**RINGKASAN HASIL EVALUASI**
**PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK FASE I/II**
**VAKSIN COVID-19 UNAIR *INACTIVATED* PRODUKSI PT. BIOTIS**
**SEBAGAI VAKSIN PRIMER PADA DEWASA**

**Informasi Umum**

1. Vaksin COVID-19 UNAIR *Inactivated* atau Vaksin Merah Putih 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. Uji nonklinik telah dilakukan pada mencit dan macaca untuk mengetahui keamanan dan imunogenisitas vaksin.

**Informasi Uji Klinik**

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| 1. | Judul Protokol | : | ***Safety and Immunogenicity of UNAIR Inactivated Covid-19 Vaccine in Healthy Population Aged 18 Years and Above (Phase I/II)***<br>*Versi 9a Tanggal 25 Desember 2021.* |
| 2. | Produk Uji | : | Unair Inactivated COVID-19 Vaccine (SARS COV-2 Inactivated 3 & 5 mcg) diberikan 2 kali secara intramuskular.<br>Produsen: PT. Biotis |
| 3. | Produk Pembanding | : | CoronaVac (Vaksin SARS-CoV-2 inactivated 600 SU) diberikan 2 kali secara intramuskular<br>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<br>2. PT. Biotis<br>3. Universitas Airlangga (UNAIR) |
| 6. | Persetujuan Etik | : | Persetujuan No. 0270/KEPK/X?2021 Tanggal 1 Oktober 2022 dan Persetujuan Amandemen No. 09/113/Komitlitkes/I/2022 tanggal 24 Januari 2022 dari Komite Etik Penelitian Kesehatan RSUD Dr Soetomo Surabaya |
| 7. | Desain Uji Klinik | : | ***Phase I***<br>*Randomized, double blind, controlled, with 2 main and 1 control groups. The safety, reactogenicity, and immunogenicity will be evaluated at 2 dose levels (3 and 5 µg), administered intramuscularly with 2-dose schedule. All cohorts will be followed for 6 months.*<br>***Phase II***<br>*Randomized, double blind, controlled, with 2 main and 1 control groups. The vaccine will be administered intramuscularly with 2-dose schedule. The phase II part will be started as early as 28 days after the second dose of vaccine in phase I is already administered. Both doses at phase I (3 and 5 µg) will be used for the phase II. All cohorts will be followed for 6 months* |

8. Jumlah Subjek : ***Phase I:***
*90 subjects 18 years old and above, male and female, divided into 3 groups, 1 group of control (consist of 30 subjects), and 2 groups of adult 18 year-old and above using different doses i.e. 3 and 5 µg (each group consists of 30 subjects).*
***Phase II:***
*405 subjects 18 years old and above, male and female, divided into 3 groups, 1 group of control (135 subjects), and 2 groups of adult age 18 year old and above (each 135 subjects, using 3 and 5 µg doses of vaccine).*

9. Tujuan Uji Klinik : ***Phase I***
*Primary Objective*
*To evaluate **safety and reactogenicity** within 7 days following each vaccination with two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults and elderly.*
*Secondary Objective*
*To evaluate safety and reactogenicity within 28 days following each vaccination with two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults and elderly*

*To evaluate the preliminary humoral immune response following vaccination with two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults and elderly*

*To evaluate the preliminary cellular immune response following vaccination with two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults and elderly*

***Phase II***
*Primary Objective*
*To evaluate the immunogenicity profile (humoral and cellular immune responses) of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults and elderly.*

*Secondary*
*To evaluate safety and reactogenicity within 28 days following vaccination with two doses of Unair Inactivated Covid-19 Vaccine administered intramuscularly in healthy adults*

10. Kriteria Eligibilitas : Kriteria Inklusi / *Inclusion criteria*
1. *Healthy adults and elderly, males and females, 18 years of age and up. Healthy status will be determined by the investigator based on medical history, clinical laboratory results, vital sign measurements, and physical examination 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. *Female subjects of childbearing potential must agree to heterosexually inactive from at least 21 days prior to enrollment and through 6 months after the last vaccination OR agree to consistently use any methods of contraception (except the periodic abstinence) from at least 21 days prior to enrollment and through 6 months after the last vaccination.*
5. *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.*
6. *Participants must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.*

Kriteria Eksklusi / *Exclusion criteria*

1. *Subjects concomitantly enrolled or scheduled to be enrolled in another 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 symptoms 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 has 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. Inhaled glucocorticoids is prohibited.*
7. *Chronic disease, inclusive of uncontrolled hypertension, congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic urticaria, diabetes requiring use of medicine.*
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 in the period of 6 months prior to enrollment of this study.*
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. *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.*

