse events were 0.67% in the low-dose 2 vaccinations group, high-dose 2 vaccinations group and low-dose 3 vaccinations group, 1.33% in high-dose 3 vaccinations group and placebo 3 vaccinations group, and 0.00% for placebo 2 vaccinations group. However, none of the serious and ⩾ Grade 3 adverse events were judged to be related to the investigational vaccine or statistically significant.

Table 1. Post-Vaccination Overall AEs in Adult Subjects

Analyzed Item	Low-dose 2-vaccination group		High-dose 2-vaccination group		Placebo 2-vaccination group		Low-dose 3-vaccination group		High-dose 3-vaccination group		Placebo 3-vaccination group		*P*
	Cases	Incidence (%)	Cases	Incidence (%)	Cases	Incidence (%)	Cases	Incidence (%)	Cases	Incidence (%)	Cases	Incidence (%)	
Overall Trial													
All AEs	43	28.67	51	34.00	37	24.67	72	48.00	65	43.33	49	32.67	0.0001
AEs related to vaccine	30	20.00	36	24.00	22	14.67	59	39.33	48	32.00	31	20.67	<0.0001
Systemic adverse reaction	15	10.00	16	10.67	8	5.33	15	10.00	13	8.67	16	10.67	0.5890
Grade 3 or above	2	1.33	0	0.00	0	0.00	0	0.00	0	0.00	1	0.67	0.2189
Local adverse reaction	17	11.33	19	12.67	9	6.00	45	30.00	35	23.33	6	4.00	<0.0001
Grade 3 or above	0	0.00	1	0.67	0	0.00	2	1.33	5	3.33	0	0.00	0.0121
Unsolicited adverse reactions	5	3.33	5	3.33	9	6.00	10	6.67	9	6.00	15	10.00	0.1415
Grade 3 or above	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.67	0.4152
AEs unrelated to the vaccine	22	14.67	23	15.33	19	12.67	27	18.00	31	20.67	26	17.33	0.5023
SAE	1	0.67	1	0.67	0	0.00	1	0.67	2	1.33	2	1.33	0.7844

Phase 3 Global Clinical Study

Safety data come from 27,470 adult and elderly subjects aged 18 and over outside China (Indonesia, Uzbekistan, Ecuador, and Pakistan) who received at least one dose of this product, including 13,725 in the placebo group and 13,745 in the vaccine group.
The incidence of AE during vaccination was 37.65% among all subjects. The incidence in vaccine group and placebo group was 38.09% and 37.21%, respectively with no statistical difference. The incidence of vaccine-related AE in the vaccine group and placebo group was 31.01% and 30.07%, respectively, also with no statistical difference.
The main adverse reaction symptoms in the vaccine group were headache (12.54%), tiredness / fatigue (8.10%), fever (7.85%), myalgia (5.79%), cough (4.55%), nausea (3.59%), diarrhea (2.49%), and routine adverse reactions such as pain at the injection site (15.99%), pruritus (2.95%), swelling (0.79%), induration / sclerosis (0.37%), redness / erythema (0.73%) after vaccination, and the severity was mainly grade 1 and grade 2.
Out of 212 SAE cases, 105 cases were in vaccine group and 107 cases were in placebo group, with an incidence of 0.76% and 0.78%, respectively, but there was no significant difference (P=0.8906). For vaccine-related SAE, there were 3 cases in the vaccine group (0.02%) and 2 cases in the placebo group (0.01%), with no significant difference (P =1.0000). As of the time of this analysis, there were no SAE associated with the study vaccine resulting in death, and no adverse events of particular concern such as ADE/VED were observed.

Booster Clinical Study in Hunan, China

Heterologous booster immunization clinical study in China involved 360 subjects aged 18 years and above who had received 2 doses of inactivated virus COVID-19 vaccine injection in the prior 3-13 months.

