RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK FASE III
VAKSIN MERAH PUTIH-UA SARS-COV-2 PRODUKSI PT. BIOTIS
SEBAGAI VAKSIN PRIMER PADA DEWASA

Informasi Umum

1. Vaksin Merah Putih-UA SARS-CoV-2 dikembangkan oleh Universitas Airlangga (UNAIR) bekerja sama dengan PT. Biotis. Pengembangan vaksin tersebut menggunakan virus SARS-CoV-2 yang diisolasi dari pasien COVID-19 di Surabaya.
2. Vaksin telah melalui tahapan uji non klinik pada mencit dan *macaca* serta uji klinik fase I dan II untuk mengetahui keamanan, imunogenisitas dan dosis efektif vaksin.

Informasi Uji Klinik

1.	Judul Protokol	:	*A Multicenter, Randomized, Double Blind, Controlled, Phase III Clinical Trial (Bridging Study) of Vaksin Merah Putih-UA SARS-CoV-2 (Vero Cell Inactivated) in Healthy Population Aged 18 Years and Above* *Version No. 3d.0 date 6 June 2022*
2.	Produk Uji	:	Vaksin Merah Putih-UA SARS-CoV-2 (SARS COV-2 Inactivated 5 mcg) diberikan 2 kali secara intramuskular. Produsen: PT. Biotis
3.	Produk Pembanding	:	CoronaVac (Vaksin SARS-CoV-2 inactivated 600 SU) diberikan 2 kali secara intramuscular Produsen: Sinovac
4.	Center / Peneliti	:	RSUD Dr. Soetomo, Surabaya / Dr. dr. Dominicus Husada, DTM&H.,MCTM(TP).,SpA(K)
5.	Sponsor	:	1. Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia 2. PT. Biotis 3. Universitas Airlangga (UNAIR)
6.	Persetujuan Etik	:	Persetujuan No. 0427/KEPK/VI/2022 Tanggal 8 Juni 2022 dari Komite Etik Penelitian Kesehatan RSUD Dr Soetomo Surabaya
7.	Desain Uji Klinik	:	*This is a double blind randomized controlled trial – immunobridging study. There will be 2 groups in the study. One adult group (18 year-old and above) with 5 µg dose, and 1 control group using CoronaVac Bio Farma. Both vaccines will be administered with 2-dose schedule, intramuscularly. All cohorts will be followed for 6 months. This study will have two interim and one full analysis The main focus is immunogenicity and safety or reactogenicity issues.*
8.	Jumlah Subjek	:	*The test uses efficacy assumption difference between CoronaVac and Unair vaccine as 3% (The lower limit of the trial vaccine is 67% and the difference between both vaccines should not exceed 10%). If the delta is 0.1, α is 0.05 and the power of test is 20%, by this formula, there will be 953 subjects for each group, and if the predicted drop out is approximately 5% then the total subjects will be 1000 people for each group. In total, 2000 subjects will be needed. Based on the Revised Edition of WHO's Considerations for Evaluation of Covid19 Vaccines, at least 3000 subjects should receive the trial vaccine. By adding additional*

2000 subjects, the total number of subjects will be 4000 people. Divided into 2 groups: 1000 for CoronaVac Bio Farma and 3000 for UNAIR vaccine

9. Tujuan Uji Klinik : *Primary Objective*

To evaluate humoral immunogenicity within 28 days following two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults age 18 year and above

Secondary Objective

1. *To evaluate safety and reactogenicity within 30 minutes, 24 hours, 7 and 28 days following the first dose and 30 minutes, 24 hours, 7 and 28 days, 3 and 6 months after the second doses of Unair Inactivated Covid-19 Vaccine compared with CoronaVac administered intramuscularly in healthy adults age 18 year and above*
2. *To evaluate the humoral immunogenicity profile within 3 and 6 months, following vaccination with two doses of Unair Inactivated Covid-19 Vaccine compared with CoronaVac administered intramuscularly in healthy adults age 18 year and above*
3. *To evaluate the cellular immunogenicity profile within 28 days, 3 and 6 months, following vaccination with two doses of Unair Inactivated Covid-19 Vaccine compared with CoronaVac administered intramuscularly in healthy adults age 18 year and above.*
4. *To evaluate the persistence of antibody level and the need for booster*
5. *To evaluate lot to lot consistency*

10. Kriteria Eligibilitas : Kriteria Inklusi / *Inclusion criteria*

1. *Healthy adults and elderly, males and females, 18 years of age and above. Healthy status will be determined by the investigator based on medicalhistory, clinical laboratory results, vital sign measurements, and physicalexamination at screening.*
2. *Subjects have been informed properly regarding the study and signed the informed consent form*
3. *Subject will commit to comply with the instructions of the investigator and the schedule of the trial*
4. *Participants agree not to donate bone marrow, blood, and blood products from the first study vaccine administration until 3 months after receiving the last dose of study vaccine.*
5. *Participants must be willing to provide verifiable identification, has means to*

