RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN VLP-POLIO
PRODUKSI CANSINO BIOLOGICS INC. (CANSINO BIO, CHINA)

Informasi Umum

1. Vaksin Recombinant Trivalent Poliomyelitis (Sf- RVN Cells) atau disingkat VLP-Polio merupakan vaksin Polio yang menggunakan *Virus-like Particle* (VLP). Vaksin ini dikembangkan oleh CanSino Biologics Inc. (CanSino BIO, China). Uji klinik ini ditujukan untuk rencana registrasi di Indonesia dengan pendaftar PT. Etana Biotechnologies Indonesia dan diikuti alih teknologi.
2. VLP-Polio dikembangkan menggunakan teknologi DNA rekombinan dan terdiri dari komponen struktur protein Type I/SN1 (protein struktural dari attenuated strain Sabin I), Type II/SK2 (wild strain MEF-1) dan Type III/SN3 (attenuated strain Sabin 3).
3. Pengembangan produk ini dilatarbelakangi oleh adanya *circulating vaccine-derived poliovirus* (cVDPV) di lingkungan akibat pemberian imunisasi OPV sehingga beberapa negara beralih ke IPV. Namun produksi IPV dari virus hidup juga memiliki risiko dalam mencapai dan mempertahankan eradikasi poliomyelitis. Berdasarkan laporan WHO pada Aug 2022 hingga Aug 2023, telah dilaporkan sekitar 611 kasus poliomyelitis karena cVDPV, dan 8 kasus karena WPV1 (Wild Polio Virus type 1). Oleh karena itu, diperlukan generasi baru vaksin berasal dari *non-living virus*.
4. Vaksin Polio yang sudah disetujui di Indonesia pada saat pengajuan menggunakan *platform inactivated* dan *oral live-attenuated.*

Informasi Uji Klinik

1.	Judul Protokol	:	***A phase I/II randomized, double-blind, positive-controlled dose-exploration study to evaluate the safety and immunogenicity of a virus-like particle (VLP) based vaccine against Poliomyelitis (VLP-Polio) in infants from 6 weeks of age and toddlers 12-18 months of age*** No. studi CTP-VLP-002, Versi 1.1, Tanggal 22 Agustus 2024
2.	Produk Uji	:	- ***Low-adjuvant dose of VLP-Polio (Dose A)****: Each 0.5mL dose is formulated to contain 45 D antigen units of Type 1, 8 D antigen units of Type 2, and 25 D antigen units of Type 3 poliovirus, with 0.1mg Aluminum phosphate adjuvant* - ***Medium-dose of VLP-Polio (Dose M)****: Each 0.5mL dose is formulated to contain 45 D antigen units of Type 1, 8 D antigen units of Type 2, and 25 D antigen units of Type 3 poliovirus, with 0.3mg Aluminum phosphate adjuvant* - ***High-dose of VLP-Polio (Dose H)****: Each 0.5mL dose is formulated to contain 90 D antigen units of Type 1, 12 D antigen units of Type 2, and 45 D antigen units of Type 3 poliovirus, with 0.3mg Aluminum phosphate adjuvant* 0,5 mL per dosis diberikan: - 1 kali pada subjek toddler (usia 12-18 bulan) secara intramuskular. - 4 kali pada subjek infant (usia 6 minggu-2 bulan) terdiri atas 3 dosis primer pada D0, D28 dan D28 setelah dosis kedua, serta 1 dosis booster pada usia 12-18 bulan, secara intramuskular.
3.	Produk Pembanding	:	Vaccine Poliomyelitis Inactivated (IPV) produksi PT. Bio Farma 0,5 mL per dosis dengan waktu pemberian yang sama dengan produk uji, secara intramuskular
4.	Peneliti Koordinator	:	dr. Nina Dwi Putri, SpA.SubsIPT(K), MSc