Incidence of adverse events in 3-4, 6-8, and 11-13 month groups were 35.83%, 40.83%, and 26.67% respectively. The incidence of adverse reactions were 30.00%, 37.50% and 25.83%, respectively; Most of them are solicited AR. There was no significant difference in AE between groups. The incidence of local adverse reactions were 23.33%, 28.33% and 21.67% respectively consisting mostly of local pain at injection site, and the incidence of systemic adverse reactions were 15.00%, 14.17% and 7.50% respectively consisting of mostly fatigue. Severity of AR was mostly grade 1 or grade 2. The incidence of grade 3 AR was 0.83% in each group. No AR ≥ grade 4 occurred. No vaccine related SAE occurred.

Humoral immunogenicity and reactogenicity of CoronaVac or ZF2001 booster after two doses of inactivated vaccine

The overall incidence of adverse reactions were 39.0% (CoronaVac) and 23.5% (Zifivax). Most common ARs were local injection site reactions and all ARs were grade 1.

Cao, Y., Hao, X., Wang, X. *et al.* Humoral immunogenicity and reactogenicity of CoronaVac or ZF2001 booster after two doses of inactivated vaccine. *Cell Res* **32,** 107–109 (2022). https://doi.org/10.1038/s41422-021-00596-5

Recombinant protein subunit vaccine booster following two- dose inactivated vaccines dramatically enhanced anti-RBD responses and neutralizing titers against SARS-CoV-2 and Variants of Concern

Solicited injection site adverse reactions rate was 42.30% and for systemic was 11.30%. The most common injection site and systemic adverse reaction were pain (28.20%) and fatigue (8.50%). Only 4 (5.60%) and 1 (1.40%) participant reported emerging or persisting injection site adverse reactions from day 4 to 14 and from day 15 to 28, respectively, and 2 (2.80%) and 1 (1.40%) reported solicited systemic adverse reactions in these periods.

Ai, J., Zhang, H., Zhang, Q. *et al.* Recombinant protein subunit vaccine booster following two-dose inactivated vaccines dramatically enhanced anti-RBD responses and neutralizing titers against SARS-CoV-2 and Variants of Concern. *Cell Res* **32,** 103–106 (2022). https://doi.org/10.1038/s41422-021-00590-x

Safety in Elderly

Phase 1 clinical study in China involved 50 participants of age 60 years and above which are included in the safety analysis that consists of 20 in high-dose vaccine group (50 µg/0.5 mL), 20 in low-dose vaccine group (25 µg/0.5 mL), and 10 in placebo vaccine group. According to the observation until 30 days after three vaccinations, the incidence rate of adverse events in high-dose group, low-dose group and placebo group was 60.00%, 55.00% and 40.00% respectively, and there was no significant difference between groups (P = 0.7050).
The incidences of adverse events related to the vaccination were 50.00% in high-dose group, 50.00%, in low-dose group and 30.00% in placebo group, and there was no significant difference between groups. The most common adverse events were local adverse events in all groups (all 10% incidences) with no significant difference, manifested as pain and itching at the injection site. All of the adverse events were Grade 1 or 2, no adverse reactions ≥ Grade 3 were observed. No serious adverse event occurred in the trial.

Table 2. Overall Adverse Events Post-Vaccination in Elderly Subjects

Analytical items	Low-dose group (N=20)			High-dose group (N=20)			Placebo group (N=10)			*P* value
	No. of AEs	Number of Subjects	Incidence (%)	No. of AEs	Number of Subjects	Incidence (%)	No. of AEs	Number of Subjects	Incidence (%)	
AEs after vaccination	15	11	55.00	17	12	60.00	7	4	40.00	0.7050
Study vaccine-related AEs	13	10	50.00	14	10	50.00	4	3	30.00	0.5405
Investigational drug-unrelated AEs	2	2	10.00	3	3	15.00	3	2	20.00	0.8699
Grade 3 or above AEs	0	0	0.00	0	0	0.00	0	0	0.00	1.0000
Grade 3 or above investigational drug-related AEs	0	0	0.00	0	0	0.00	0	0	0.00	1.0000
Adverse events leading to withdrawal from treatment	0	0	0.00	0	0	0.00	0	0	0.00	1.0000
Investigational drug-related AEs leading to withdrawal from trial	0	0	0.00	0	0	0.00	0	0	0.00	1.0000

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of action

COVID-19 Vaccine (CHO cell), purified NCP-RBD protein from receptor-binding domain of SARS-CoV-2 spike glycoprotein expressed in recombinant CHO cells, developed by Anhui Zhifei Longcom Biopharmaceutical Co. Ltd., can induce immune response to SARS-CoV-2 by producing neutralizing antibody and RBD protein binding antibody.