Kriteria Eksklusi / *Exclusion criteria*

1. *Subjects concomitantly enrolled or scheduled to be enrolled in another vaccine trial*
2. *Evolving mild, moderate, and severe illness, especially infectious diseases or fever (axillary temperature 37.5^{o}C or more) concurrent or within 7 days prior to first study vaccination. This includes respiratory or constitutional symptms consistent with SARS-CoV-2 (cough, sore throat, difficulty in breathing, etc)*
3. *Known history of allergy to any component of the vaccines*
4. *History of uncontrolled coagulopathy or blood disorders contraindicating intramuscular injection*
5. *Any autoimmune or immunodeficiency disease/condition*
6. *Subjects who have received in the previous 4 weeks a treatment likely to alter the immune response (intravenous immunoglobulin, blood derived products, long term corticosteroid – more than 2 weeks, and so on), OR anticipation of the need for immunosuppressive treatment within 6 months after last vaccination. The use of topical or nasal steroid will be permitted*.
7. *Unstable chronic disease, inclusive of uncontrolled hypertension, congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic urticaria, diabetes requiring use of medicine. The final decision regarding this condition will be decided by the attending field clinicians or investigator.*
8. *Any abnormality or chronic disease which according to the investigator might interfere with the assessment of the trial objectives*
9. *Individuals who previously receive any vaccines against Covid-19*
10. *Subjects already immunized with any vaccine within 4 weeks prior and expect to receive other vaccines within 60 days following the first dose*
11. *Individuals who have a previously ascertained Covid-19 in the period of 3 months before the first recruit of this study, or in a close contact in the last 14 days with confirmed case of Covid-19.*
12. *Individuals who have a previously ascertained Covid-19 in the period of 3 months before the first recruit of this study, or in a close contact in the last 14 days with confirmed case of Covid-19*
13. *Positive test for SARS-CoV-2 (Antigen or PCR) at screening prior to first vaccination. Testing may be repeated during the screening period if exposure to positive confirmed case of SARS-CoV-2 is suspected, at the discretion of investigator.*
14. *Alcohol or substance abuse*
15. *HIV patients.*
16. *Malignancy patients within 2 years prior to first study vaccination.*
17. *Any neurological disease or history of significant neurological disorder such as meningitis, encephalitis, Guillain-Barre Syndrome, multiple sclerosis, etc*
18. *Vital sign abnormalities and clinical laboratory abnormalities as decided by the investigators. Vital sign measurements and clinical laboratory testing may be repeated before the final decision.*
19. *Women who are pregnant or who plan to become pregnant during the study.*
20. *Participant has major psychiatric problem or illness*

21. *Participant cannot communicate reliably with the investigator*
22. *Participant has contraindication to intramuscular injection and blood draws, such as bleeding disorders or phobia.*
23. *Any condition that in the opinion of the investigators would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine or interpretation of the study results*
24. *Study team members*
25. *Subject planning to move from the study area before the end of study period*

11. Luaran Uji Klinik :

Primary Endpoints:

1. *SARS-CoV-2 Neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay, within 28 days after two doses vaccination of Unair Inactivated Covid-19 Vaccine*
2. *SARS-CoV-2 binding antibodies measured by ELISA: analysis of antibodies binding to the SARS-CoV-2 S-protein, within 28 days after two doses vaccination of Unair Inactivated Covid-19 Vaccine*

Secondary Endpoints:

– *Safety*
  1. *Percentage of subjects with at least one of these adverse events, solicited and unsolicited, within 7 and 28 days after each vaccination, then 3 and 6 months after the second vaccination*
  2. *Number and percentage of subjects with serious adverse events from inclusion until 6 months after the second vaccination.*
  3. Serious adverse event (SAE) throughout the study (from the firstvaccination)
– *Humoral Immunogenicity*
  1. *SARS-CoV-2 Neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay, within 3 and 6 months after the second vaccination of Vaksin Merah Putih – UA SARS-CoV-2 (Vero Cell Inactivated)*
  2. *SARS-CoV-2 binding antibodies measured by CLIA: analysis of antibodies binding to the SARS-CoV-2 S-protein, within 3 and 6 months after the second vaccination of Vaksin Merah Putih – UASARS-CoV-2 (Vero Cell Inactivated)*
  3. Persistence of antibodies over time for 6 months after the secondinjection.
– *Celluler Immunogenicity*
  Th1 and Th2 immune responses as assessed by: Flow cytometri after stimulation of PBMC and intracellular staining (ICS) including CD4+/CD8+. IL-2, IL-4, TNF alpha, IFN gamma, and other markers after stimulation of PBMC with SARS-CoV-2 protein peptides and Interferon gamma release assay (IGRA) to assess the production of IFN-γ from stimulated CD4+ and CD8+ with antigen peptides specific to SARSCoV-2, after 28 days, 3 and 6 months after the second vaccination.
– *Lot to lot consistency*
  To analyse lot to lot consistency for safety and immunogenicity among three lots of trial vaccine

Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik fase III untuk Vaksin Merah Putih-UA SARS-CoV-2. Hasil evaluasi telah didukung tim ahli melalui rapat pada 27 Mei 2022 dengan hasil sebagai berikut:

1. Uji non klinik pada dengan posologi yang sama dengan uji klinik telah dilakukan pada mencit dan *macaca*.
2. Hasil uji non klinik dan uji klinik fase I dan II menunjukkan vaksin dapat ditoleransi dengan baik dan menghasilkan respon imun antibodi (IgG dan netralisasi antibodi) setelah pemberian suntikan kedua.
3. Desain uji klinik telah memadai termasuk pemilihan CoronaVac sebagai vaksin pembanding yang memiliki *platform* yang sama dengan vaksin uji yaitu *inactivated*.
4. Vaksin uji yang akan digunakan telah memenuhi persyaratan mutu.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas disetujui melalui penerbitan Persetujuan Pelaksanaan Uji Klinik (PPUK) No. RG.01.06.1.3.06.22.107 tanggal 24 Juni 2022.