RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK FASE III
VAKSIN SARS-COV-2 AJUVAN ALUM + CYTOSINE-PHOSPHATE-GUANINE (CPG)
PRODUKSI PT BIO FARMA
SEBAGAI VAKSIN PRIMER PADA ANAK USIA 12-17 TAHUN

Informasi Umum

1. Vaksin SARS-CoV-2 adalah vaksin dengan platform subunit protein yang dikembangkan oleh PT Bio Farma menggunakan *seed* vaksin dari Baylor College of Medicine (BCM). Vaksin uji menggunakan ajuvan Alum dan Cytosine-Phosphate-Guanine oligodeoxynucleotides (CpG)-1018.
2. Uji klinik Vaksin SARS-CoV-2 sebagai vaksin primer untuk anak usia 12 – 17 didukung oleh data keamanan dan imunogenisitas uji klinik fase 3 sebagai vaksin primer pada dewasa.

Informasi Uji Klinik

1.	**Judul Protokol**	**:**	*A Phase III, Observer-Blind, Randomized, Controlled Study of the Safety and Immunogenicity of SARS-CoV-2 Protein Subunit Recombinant Vaccine in Healthy Children Aged 12-17 Years in Indonesia* *Version 2.b, September 26th 2022*
2.	**Produk Uji**	**:**	Vaksin SARS-COV-2 0,5 mL (25 mcg protein rekombinan subunit *Receptor Binding Domain* (RBD) SARS-CoV-2 dan 750 mcg CpG 1018) diberikan 2 kali secara intramuskular Produsen: PT. Bio Farma
	Produk Pembanding	**:**	Vaksin Covovax (SARS-CoV-2 rS Protein (COVID-19) recombinant spike protein nanoparticle vaccine 5 mcg per dose) diberikan 2 kali secara intramuscular. Produsen: Serum Institute of India Pvt. Ltd., India
3.	**Center/ Peneliti**	**:**	1. Center for Child Health Universitas Gadjah Mada (UGM), Yogyakarta / dr. Cahya Dewi Satria, M.Kes., Sp.A(K) 2. Faculty of Medicine Andalas University, Padang / dr. Asrawati, M.Biomed., Sp.A(K)
4.	**Sponsor/ ORK**	**:**	PT Bio Farma/ PT Equilab International
5.	**Persetujuan Etik**	**:**	1. Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito No. KE/FK/1109/EC tanggal 28 September 2022 2. Komisi Etik Penelitian Fakultas Kedokteran Universitas Andalas No. 967/UN.16.2/KEP-FK/2022 tanggal 23 September 2022
6.	**Desain Uji Klinik**	**:**	1. Main Study: Randomized, observer-blind, controlled, prospective intervention study 2. Exploratory Study subset: Randomized, observer-blind, active-controlled prospective intervention study
7.	**Jumlah Subjek**	**:**	1050 subjek (1000 subjek untuk *main study* dan 50 subjek untuk *exploratory study*)
8.	**Tujuan Uji Klinik**	**:**	Primary Objective:

To evaluate immunogenic non-inferiority immune response of SARS-CoV-2 neutralizing antibody of Bio Farma vaccine compared to vaccine control at 14 days after primary series.

Secondary Objective:

1. To evaluate SARS-CoV-2 (RBD)-binding IgG antibody titer before and 14 days after primary series of Bio Farma vaccine
2. To evaluate safety of SARS-CoV-2 Protein Subunit Recombinant Vaccine (Bio Farma).
3. To compare safety and immunogenicity between SARS CoV-2 protein subunit recombinant vaccine (Bio Farma) and control group.
4. To evaluate antibody persistence 3, 6 and 12 months after primary series.
5. Exploratory: to assess cellular immunity of the vaccine at baseline, 14 days, 6 months and 12 months after primary series (for Exploratory Study subset)

9. Kriteria Eligibilitas :

Kriteria Inklusi

1. Clinically healthy children aged 12-17 years.
2. Parent/legal guardian and subject has been informed properly regarding the study, and signed the informed consent form (parent/legal guardian) and assent form (subject).
3. Parent/legal guardian and subject will commit to comply with the instructions of the investigator and the schedule of the trial.