Preclinical Studies

Single-dose toxicity tests in cynomolgus monkeys (50 μg and 100 μg) and rats (2 human doses) showed no toxicity. A 4-week repeat-dose toxicity test in rats (0.5 and 1 human doses) and monkeys (1 human dose) did not cause toxicity. A 10-week repeated-dose toxicity test in cynomolgus monkeys (1 and 2 human doses) also did not produce toxicity. Embryo-fetal developmental toxicity test in pregnant rats had no significant toxic effects on the parental pregnant rat and embryo-fetal development, and produced antibodies that could cross the placental barrier. Muscle irritation test in rabbits showed slight stimulus response consistent with aluminum adjuvant.

Protective effects were evaluated by infecting vaccinated rhesus monkeys (3 doses of 25 μg and 50 μg) and mice which showed that they had significantly lower or negative viral load titers and only mild interstitial pneumonia compared to severe interstitial pneumonia in control group. Efficacy test conducted on mouse at 2 doses of 10 μg stimulated RBD-specific IgG and neutralizing antibodies which persisted for weeks observed with significantly lower viral loads and much milder interstitial pneumonia than placebo.

CLINICAL STUDIES

Immunogenicity

Phase 1 study of adult subjects in China

Immunogenicity analysis in Phase 1 clinical study was carried out in 2 different doses, the low dose (25 μg/0.5 mL) and the high dose (50 μg/0.5 mL) with vaccination schedule month 0, 1, 2. The positive conversion rates of live virus neutralizing antibody and RBD protein binding antibody in low-dose and high-dose groups were 100% on Day 7 after the 3rd vaccination, and remained 100.00% 1 month after third dose for RBD protein binding antibody. The GMT of neutralizing antibody on Day 7 after the 3rd vaccination for low-dose and high-dose group were 94.5 and 117.8 respectively. The GMT of RBD protein binding antibody on Day 7 after 3rd vaccination were 2016.24 and 2409.96 respectively, and on Day 30 after 3rd vaccination were 2719.53 and 2776.75 respectively.

Phase 2 study of adult subjects in China

Immunogenicity was evaluated in two different doses and two different number of vaccinations. The positive conversion rates of euvirus neutralizing antibody 14 days after full course vaccination were 76.00% (low-dose-2-vaccination), 72.00% (high-dose-2-vaccination), 96.62% (low-dose-3-vaccination), and 93.24% (high-dose-3-vaccination). The positive conversion rates of RBD protein binding antibody 14 days after full course vaccination are 92.52% (low-dose-2-vaccination), 93.20% (high-dose-2-vaccination), 99.31% (low-dose-3-vaccination), and 97.20% (high-dose-3-vaccination). The GMT values of neutralizing antibody were significantly higher on Day 14 after the 3rd vaccination (low dose–102.5; high dose–69.1) than Day 14 after the 2nd vaccination (low doses–17.7, 19.5; high doses–14.1, 12.6). GMTs for both placebo groups were 2.0. The GMT values of RBD protein binding antibodies were also significantly higher on Day 14 after the 3rd vaccination (low dose–1782.26; high dose–1139.97) than Day 14 after the 2nd vaccination (low doses – 439.82, 483.94; high doses–338.04, 265.43). GMTs were higher in low-dose groups than high-dose groups for both antibodies.

