RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN *PLASMODIUM FALCIPARUM SPOROZOITE* (PFSPZ) DAN
VAKSIN *PLASMODIUM FALCIPARUM SPOROZOITE CHALLENGE* (PFSPZ-C)
PRODUKSI SANARIA INC, USA

Informasi Umum

1. Uji klinik fase 2 vaksin *Plasmodium falciparum Sporozoite* (PfSPZ) dan vaksin *Plasmodium falciparum Sporozoite Challenge* (PfSPZ-C) merupakan bagian dari pengembangan (*investigational new drug* / IND) vaksin oleh Sanaria, Inc, USA dan diajukan oleh *Eijkman-Oxford Clinical Research Unit (*EOCRU) sebagai *Clinical Research Organization* (CRO). Studi fase 1 dan 2 telah dilakukan di negara Mali, Tanzania, Amerika Serikat, Equatorial Guinea, Germany, Kenya, Gabon dan Burkina Faso.
2. Protokol uji klinik vaksin PfSPZ dan PfSPZ *Challenge* di Indonesia sudah diajukan ke USFDA sebagai bagian dari pengajuan IND pada tanggal 1 Juni 2018. Pada 26 Juli 2018, FDA menginformasikan kepada sponsor (Sanaria) bahwa tidak ada isu klinik terkait protokol tersebut dan uji klinik dapat dilakukan
3. Uji klinik ditujukan untuk mencegah malaria pada subjek tentara yang akan diberangkatkan ke Indonesia Timur (Papua) yang merupakan daerah endemik malaria.

Informasi Uji Klinik

1.	Judul protokol	:	***"Safety, Tolerability, Immunogenicity and Protective Efficacy Againts Naturally-Transmitted Malaria in Eastern Indonesia of Two Plasmodium falciparum Sporozoite Vaccine and Sanaria® PfSPZ-CVac: A Randomized, Double Blind, Placebo-Controlled Phase 2 Trial in Healthy Indonesian Adults"*** *Protocol IDSPZV1 version 2.0 date 31 January 2019*
2.	Produk Uji	:	1. *Plasmodium falciparum Sporozoite (PfSPZ) Vaccine* diberikan 3 kali secara intramuskular produsen Sanaria Inc, USA 2. *Plasmodium falciparum Sporozoite (*PfSPZ) Challenge Vaccine diberikan 3 kali secara intramuskular produsen Sanaria Inc, USA 3. *Chloroquine phosphate* diberikan *loading dose* (1 kali) dan weekly dose (9 kali) secara oral produsen Anderson Bercon (UK) Limited
3.	Produk Pembanding	:	*Phosphate buffered saline* (PBS) diberikan 3 kal secara intramuskular produsen Sanaria Inc, USA
4.	Center/Peneliti	:	Divisi Penyakit Infeksi dan Tropis, Departemen Penyakit Dalam, Fakultas Kedokteran Universitas Indonesia Jakarta/ dr. Erni Juwita, SpPD
5.	Sponsor/ ORK	:	Sanaria Inc, USA / *Eijkman Oxford Clinical Research Unit* (EOCRU)
6.	Persetujuan Etik	:	Persetujuan Komisi Etik Penelitian Kesehatan FKUI-RSCM Nomor ND-323/UN2.F1/ETIK/PPM.00.02/2019 tanggal 18 Maret 2019
7.	Desain Uji Klinik	:	*Single site, double blind, randomized, placebo-controlled, phase 2 clinical trial.*
8.	Jumlah subjek	:	420 subjek dewasa
9.	Tujuan uji klinik	:	***Primary objective:*** 1. *To assess the safety and tolerability of PfSPZ Vaccine and PfSPZ-Cvac compared to placebo among men naturally exposed to malaria* 2. *To assess the protective efficacy (vaccine efficacy = VE) againts Pf naturally transmitted mosquito-borne attack diagnosed by thick blood smear (TBS) microscopy of*

PfSPZ Vaccine and PfSPZ-Cvac compared to placebo among men naturally exposed to Pf.

Secondary objective:

1. *To assess the protective efficacy of PfSPZ Vaccine and PfSPZ-CVac againts naturally transmitted mosquito-borne Pv primary attack diagnosed by TBS microscopy*
2. *To assess the protective efficacy of PfSPZ Vaccine and PfSPZ-CVac againts secondary attacks from latent liver stages of Pv by TBS duirng the six months post exposure period in a malaria free area*
3. *To assess the protective efficacy of PfSPZ Vaccine and PfSPZ-CVac againts naturally transmitted Pf and PV primary and secondary attacks diagnosed by quantitative polymerase chain reaction (qPCR).*
4. *To determine the immunogenicity of PfSPZ Vaccine and PfSPZ-CVac*
5. *To determine if any immune response to Pf or Pv are predictive of VE*

To identify markers of latent infection with Pv

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

1. *A male aged 18-55 years at the time of screening*
2. *Assigned to the batalion of study and programmed to accompany it to eastern Indonesia for the duration of the development*
3. *Freely provides written informed consent to participate in the study*
4. *Agrees to adhere to Indonesian military medical guidance regarding screening and treatment of malaria.*
5. *Physical examination and laboratory results without clinically significant findings and a body mass index (BMI) ≤35 kg/m2*

Exclusion criteria :