13. *History of alcohol or substance abuse.*
14. *Patients of Hepatitis B, Hepatitis C, and HIV per medical history (by history taking from the participants).*
15. *Malignancy patients within 5 years prior to first study vaccination.*
16. *Any neurological disease or history of significant neurological disorder such as meningitis, encephalitis, Guillain-Barre Syndrome, multiple sclerosis, etc.*
17. *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.*
18. *Women who are pregnant, breastfeeding, or who plan to become pregnant during the study.*
19. *Participant has major psychiatric problem or illness.*
20. *Participant cannot communicate reliably with the investigator.*
21. *Participant has contraindication to intramuscular injection and blood draws, such as bleeding disorders or phobia.*
22. *Participant had major surgery within 12 weeks before vaccination which will not be fully recovered, or has major surgery planned during the time participant is expected to participate in the study or within 6 months after the last dose of study vaccine administration.*
23. *Any condition that in the opinion of the investigators would pose a helath 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 / *Endpoint* : **Phase I:**

*Primary Endpoints*:

1. *Solicited – clinical (local and systemic) and laboratory adverse events for 7 days after each vaccination.*
2. *Unsolicited adverse events for 7 days after each vaccination.*
3. *Serious adverse event (SAE) throughout the study (from the first vaccination)*

*Secondary Endpoints:*

1. *Solicited – clinical (local and systemic) and laboratory adverse events for 28 days after each vaccination*
2. *Unsolicited adverse events for 28 days after each vaccinaton*
3. *SARS-CoV-2 Neutralization*
4. *SARS-CoV-2 binding antibodies measured by ELISA*
5. *Preliminary Th1 and Th2 immune responses*
6. *Preliminary Cytokine profiling*

*Exploratory Endpoints:*

*Whole genome sequencing (WGS) of S protein of SARS-CoV-2 virus from positive Covid-19 cases during the study*

**Phase II:**

*Primary Endpoints:*

1. *SARS-CoV-2 Neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay*
2. *SARS-CoV-2 binding antibodies measured by ELISA or chemiluminescence: antibodies binding to the SARS-CoV-2 S or S-RBD protein quantitatively*

3. *Th1 and Th2 immune responses as assessed by: Flow cytometri after stimulation of PBMC and intracellular staining (ICS) including CD4+/CD8+. IL2, IL-4, TNF alpha, and other markers after stimulation of PBMC with SARSCoV-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 SARS-CoV-2*
4. *Cytokine profiling: analysis of cytokines, chemokines, and other proteins of the innate or adaptive immune response in the supernatant of the stimulated PBMC with SARS-CoV-2 protein peptide*

*Secondary Endpoints:*

1. *Solicited – clinical (local and systemic) and laboratory adverse events for 28 days after each vaccination*
2. *Unsolicited adverse events for 28 days after each vaccinaton*
3. *Serious adverse event (SAE) throughout the study (from the first vaccination)*

**Luaran Sekunder /** *Secondary endpoints*

*Phase I and II:*

1. *To evaluate safety and reactogenicity within 3, 6, and 12 months following each vaccination with two doses of Unair Inactivated Covid-19 Vaccine compared with Coronavac Vaccine administered intramuscularly in healthy adults aged 18 year and above*
2. *To evaluate safety and reactogenicity within 28 days (for phase II) following vaccination with two doses of Unair Inactivated Covid-19 Vaccine compared with Coronavac Vaccine administered intramuscularly in healthy adults aged 18 year and above*
3. *To evaluate the humoral immune response at 14 days following vaccination with one dose and 3, 6, and 12 months with two doses of Unair Inactivated Covid-19 Vaccine compared with Coronavac Vaccine administered intramuscularly in healthy adults aged 18 year and above*
4. *To evaluate the humoral and cellular immune response at 28 days following vaccination with two doses of Unair Inactivated Covid-19 Vaccine compared with Coronavac Vaccine administered intramuscularly in healthy adults aged 18 year and above (for phase I)*
5. *To evaluate the cellular immune response at 14 days following vaccination with one dose and 3, 6, and 12 months with two doses of Unair Inactivated Covid-19 Vaccine compared with Coronavac Vaccine administered intramuscularly in healthy adults aged 18 year and above*
6. *To evaluate the persistence of antibody level and the need for homologus booster.*

**Ringkasan Hasil Evaluasi**

Badan POM telah melakukan evaluasi protokol uji klinik fase I/II untuk Vaksin COVID-19 UNAIR *Inactivated*. Hasil evaluasi telah didukung tim ahli melalui rapat pada 17 Desember 2021 dengan hasil sebagai berikut:

1. Uji non klinik pada dengan posologi yang sama dengan uji klinik telah dilakukan pada mencit dan *macaca*. Hasil uji non klinik menunjukkan vaksin dapat ditoleransi dengan baik dan menghasilkan respon imun antibodi (IgG dan netralisasi antibodi) setelah pemberian suntikan kedua.
2. Desain uji klinik yang diajukan telah memadai terutama untuk menjamin keselamatan subjek, antara lain telah terdapat mitigasi risiko yaitu melakukan pelaksanaan rekrutmen subjek secara bertahap pada uji klinik fase I (*first in human*) dan dilakukan evaluasi keamanan terlebih dahulu oleh *Data Safety Monitoring Board* (DSMB) sebelum dapat dilanjutkan ke tahap berikutnya untuk merekrut seluruh subjek.
3. Uji klinik fase II dapat dilakukan setelah diperoleh data interim uji klinik fase I yang menunjukkan vaksin aman untuk digunakan pada subjek.
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 No. RG.01.06.1.1.02.22.14 tanggal 5 Februari 2022