Booster Clinical Study of adult and elderly subjects in Hunan, China

Immunogenicity was evaluated in 3 groups differentiated by the interval between the last dose of Inactivated Vaccine and booster dose. Positive conversion rate of neutralizing antibody is analyzed 14 days after booster. The prototype positive rates are 90.83% (3-4 month), 95.00% (6-8 month), and 66.67% (11-13 month). The delta positive conversion rates are 91.67%, 90.00%, and 68.33% respectively. The GMT of prototype neutralizing antibody were 28.3, 49.1, and 16.6 with growth multiples of 12.9, 23.7, and 7.2. The GMT of delta neutralizing antibody were 57.3, 104.6, and 29.3 with growth multiples of 27.1, 50.2 and 13.2. Comparing the GMT of SARS-CoV-2 prototype neutralizing antibody in each group, the 6-8 month group is twice that of 3-4 month group and 3.2 times that of 11-13 month group, and for delta is 2 times higher than that of 3-4 month group and 3.8 times higher than that of 11-13 month group, suggesting that a booster dose interval of 6-8 months after two doses of Inactivated Vaccine can induce a relatively good immunogenicity.

Humoral immunogenicity and reactogenicity of CoronaVac or ZF2001 booster after two doses of inactivated vaccine

Overall, the humoral immune response induced by Zifivax was higher than CoronaVac. The GMTs on Day 14 compared to Day 0 in CoronaVac group rose 23.3 fold (prototype), 18.6 fold

(Beta), 23.8 fold (Gamma), and 18.4 fold (Delta) while in Zifivax group 33.9 fold (prototype), 44.5 fold (Beta), 32.7 fold (Gamma), and 39.1 fold (Delta). No significant changes in control group. Seroconversion rates 14 days after booster were all above 90% for Zifivax and CoronaVac group. The neutralizing GMTs for CoronoVac and Zifivax against the variants are shown in the Table 3 below.

Table 3. Neutralization antibody titers among all participants in vaccinated groups (GMT, 95% CI)

Characteristics	Group	No. of person	Day 0				Day 14			
			Prototype	Beta	Gamma	Delta	Prototype	Beta	Gamma	Delta
Total	CoronaVac	41	34 (27, 43)	7 (5, 8)	7 (6, 8)	5 (4, 5)	794 (589, 1069)	123 (89, 168)	162 (116, 226)	86 (62, 118)
	ZF2001	81	39 (30, 50)	7 (6, 8)	8 (7, 10)	5 (5, 6)	1306 (995, 1713)	301 (226, 401)	274 (207, 364)	205 (158, 267)
Age (years)										
<40	CoronaVac	25	33 (25, 43)	7 (5, 9)	7 (5, 9)	5 (4, 6)	830 (558, 1235)	145 (101, 210)	198 (130, 302)	97 (62, 151)
	ZF2001	39	43 (30, 63)	7 (6, 9)	8 (6, 11)	5 (4, 7)	1388 (953, 2021)	312 (206, 473)	279 (182, 427)	223 (156, 317)
≥40	CoronaVac	16	36 (23, 57)	6 (5, 8)	6 (5, 9)	4 (4, 5)	736 (468, 1157)	92 (52, 163)	116 (69, 195)	71 (46, 108)
	ZF2001	42	35 (24, 49)	7 (5, 8)	9 (6, 11)	5 (4, 6)	1234 (832, 1830)	292 (195, 435)	270 (185, 395)	190 (129, 281)
Gender										
Male	CoronaVac	10	42 (28, 63)	6 (4, 8)	8 (5, 13)	5 (4, 6)	950 (559, 1616)	151 (94, 241)	209 (135, 326)	112 (65, 192)
	ZF2001	25	24 (14, 39)	6 (4, 8)	6 (4, 8)	5 (4, 6)	690 (473, 1008)	161 (104, 248)	145 (94, 225)	115 (77, 172)
Female	CoronaVac	31	32 (24, 43)	7 (6, 9)	6 (5, 8)	5 (4, 5)	747 (523, 1068)	115 (77, 170)	149 (98, 226)	79 (53, 115)
	ZF2001	56	48 (36, 63)	7 (6, 9)	10 (8, 12)	6 (5, 7)	1736 (1248, 2414)	399 (283, 563)	364 (260, 510)	266 (194, 364)
Interval between second and third doses (months)										
4-5	CoronaVac	17	34 (24, 47)	7 (5, 10)	7 (5, 10)	5 (4, 5)	873 (574, 1329)	131 (87, 195)	181 (124, 262)	81 (53, 124)
	ZF2001	36	41 (28, 59)	6 (5, 7)	8 (6, 11)	5 (4, 6)	1611 (1072, 2421)	360 (246, 527)	331 (221, 496)	238 (161, 350)
6-8	CoronaVac	24	34 (24, 49)	6 (5, 8)	7 (5, 9)	5 (4, 6)	739 (486, 1125)	117 (73, 187)	150 (90, 251)	89 (56, 142)
	ZF2001	45	37 (26, 53)	8 (6, 10)	9 (6, 11)	5 (5, 6)	1104 (769, 1584)	261 (172, 395)	236 (159, 349)	183 (128, 261)