Kriteria Eksklusi

1. Subjects concomitantly enrolled or scheduled to be enrolled in another trial.
2. History of vaccination with any COVID-19 vaccine (based on anamnesis).
3. History of COVID-19 within 3 months prior to enrollment (based on anamnesis).
4. Evolving mild, moderate or severe illness, especially infectious disease or fever (body temperature ≥37.5℃, measured with infrared thermometer/thermal gun).
5. History of asthma, history of allergy to vaccines or vaccine ingredients, and severe adverse reactions to vaccines, such as urticaria, dyspnea, and angioneurotic edema.
6. History of uncontrolled coagulopathy or blood disorders contraindicating intramuscular injection.
7. Patients with serious chronic diseases (serious cardiovascular diseases, uncontrolled hypertension and diabetes, liver and kidney diseases, malignant tumors, etc) which according to the investigator might interfere with the assessment of the trial objectives.
8. Subjects who have any history of confirmed or suspected immunosuppressive or immunodeficient state, or received in the previous 4 weeks a treatment likely to alter the immune response (intravenous immunoglobulins, blood-derived products or long-term corticosteroid therapy (> 2 weeks)).
9. Subjects who have history of uncontrolled epilepsy or other progressive neurological disorders, such as Guillain-Barre Syndrome.

10. Subjects receive any vaccination (other than COVID 19 vaccine) within 1 month before and after IP immunization
11. Female who are pregnant or planning to become pregnant during the study period (judged by self report of subjects and urine pregnancy test results).
12. Subjects plan to move from the study area before the end of study period.

10. Luaran Uji Klinik/ Endpoint : Primary Evaluation Criteria:

Geometric Mean Titer (GMT) and GMT ratio of neutralizing antibody to the SARS-CoV-2, measured by neutralization assay (against omicron variant) at 14 days after primary series.
Secondary Evaluation Criteria:

Immunogenicity

- Seropositive rate of neutralizing antibody at baseline, 14 days, 3, 6 and 12 months after primary series vaccination.
- Seroconversion rate of neutralizing antibody at baseline and 14 days after primary series vaccination.
- Seropositive rate and Geometric means of titers (GMTs) of SARS-CoV-2 (RBD)-binding IgG antibody measured by chemiluminescent microparticle immunoassay (CMIA) at baseline, 14 days, 3, 6 and 12 months after primary series vaccination.
- Seroconversion rate of SARS-CoV-2 (RBD)-binding IgG antibody measured by chemiluminescent microparticle immunoassay (CMIA) at baseline and 14 days after primary series vaccination.
- Comparison of GMTs, seroconversion rate, seropositive rate of SARS-CoV-2 (RBD)-binding IgG antibody and neutralizing antibody between vaccine and control group.

Exploratory Study (Cellular immunity)

- Positive rate of specific T-cell response (CD4, CD8, IFN-γ, TNF-α, IL-2, IL-4) at 14 days, 6 months and 12 months after two-dose primary series.
- GMT and seropositive rate of SARS-CoV-2 (RBD) binding IgG antibody at 14 days, 6 months and 12 months after two-dose primary series.
- GMT and seropositive rate of neutralizing antibody at 14 days, 6 months and 12 months after two-dose primary series.
- Seroconversion rate of SARS-CoV-2 (RBD)-binding IgG antibody at 14 days after two-dose primary series.
- Seroconversion rate of neutralizing antibody at 14 days after two-dose primary series.

Safety

- Number and percentage of subjects with solicited and unsolicited adverse events within 30 minutes, 7 days, and 28 days after each dose of primary series.

- Number and percentage of subjects with serious adverse events within 28 days after each dose.
- Comparison of number and percentage of subjects with adverse events and serious adverse events between vaccine and active control group within 28 days after each dose.
- Number and percentage of subjects with adverse events until 12 months after two-dose primary series (for Main Study and Exploratory Study subjects).
- Number and percentage of subjects with serious adverse events until 12 months after two-dose primary series (for Main Study and Exploratory Study subjects).

Hasil Evaluasi

Badan POM telah melakukan evaluasi terhadap protokol yang diajukan dan telah dibahas bersama tim ahli pada tanggal 13 September 2022. Uji klinik fase III pada anak usia 12 – 17 tahun menggunakan dosis yang sama dengan uji klinik fase III vaksin primer pada dewasa, yaitu dosis antigen 25 mcg dengan CPG 750 mcg yang diberikan 2 (dua) kali dengan interval 28 hari.

Vaksin SARS-COV-2 produksi PT. Bio Farma telah mendapatkan persetujuan penggunaan darurat/ *Emergency Use Authorization* (EUA) pada 24 September 2022 untuk penggunaan vaksin primer pada dewasa. Mengacu pada data keamanan pada uji klinik fase III dewasa, vaksin SARS-CoV-2 Bio Farma dapat ditoleransi dengan baik dan menghasilkan respon imun antibodi (IgG dan netralisasi antibodi) setelah pemberian suntikan kedua. Desain uji klinik yang diajukan telah memadai untuk mencapai tujuan uji klinik.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas disetujui melalui penerbitan Persetujuan Pelaksanaan Uji Klinik Nomor RG.01.06.1.2.09.22.164 tanggal 30 September 2022.