Dirilis oleh BPOM 4 Oktober 2024

5.	*Center* / Peneliti	:	1. RSUPN Dr. Cipto Mangunkusumo / dr. Nina Dwi Putri, SpA.SubsIPT(K), MSc *Field sites:* Puskesmas Pulogadung, Puskesmas Sawah Besar, Puskesmas Cilincing, Puskesmas Cengkareng, dan Puskesmas Mampang Prapatan 2. RS Universitas Airlangga / Prof. Dr. Nasronudin dr., Sp.PD., KPTI.FINASIM *Field sites*: Puskesmas Tambelangan, Sampang, Madura dan Puskesmas Banjar, Sampang, Madura
6.	Sponsor / ORK	:	PT Etana Biotechnologies Indonesia / Tigermed Consulting, Co., Ltd. Indonesia
7.	Persetujuan Etik	:	1. No. KET-1294/UN2.F1/ETIK/PPM.00.02/2024 tanggal 13 September 2024 dari Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Indonesia / Rumah Sakit Dr. Cipto Mangunkusumo 2. No. 133/KEP/2024 tanggal 9 September 2024 dari Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Airlangga
8.	Desain Uji Klinik	:	*Phase I and Phase II are randomized, double-blind, and positive-controlled studies. The total sample size is 96 for Phase I and 384 for Phase II, randomized into either experimental or control arm.*
9.	Jumlah Subjek	:	*96 in Phase I and 384 in Phase II*
10.	Tujuan Uji Klinik	:	***Primary Objective*** ***Phase I*** *To assess the safety and tolerability of VLP-Polio* ***Phase II*** *To assess the safety and immunogenicity of VLP-Polio* ***Secondary Objectives*** ***Phase I*** *To assess the immunogenicity of VLP-Polio* ***Phase II*** *To assess the immune-persistency of VLP-Polio* ***Exploratory Objectives*** **Phase II** To assess the mucosal immunogenicity of VLP-Polio
11.	Kriteria Eligibilitas	:	***Inclusion criteria*** *1. Healthy toddlers aged 12-18 months at the time of screening, and have completed primary immunization of polio vaccine according to the national government program in the first year of life.* *2. Infants aged 6 weeks to 2 months (42 to 98 days, with the day of birth considered day of life 1), who have not received any polio vaccines.* *3. Able to obtain written informed consent from parent(s) or legal guardian(s).* *4. Participants and their parents or legal guardian(s) can comply with trial procedures, are available for the duration of follow-up, and have a suitable telephone contact available.* ***Exclusion criteria for first dose***

1. *Current polio disease or history of polio disease.*
2. *Toddlers who have an interval of less than 5 months since their last dose of the polio vaccine.*
3. *Infant born at < 37 weeks of gestation.*
4. *Children with a birth weight < 2500g and a body weight < 3500g at the time of enrollment.*
5. *Axillary temperature ≥37.5oC (the visit may be rescheduled when this criterion is met).*
6. *Have congenital malformations or developmental disorders, genetic defects, severe malnutrition, etc.*
7. *Any moderate or severe acute illness.*
8. *Any abnormal vital signs.*
9. *History of epilepsy, convulsions, or parent with congenital cognitive disability, dementia, or intellectual disabilities.*
10. *Have received immunosuppressive treatment, cytotoxic treatment, glucocorticoid treatment, etc. (excluding local treatment, surface treatment of acute non-concurrent dermatitis, or spray treatment of allergic rhinitis).*
11. *Received or planned to receive blood/plasma products or immunoglobulins throughout the study period or prior to study vaccination*
12. *Historyofseriousadverseeventsand/orsevereallergicreactions(e.g., systemicallergicreactions) to any component of the study vaccine.*
13. *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).*
14. *Immunocompromised individuals with known or suspected immunodeficiency as determined by medical history and/or physical examination (e.g., history of pancreatic, liver, spleen, kidney disease or history of resection).*
15. *Administration of other vaccines within 7 days.*
16. *Participation in other interventional studies within 28 days prior to screening and/or during study participation.*
17. *Household member or sibling who has received or is scheduled to receive OPV in the previous 3 months until 5 weeks after the third dose of the primary immunization series.*
18. *The participant is a direct descendant (child or grandchild) of any person employed by the Sponsor, the CRO, the investigator, or study site personnel.*
19. *History or current evidence of any condition or therapy which might confound the results of the study, interfere with the participant's participation for the full duration of the study, indicate suspected diseases or is not in the best interest of the participants to participate, in the opinion of the treating investigator.*
20. *Family history of any medical conditions, that in the investigating doctor's opinion, could affect the trial outcomes.*
21. *Any reason or condition the investigator considers sufficient to make a participant ineligible for participation in the study*

Exclusion criteria for subsequent dose

22. *Severe allergic reaction after the previous vaccination.*
23. *Serious adverse events caused by the previous vaccination.*
24. *Newly identified symptoms or newly occurred cases after the first vaccination that do not meet the inclusion criteria for the first dose, or that meet the exclusion criteria for the first dose. The decision to discontinue participation is determined by the investigator.*
25. *Other reasons for exclusion considered by the investigating doctor.*