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Recombinant protein subunit vaccine booster following two- dose inactivated vaccines dramatically enhanced anti-RBD responses and neutralizing titers against SARS-CoV-2 and Variants of Concern

Booster induced at least 70-fold increase in neutralizing GMT levels on Day 14 against four variant pseudoviruses compared to the baseline level as shown in Table 4 and 5 below.

Table 4. pVNT Day 0 (GMT [95% CI])

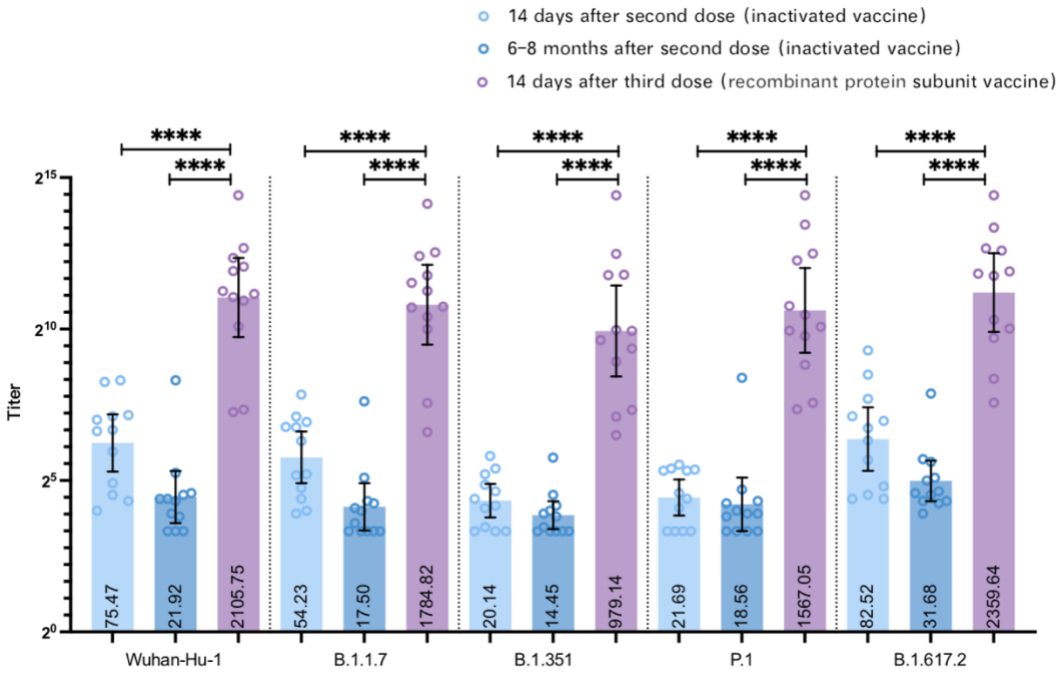
	Whole Booster group (n=71)	BBIBP-CorV Booster Group (n=69)	*P* value
Wuhan-Hu-1	24.89(20.63,30.02)	25.07(20.64,30.46)	0.9564
Alpha	15.78(13.1,19.00)	15.77(13.01,19.11)	0.9967
Beta	10.65(9.19,12.35)	10.59(9.07,12.35)	0.9562
Gamma	16.79(14.15,19.91)	17.24(14.49,20.52)	0.8274
Delta	22.56(18.89,26.96)	22.47(18.68,27.03)	0.9747

