RINGKASAN HASIL EVALUASI PERMOHONAN
PERSETUJUAN PELAKSANAAN UJI KLINIK FASE III
INAVAC (Vaksin Merah Putih-UA SARS-CoV-2) PRODUKSI PT. BIOTIS
SEBAGAI VAKSIN PRIMER PADA ANAK 12-17 TAHUN

Informasi Umum

1. Vaksin Merah Putih-UA SARS-CoV-2 dengan nama dagang INAVAC telah memperoleh *Emergency Use Authorization* (EUA) pada 1 November 2022 untuk indikasi sebagai pencegahan COVID-19 yang disebabkan oleh SARS CoV-2 pada individu berusia 18 tahun ke atas.
2. Hasil uji klinik akan digunakan sebagai data dukung penambahan posologi dan indikasi vaksin untuk anak 12-17 tahun.

Informasi Uji Klinik

1.	Judul Protokol	:	*An Open Label, Phase III Clinical Trial (Immunobridging Study) of INAVAC (Vaksin Merah Putih – UA-SARS CoV-2 (Vero Cell Inactivated)) in Healthy Population Aged 12 to 17 Years Old* *Version No. 3a.0 date 31 March 2023*
2.	Produk Uji	:	INAVAC (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 / ORK	:	1. Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia 2. PT. Biotis 3. Universitas Airlangga (UNAIR)
6.	Persetujuan Etik	:	Persetujuan No. 0645/KEPK/IV/2023 Tanggal 11 April 2023 dari Komite Etik Penelitian Kesehatan RSUD Dr Soetomo Surabaya
7.	Desain Uji Klinik	:	*This is an open label, phase III trial – immunobridging study. There will be only 1 group in the study. All subjects (12 to 17 years old) will receive INAVAC 5 µg dose. The vaccine will be administered with 2-dose schedule, intramuscularly, with 28 day interval. All subjects will be followed for 12 months.*
8.	Jumlah Subjek	:	*The test uses immunogenicity estimation difference between INAVAC phase III in adults and this adolescents trial as 10% (The lower limit of the trial vaccine according to WHO is 67% and the difference between both vaccines should not exceed 10%). The GMT of PRNT of phase III in adults was 501.739 (SD 225). If the deviation of our prediction is 0.1, α is 0.05 and the power of test is 90%, by this formula, there will be 346 subjects for each group, and if the predicted drop out is approximately 16% then the total subjects will be approximately 400 people. Cellular immunogenicity will be evaluated from 60 subjects of those who will have immunogenicity data. There is no specific statistical calculation to*

determine this number of subjects with cellular immunogenicity examination. All 60 subjects in this group will be selected based on "first come first served" basis.

9. Tujuan Uji Klinik : *Primary Objective*

To evaluate neutralizing antibody at 28 days following two doses of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).

Secondary Objective

1. *To evaluate safety and reactogenicity at 30 minutes, 24 hours, 7 and 28 days following the first dose and 30 minutes, 24 hours, 7 and 28 days, 3, 6 and 12 months after the second doses of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
2. *To evaluate the neutralizing antibody profile at 3, 6, and 12 months, following vaccination with two doses of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
3. *To evaluate the IgG RBD SARS-CoV-2 profile at 28 days, 3, 6, and 12 months, following vaccination with two doses of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
4. *To evaluate the cellular immunogenicity profile at 28 days, 3, 6, and 12 months, following vaccination with two doses of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
5. *To evaluate the persistence of antibody level and the need for booster.*

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

1. *Healthy adolescents, age 12 to 17 years old, males and females. 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 and the parents or guardians have been informed properly regarding the study and signed the informed consent and assent forms*
3. *Subject and the parents or guardians 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. *Subjects and the parents or guardians 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 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 1 month (for mild, moderate, or asymptomatic people) or 3 months (for severe Covid-19) 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 test or, if necessary, PCR test) 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. *Alcohol or substance abuse*
14. *HIV patients.*
15. *Malignancy patients within 2 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 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 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:

Vaccine neutralizing antibody profile: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay, at 28 days after two doses vaccination of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).

Secondary Endpoints:

– *Safety*
  1. *Solicited – clinical (local and systemic) adverse events for 30 minutes, 24 hours, 7 and 28 days after the first and second vaccination, and then 3, 6, and 12 months after the second injection of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
  2. *Unsolicited adverse events for 30 minutes, 24 hours, 7 and 28 days after the first and second vaccination, and then 3, 6, and 12 months after the second injection of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
  3. *Serious adverse event (SAE) throughout the study (from the first vaccination)*
– *Humoral Immunogenicity*
  1. *SARS-CoV-2 Neutralization antibody: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay, at 3, 6, and 12 months after the second vaccination of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
  2. *SARS-CoV-2 binding antibodies measured by CLIA: analysis of antibodies binding to the SARS-CoV-2 S-protein, at 28 days, 3, 6, and 12 months after the second vaccination of INAVAC in healthy adolescents age 12 to 17 years old, compared with previous results in adults with two doses of similar vaccine (phase 3 in adults).*
  3. *Persistence of antibodies over time for 12 months after the second injection.*

– *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.

Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik Vaksin Merah Putih-UA SARS-CoV-2 (INAVAC) sebagai vaksin primer pada anak 12-17 tahun. Hasil evaluasi telah didukung tim ahli melalui rapat pada 10 Maret 2023 dengan hasil sebagai berikut:

1. Desain uji klinik yang diajukan telah memadai termasuk penggunaan *historical control* untuk membandingkan data keamanan dan imunogenisitas pada anak dengan data hasil uji klinik pada subjek dewasa (≥ 18 tahun) yang diperoleh dari uji klinik fase 3 pada dewasa. Penggunaan *historical control* telah sesuai *guidance international* yaitu kriteria inklusi dan eksklusi telah mencantumkan kriteria yang terperinci meliputi data demografi, *baseline* status dan terapi yang diberikan untuk mendapatkan kemiripan antara kelompok uji (subjek anak) dan dengan kelompok kontrol (subjek dewasa) untuk meminimalkan bias dalam studi. Selain itu, intervensi (waktu vaksinasi dan pengamatan keamanan & imunogenisitas) pada kelompok uji dilakukan sama dengan subjek dewasa.
2. 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.01.06.1.3.04.23.17 tanggal 26 April 2023.