1. *Previous vaccination with an investigational malaria vaccine*
2. *Use of an investigational or non-registered drug or vaccine other than the study vaccine(s) within 30 days before the first study vaccination, or planned use up to 30 days after last vaccination*
3. *Chronic administration (defined as more than 14 days) of immunosuppresant or other immune-modifying drugs within six months before the first vaccination. This includes any dose level of oral steroids, but not inhaled steroids or tropical steroids*
4. *Planned administration of 3 or more vaccines not foreseen by the study protocol within 28 days before the first study vaccination and for 28 days after the last vaccination*
5. *Confirmed or suspected immunosuppressive or immunodeficient condition*
6. *Confirmed or suspected autoimmune disease*
7. *History of allergic reactions or anaphylaxis to CQ or other 4-aminoquinolone derivatives*
8. *History of serious allergic reactions to a drug requiring hospitalization*
9. *History of allergy to phosphate buffered saline or human serum albumin*
10. *Use or planned use of any drug wth anti-malarial activity during the course of the study except for antimalarial medication administered by study clinicians*
11. *History of splenectomy*
12. *Laboratory evidence of liver disease (the final decision will be made by the PI and clinical officers, but ini general a*

volunteer will be excluded if any of the screening liver function tests (ALT, bilirubin, gamma GTP) are > double the upper limit of normal measured twice without an expalanation for the abnormal values)

13. *Laboratory evidence of renal disease (serum creatinine >1,5 mg/dl measured twice*
14. *Laboratory evidence of hematologic disease (platelet count or hemoglobin <80% of the lower limit of normal for Indonesia measured twice)*
15. *Abnormal screening ECG considered by a cardiologist to be indicative or acute or chronic cardiovascular disease*
16. *Acute or chronic pulmonary, cardiovascular, hepatic renal or neurological condition, severe malnutrition, or any other clinical findings that may increase the risk of participating in the study as determined by the principal investigator or her designee*
17. *Administration of immunoglobulin and/or any blood products within the three months preceding the first study vaccination or planned administration during the study period*
18. *Simultaneous participaction in any other interventional clinical trial*
19. *Other conditions that in the opinion of the principal investigator or her designee would jeopardize the safety or rights of a participant in the trial or would render the participant unable to comply with the protocol*
20. *Any evidence of active malaria, whether symptomatic or asymptomatic, confirmed by RDT,microscopy or PCR less than 3 weeks before first injection of PfSPZ vaccine or PfSPZ-CVac*
21. *History of non febrile seizures or a typical febrile seizures*
22. *Under treatment for tuberculosis*
23. *Subjects with ≥ 5% 5-year cardiovascular risk (fatal and non fatal) based on the Gaziano scoring system (Appendix A); subjects in the 18-34 year old age group will be assessed as through they are in the 35-44 age group*
24. *History of psychiatric disorders (such as personality disorders (such as personality disorders, anxiety disorders or schizoprenia) or behavioral tendencies (including active alcohol or drug abuse) discovered during the screening process that in the opinion of the investigator would make compliance with the protocol difficult.*

a. Luaran Uji Klinik/ Endpoint : ***Primary outcome***

1. *The number of adverse events occuring after vaccination and placebo administration:*
   a. *The number of SAEs related to vaccination or placebo administration during active participation in the trial*
   b. *The number and severity of solicited AEs occuring within 7 days (PfSPZ Vaccine) or 12 (first two doses) or 14 (third dose) days (PfSPZ-CVac) of each administration of investigational product (IP) related to vaccination or placebo administration*
   c. *The number and severity of unsocilited AEs occuring within 28 days of each administration of investigational product (IP) related to vaccination or placebo administration.*
2. *The number of microscopy confirmed first infections with Pf among subjects receiving vaccine vs placebo during the period from 10 days after arriving in eastern Indonesia through 10 days after leaving eastern Indonesia.*

Secondary outcome

1. *The number of microscopy confirmed first infection with Pv among subjects receiving vaccine vs placebo during the period from 10 days after arriving in eastern Indonesia through 10 days after leaving eastern Indonesia*
2. *The number of microscopy confirmed fisrt infection with Pv among subjects receiving vaccine vs placebo for 6 months post exposure beginning 10 days after leaving eastern Indonesia*
3. *The number of PCR confirmed first infections*
4. *The immune responses induced by vaccination compared to those induced by placebo administration*
5. *Associations between immune responses and protection among subjects receiving vaccine vs placebo during the period from 10 days after arriving in eastern Indonesia through 10 days after leaving eastern Indonesia*
6. *Associations between immune responses measured prior to the 24 week period of surveillance beginning after return to Java and the risk of relapse during that period*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik *Plasmodium falciparum Sporozoite (PfSPZ) Vaccine* yang didukung oleh tim ahli melalui rapat pada tanggal 8 Oktober 2018.

Tersedia data uji klinik:

1. Fase I dan II pada subjek sehat dewasa (tentara) yang menunjukkan vaksin dapat ditoleransi dengan baik dan memberikan respon imun setelah 28 hari setelah dosis lengkap.
2. *PfSPZ Vaccine challenge* diberikan bersama dengan klorokuin pada bertujuan untuk membunuh parasit pada *PfSPZ-Cvac* dan tidak dimaksudkan untuk mengobati parasit malaria yang diperoleh secara alami oleh gigitan nyamuk di Indonesia mengingat *PfSPZ Vaccine challenge* adalah vaksin yang mengandung *Plasmodium falciparum Sporozoite* yang masih aktif (*non-attenuated*) sehingga bisa menginfeksi.

Desain uji klinik memadai dan vaksin uji klinik yang akan digunakan telah memenuhi persyaratan mutu.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas disetujui melalui penerbitan Persetujuan Pelaksanaan Uji Klinik (PPUK) Nomor B-PN.01.06.3.321.05.19.1739 tanggal 10 Mei 2019.