Table 5. pVNT Day 14 (GMT [95% CI])

	Whole Booster group (n=71)	BBIBP-CorV Booster Group (n=69)	*P* value
Wuhan-Hu-1	1881.01(1375.56,2572.19)	1865.80(1346.87,2584.68)	0.9517
Alpha	1523.21(1100.68,2107.95)	1513.38(1079.37,2121.9)	0.9781
Beta	785.92(543.66,1136.12)	773.55(527.85,1133.61)	0.9526
Gamma	1307.73(921.14,1856.56)	1288.62(895.63,1854.06)	0.9537
Delta	1944.15(1403.33,2693.39)	1882.68(1342.72,2639.76)	0.8916

A third booster dose following previous two-dose inactivated vaccines could significantly recall and increase functional B cell responses by 27- to 75-fold compared to those 14 days post the second vaccination shot for all tested VOCs as shown in Figure 1 below.

Figure 1. Neutralizing titer 14 days after primary and booster vaccination



Ai, J., Zhang, H., Zhang, Q. *et al.* Recombinant protein subunit vaccine booster following two-dose inactivated vaccines dramatically enhanced anti-RBD responses and neutralizing titers against SARS-CoV-2 and Variants of Concern. *Cell Res* **32,** 103–106 (2022). https://doi.org/10.1038/s41422-021-00590-x

Immunogenicity in Elderly

Immunogenicity in elderly was evaluated in phase 1 clinical study in China involving 50 subjects.

In the phase 1 study, the positive conversion rates of SARS-CoV-2 euvirus neutralizing antibody in the high dose, low dose and placebo group were 95.00%, 94.74%, and 0.00% 30 days after full course vaccination . The GMT values were 37.4, 55.0, and 2.0 respectively.The positive conversion rate of RBD protein binding antibody in the high dose, low dose and placebo group were 100%, 100%, and 0.00% 30 days after full course vaccination. The GMT values were 578.60, 897.48, and 5.50 respectively.

Efficacy

Efficacy was evaluated based on a global Phase 3 study involving 28,500 adult and elderly subjects aged 18 years and above in China, Indonesia, Uzbekistan, Ecuador, and Pakistan.

Based on the global Phase 3 interim report (cut-off date 30 June 2021), the evaluation of efficacy of Zifivax vaccine in preventing COVID-19 infection compared to placebo was based on the symptomatic cases confirmed by RT-PCR testing 7 days after full course vaccination. Based on the E-mFAS set, primary efficacy analysis based on any severity of COVID-19 cases 7 days after full vaccination is conducted based on 221 COVID-19 cases and is **81.76%** (221 cases: 35 vaccine group and 186 placebo group). Based on the E-PPS set, among the COVID-

19 cases of any severity 7 days after full vaccination, 35 cases are in the vaccine group and 186 cases are in the placebo group. Compared with the placebo group, the protection rate of the vaccine group based on the person-year incidence is **81.71%.**
At present, 117 primary endpoint cases have been genotyped (52.94% of all primary endpoint cases).The preliminary analysis showed that 7 days after three doses of vaccination, the efficacy against Alpha variant (British strain) was **92.93%** (2 cases in vaccine group and 28 cases in placebo group), the efficacy against Delta variant (Indian strain) was **77.54%** (12 cases in vaccine group and 52 cases in placebo group).

For severe or above COVID-19 cases, there were 0 cases in the vaccine group and 12 cases in the placebo group, and the efficacy based on the E-mFAS set was 100%. For deaths resulting from COVID-19, there were 0 in the vaccine group and 6 in the placebo group and the efficacy was 100%. As secondary efficacy endpoint, of the 179 COVID-19 cases of any severity 14 days after full vaccination, 29 were in the vaccine group and 150 were in the placebo group. The vaccine efficacy based on the E-mFAS set is 81.46%. The vaccine efficacy based on the E-PPS set is 81.40%.

