RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN *13-VALENT PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE* (PCV13-TT)
PRODUKSI YUXI WALVAX BIOTECHNOLOGIES

Informasi Umum

1. Vaksin PCV13-TT merupakan vaksin yang dikembangkan oleh Yuxi Walvax Biotechnologies dan telah mendapatkan persetujuan registrasi obat dari the *National Medical Products Administration* (NMPA) pada 30 Desember 2019 dan resmi beredar di China sejak April 2020.
2. Uji klinik fase III di Indonesia saat ini diajukan sebagai pemenuhan *post-marketing pre-requisite dari WHO* terkait dengan pengujian vaksin PCV13-TT bersama dengan vaksin *concomitant.*

Informasi Uji Klinik

1.	Judul Protokol	:	***A Phase 3, Randomized, Blinded, Active-controlled study to Evaluate the Immunogenicity and Safety of Walvax's 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT) as Compared to Pfizer's 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Co-administered with EPI Vaccines at 2, 4, and 12-15 Months of Age, to Healthy Infants in Indonesia*** ***Protocol PCV13-004 Version 1.2 Date: June 14, 2023***
2.	Produk Uji	:	*13-valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV13-TT vaccine) with 0.5 mL/syringe, 0.5 mL per single human dose,contains serotype 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, and 6B polysaccharide.* Vaksin diberikan 3 kali pada bulan ke- 2, 4, dan 12-15 secara intramuskular. Produksi: Yuxi Walvax Biotechnologies, China.
3.	Produk Pembanding	:	Prevenar-13 Vaccine, *suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes. Each 0.5 mL dose of PCV13 is formulated to contain serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, dan 6B polysaccharides.* Vaksin diberikan 3 kali pada bulan ke- 2, 4, dan 12-15 secara intramuskular. Produksi: Pfizer Ireland Pharmaceuticals.
4.	Center/ Peneliti	:	- RSUPN Dr. Cipto Mangunkusumo / Dr. dr. Nastiti Kaswandari. ApA(K) - RSUP Prof. Dr. I.G.N.G Ngoerah / Dr.dr. I Gusti Ayu Trisna Windiani, SpA(K)
5.	Sponsor/ ORK	:	Yuxi Walvax Biotechnology Co., Ltd, PT. Etana Biotechnologies Indonesia / Prodia DiaCRO
6.	Persetujuan Etik	:	No. KET 1028/UN2.F1/ETIK/PPM.00.02/2023 tanggal 31 Juli 2023 dari Komite Etik Penelitian Kesehatan FK Universitas Indonesia – RSUPN Dr. Cipto Mangunkusumo dan No. 1286/UN14.2.2.VII.14/LT/2023 tanggal 15 Mei 2023 dan No. 1674/UN14.2.2.V.1/PT.01.01/2023 tanggal 4 Juli 2023 dari Komisi Etik Penelitian Kedokteran Universitas Udayana

7. Desain Uji Klinik : *Randomized, active-controlled, blinded, phase 3 study in healthy infants 6-8 weeks of age that will be performed in Indonesia*
8. Jumlah Subjek : *A total of approximately 600 infants 6-8 weeks of age*
9. Tujuan Uji Klinik :

1. *Primary objective*

Immunogenicity and Non-inferiority

To demonstrate the non-inferiority of the serotype-specific immune responses elicited by PCV13-TT, for the 13 vaccine-serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), as compared to the serotype-specific immune responses elicited by PCV13, based on:

1. *serotype-specific % of infants with immunoglobulin G (IgG) response ≥0.35 µg/mL,*
2. *serotype-specific IgG geometric mean concentrations (GMCs) measured 1 month after the booster dose.*

Secondary objectives

Safety

1. *To evaluate the safety and tolerability of PCV13-TT when co-administered with routine pediatric vaccines at 2, 4 and 12-15 months of age, after each dose.*
2. *To evaluate the long-term safety of PCV13-TT up to 6 months after the booster dose.*

Immune Response to primary series

To evaluate the immunogenicity of PCV13-TT 1 month after the 2nd dose.

Functional antibody responses

To evaluate the functional serotype-specific antibody responses induced by PCV13-TT, as measured by serotype-specific Opsonophagocytic Activity (OPA) before the 1st dose, 1 month after the 2nd dose, before the booster dose and 1 month after the booster dose.

Immune persistence

To evaluate the persistence of immune responses induced by PCV13-TT at 12-15 months of age, before the booster dose.

Exploratory – Non-interference

To compare the immune responses induced by routine pediatric vaccines (DTP, Hib, HepB, Polio) when co-administered with PCV13 or PCV13-TT at 2 and 4 months of age, 1 month after the 2nd dose, in different subsets of subjects.

10. Kriteria Eligibilitas **:**

Kriteria Inklusi / Inclusion criteria

Infants must meet ALL the following inclusion criteria for enrollment in the study, at the time of the screening:

1. *Healthy infants based on medical history and clinical assessment.*
2. *Age of 6-8 weeks at enrolment. Infants will be eligible since the day they reach 6 weeks of age and until 8 weeks of age included.*
3. *Body weight at enrollment ≥3.5 kg.*
4. *Infant's parent(s) or legal guardian(s) must be able and willing to provide voluntary written/thumb-printed informed consent for the infant to participate in the study.*
5. *Infant's parent(s) or legal guardian(s) must be able to comprehend and comply with study requirements and procedures and must be willing and able to return or make themselves available for all scheduled follow-up visits.*
6. *Infant's parents must have a readily identifiable place of residence in the study area, be available for the duration of trial participation, and have means of telephone contact*