12. *Endpoint* Uji Klinik :

Primary Endpoints:

Phase I

1. *Percentage of participants with solicited AEs within 7 days after each vaccination.*

Phase II

1. *Percentage of participants with solicited AEs within 7 days after each vaccination.*
2. *Seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before the vaccination and on Day 28 after the 3rd dose vaccination.*

Secondary Endpoints

Phase I

1. *Percentage of participants with unsolicited AEs within 28 days after each vaccination.*
2. *Percentage of participants with solicited AEs within 30 minutes after each vaccination.*
3. *Percentage of participants experiencing SAEs throughout the study.*
4. *GMT, seroprotection rate, and seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before vaccination and on Day 28 after the vaccination in toddlers.*
5. *GMT, seroprotection rate, and seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before the 1st dose vaccination and on Day 28 after the 3rd dose vaccination in infants.*

Phase II

1. *Percentage of participants with unsolicited AEs within 28 days after each vaccination.*
2. *Percentage of participants with solicited AEs within 30 minutes after each vaccination.*
3. *Percentage of participants experiencing SAEs throughout the study.*
4. *GMT and seroprotection rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before the 1st dose vaccination and on Day 28 after the 3rd dose vaccination.*
5. *GMT, seroprotection rate and seroconversion rate of neutralizing antibodies against Salk poliovirus type 1, 2, and 3 on Day 0 before the 1st dose vaccination and on Day 28 after the 3rd dose vaccination in immune-persistency subgroup participants.*
6. *GMT, seroprotection rate and seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Month 6 after the 3rd dose vaccination in immune-persistency subgroup participants.*

Exploratory Endpoints

Phase II

1. *GMT, seroprotection rate, and seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before booster vaccination, on Day 28 and Month 6 after the booster vaccination in immune-persistency subgroup participants.*
2. *GMT, seroprotection rate, and seroconversion rate of neutralizing antibodies against Sabin poliovirus type 1, 2, and 3 on Day 0 before vaccination and on Day 28 after the 2nd dose in extended immunogenicity subgroup participants.*

3. *GMT and GMI (geometric mean fold increase) of poliovirus type-specific neutralizing and binding antibodies (IgA, IgG, IgM) in stool samples on Day 0 before the 1st dose vaccination, on Day 14 and Day 28 after the 3rd dose vaccination, on Day 0 before the booster vaccination, on Day 14 and Day 28 after the booster vaccination in immune-persistency subgroup participants.*
4. *GMT and GMI of poliovirus type-specific neutralizing and binding antibodies (IgA, IgG, IgM) in nasal samples on Day 0 before the 1st dose vaccination, on Day 14 and Day 28 after the 3rd dose vaccination, on Day 0 before the booster vaccination, on Day 14 and Day 28 after the booster vaccination in immune-persistency subgroup participants.*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik vaksin VLP-Polio, yang didukung oleh tim ahli melalui rapat pada tanggal 6 Agustus, 12 Agustus, dan 20 September 2024 dengan hasil sebagai berikut:

1. Hasil uji non-klinik klinik toksikologi, farmakologi dan evaluasi imunogenisitas pada hewan model Sprague-Dawley rats, Guinea pig, dan Wistar rat menunjukkan produk yang akan digunakan dalam uji klinik memiliki (i) profil keamanan yang masih dapat ditoleransi dengan baik dan (ii) menginduksi respon imun humoral.
2. Uji klinik Fase 1 (*first in human*) yang sedang dilakukan pada 72 subjek sehat usia 18 – 54 tahun di Australia, menunjukkan hasil interim (i) profil keamanan dengan tolerabilitas yang memadai, tidak terdapat *Serious Adverse Event* (SAE) dan *Adverse Event* (AE) grade 3 atau lebih dan (ii) menginduksi *sero-protection rate* pada seluruh subjek.
3. Desain uji klinik adaptif yang diajukan telah memadai. Pengawasan keamanan pada kelompok sentinel, perpindahan dari masing-masing kelompok, dan perpindahan dari uji klinik fase 1 ke fase 2 dilakukan secara ketat oleh *Data and Safety Monitoring Board* (DSMB).
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.01.06.32.321.10.2024.2738 tanggal 1 Oktober 2024.