Efficacy in Elderly

Efficacy in the elderly is evaluated based on the global phase 3 study, which involved both adult and elderly subjects, as mentioned above. There was 1 case in the vaccine group and 7 cases in the placebo group and the overall primary efficacy for people over 60 years of age against any severity COVID-19 cases 7 days after full vaccination based on the E-mFAS set was **87.58%.**

STORAGE CONDITIONS

Do not reuse or save unused Zifivax vaccine. This product contains no preservative. Zifivax suspension for injection is intended for single use. Store Zifivax suspension for injection vials between 2 – 8 °C and keep away from light. Do not use after expiration date.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver information consistent with the "**Informasi Produk untuk Pasien** (Fact Sheet for Patients and Parents/Caregivers)" (and provide a copy of the Fact Sheet) prior to the patient receiving Zifivax, including:

1. That the Badan POM has authorized emergency use of Zifivax
2. The potential consequences of refusing Zifivax
3. The significant known and potential risks and benefits of Zifivax, as supplied under this EUA.
4. The alternative products that are available and their benefits and risks, including clinical trials.

MANDATORY REQUIREMENTS FOR ZIFIVAX ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

A. In order to mitigate the risks of using this product under EUA and to optimize the potential benefit of Zifivax, the following items are required. Use of Zifivax under this EUA is limited to the following (all requirements **must** be met):
   1. Zifivax is used to induce immune response against SARS-CoV-2 for the prevention of COVID-19. This product is suitable for people aged 18 years old and above.

2. As the health care provider, communicate to your patient or parent/caregiver information consistent with the "**Informasi Produk untuk Pasien**" prior to the patient receiving Zifivax. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
   a) Given the "**Informasi Produk untuk Pasien**",
   b) Informed of alternatives to receiving Zifivax, and
   c) Informed that Zifivax is an unapproved drug that is authorized for use under Emergency Use Authorization.

3. Subjects with known hypersensitivity to any ingredient of Zifivax must not receive Zifivax.

4. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory responses to requests from Badan POM for information about adverse events and medication errors following receipt of Zifivax.

5. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and adverse events (death, serious adverse events*) considered to be potentially related to Zifivax occurring after vaccination within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "**Zifivax under Emergency Use Authorization (EUA)**" in the description section of the report.
   1. Submit adverse event reports to:

      Pusat Farmakovigilans/MESO Nasional

      Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

      Badan Pengawas Obat dan Makanan https://e-meso.pom.go.id/ADR

   2. Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement **"Zifivax vaccination under EUA"**

APPROVED AVAILABLE ALTERNATIVES

There are EUAs for other COVID-19 treatments. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrolment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

Indonesian Government has declared an emergency situation as a result of pandemic outbreak of COVID- 19 that justifies the emergency need of using Zifivax as a treatment option in this situation. In response to that situation, the Badan POM has issued an Emergency Use Authorization (EUA) for the use of Zifivax is to induce immune response against SARS-CoV-2 for the prevention of COVID-19. This product is suitable for people aged 18 years old and above.

As a health care provider, you must comply with the mandatory requirements of the EUA listed above.

This product is suitable for people aged 18 years old and above, as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the

product during this emergency. Serious adverse events related to the use of Zifivax must be reported to Badan POM through Pusat Farmakovigilans/MESO Nasional, Badan Pengawas Obat dan Makanan online http://e-meso.pom.go.id/ADR. Please include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the following statement: **Zifivax Vaccination under Emergency Use Authorization(EUA).**

This EUA for Zifivax will end when the Badan POM determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

ON MEDICAL PRESCRIPTION ONLY

Packaging: Box, @0,5 mL (1 dose) or @ 1,0 ML (2 doses)

Manufactured by:
Anhui Zhifei Longcom Biopharmaceutical, Hefei, China

Imported and marketed by:
Jakarta Biopharmaceutical Industry, Banten, Indonesia