Kriteria Eksklusi / Exclusion criteria

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

1. *Use of any investigational medicinal product other than that used in the study prior to randomization or planned use of such a product during the period of study participation.*
2. *History of S. pneumoniae infection as confirmed by medical enquiry or as confirmed by laboratory testing if available.*
3. *Participant has fever (axillary temperature ≥37.5℃) within 24 hours prior to the 1st dose of vaccination; (If the subject does not meet the criteria, the visit may be rescheduled when the criteria are met.)*
4. *The infant who are children in care, preterm and low-birth-weight (Preterm infants have a gestational age below 37 weeks at birth and low-birth-weight infants have a birth weight below 2.5 kg).*
5. *History of allergic disease or history of a serious reaction to any prior vaccination or known hypersensitivity to any component of the 2 study vaccines. This includes all components of the EPI vaccines.*

6. *History of anaphylactic shock.*
7. *Any abnormal vital sign as judged by the investigator.*
8. *Any moderate or severe acute illness.*
9. *History of administration of a non-study vaccine within 30 days prior to administration of study vaccine, other than EPI vaccinations (Note: EPI vaccines other than that stipulated in the study must be given at least 14 days prior to the investigational vaccine.)*
10. *Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, epidural, or topical (skin or eyes) corticosteroids within indicated dosage are permitted.*
11. *Administration of immunoglobulins and/or any blood products or anticipation of such administration during the study period.*
12. *History of known disturbance of coagulation or blood disorder that could cause anemia or excess bleeding (e.g., thalassemia, coagulation factor deficiencies, severe anemia at birth).*
13. *History of suspected primary immunodeficiency.*
14. *History of meningitis, seizures or any neurological disorder.*
15. *A family history of congenital or hereditary immunodeficiency.*
16. *The infant is a direct descendant (child or grandchild) of any person employed by the Sponsor, the CRO, the investigator, study site personnel.*
17. *Any medical or social condition that in the opinion of the investigator may compromise the well-being of the study participant, interfere with the study objectives, pose a risk to the study participant, or prevent the study participant from completing the study follow-up.*

11. *L*uaran Uji Klinik/ *Endpoint* **:**

Primary endpoints

Immunogenicity and Non-inferiority

1. *Percentage of infants with serotype-specific IgG concentrations ≥0.35 µg/mL, measured 1 month after the booster dose, and*
2. *Serotype-specific IgG GMCs measured 1 month after the booster dose.*

Secondary endpoints

Safety

1. *Frequency and severity of solicited local and systemic adverse events (aEs) within 30 min and 7 days after each dose.*
2. *Frequency and severity of unsolicited aEs within 30 days after each dose.*
3. *Frequency of serious aEs (SAEs) from dose 1 until 6 months after booster dose.*

Immune Response to primary series

1. *Percentage of infants with pneumococcal serotype-specific IgG concentrations ≥0.35 µg/mL measured 1 month after the 2nd dose.*
2. *Serotype-specific IgG GMCs measured 1 month after the 2nd dose.*

Functional antibody responses

1. *Percentage of infants with serotype-specific OPA titer ≥1:8 measured at baseline, 1 month after the 2nd dose, before the booster dose, and 1 month after the booster dose.*
2. *Serotype-specific OPA geometric mean titers (GMTs) measured at baseline, 1 month after the 2nd dose, before the booster dose, and 1 month after the booster dose.*

Immune persistence

1. *Percentage of infants with pneumococcal serotype-specific IgG concentrations ≥0.35 µg/mL measured at 12-15 months of age, before the booster dose.*
2. *Serotype-specific IgG GMCs measured at 12-15 months of age, before the booster dose.*

Exploratory – Non-interference

1. *Percentage of infants with anti-diphtheria toxoid IgG concentrations ≥0.1 IU/mL measured 1 month after the 2nd dose.*
2. *Percentage of infants with anti-tetanus toxoid IgG concentrations ≥0.1 IU/mL measured 1 month after the 2nd dose.*
3. *Proportion of subjects with 4-fold increase in anti-pertussis IgG concentration 1 month after the 2nd dose with respect to baseline titers.*
4. *Percentage of infants with anti-Haemophilus influenzae type b (PRP) IgG concentration ≥0.15 µg/mL measured 1 month after the 2nd dose.*
5. *Percentage of infants with anti-Hepatitis B surface antigen (hBsAg) IgG concentrations ≥10 mIU/mL measured 1 month after the 2nd dose.*
6. *Percentage of infants with anti-poliovirus types 1, 2 and 3 neutralizing antibody titers ≥1:8 measured 1 month after the 2nd dose..*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik vaksin PCV13-TT, yang didukung oleh tim ahli melalui rapat pada tanggal 12 Mei 2023 dengan hasil sebagai berikut:

1. Hasil uji non-klinik tpada *white rabbit* dan macaca menunjukkan produk yang akan digunakan dalam uji klinik memiliki (i) profil keamanan yang masih dapat ditoleransi dengan baik (ii) imunogenisitas yang baik dan menginduksi imunitas terhadap infeksi pada hewan model setelah pemberian suntikan kedua.
2. Hasil uji klinik fase 1/2, 2/3 dan 3 yang telah dilakukan di China menunjukkan imunogenisitas antigen dan tedapat peningkatan kadar antibodi dan nilai antibodi positif baik untuk Ig G dan nilai OPA. Persistensi imun juga ditunjukkan dari hasil uji klinik tersebut dengan tidak ada penurunan signifikan yang diamati pada kadar antibodi pada 2 tahun pasca dosis *booster*. Secara umum vaksin dapat ditoleransi dengan baik.
3. Desain uji klinik yang diajukan telah memadai.
4. 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 Nomor RG.01.06.1.3.09.23.35 tanggal 13 September 2023