RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN TIFOID KONJUGAT VI-DT FASE III
PRODUKSI PT. BIO FARMA

Informasi Umum

1. Vaksin Tifoid Konjugat Vi-DT diajukan sebagai obat pengembangan baru. Vaksin Tifoid yang telah terdaftar yaitu tifoid polisakarida yang diberikan untuk anak lebih dari 2 tahun tetapi belum untuk anak di bawah 2 tahun. Pengembangan Vaksin tifoid yang dikonjugasi dengan Dipteri Toxoid diharapkan dapat digunakan untuk anak di bawah 2 tahun.
2. Uji klinik fase 3 yang diajukan telah didukung oleh data studi non klinik dan keamanan dan imunogenisitas uji klinik fase I dan II.

Informasi Uji Klinik

1. Judul Protokol : ***Immunogenicity and Safety of Vi-DT Typhoid Conjugate Vaccine (Bio Farma) in Adults, Children and Infants, Lot to Lot Consistency, Noninferiority to PQed TCV and Typhoid Vi Polysaccharide Vaccine (Phase III)*** *(versi 1.a November 2019)*
2. Produk Uji : Vi-DT Typhoid Conjugate Vaccine *(Purified Vi capsular polysaccharide of Salmonella typhi 25 µg)* diberikan 1 kali secara intramuskular
   Produsen PT. Bio Farma
3. Produk Pembanding :
   1. Vi-TT Typhoid Conjugate Vaccine (*Purified Vi capsular polysaccharide of Salmonella typhi Ty2 conjufate dto tetanus toxoid 25 µg*) diberikan 1 kali secara intramuskular
      Produsen Bharat Biotech International Ltd
   2. Typhoid Vi Polysaccharide Vaccine (*Purified Vi polysaccharide 0.025 µg)* diberikan 1 kali secara intramuskular
      Podusen Sanofi Pasteur
4. Center / Peneliti :
   1. Departemen Ilmu Kesehatan Anak, FKUI-RSCM, Jakarta / Bernie Endyarni Medise, dr. Sp.A(K), MPH.
      Fieldsites: Puskesmas Jatinegara, Puskesmas Matraman, Puskesmas Senen, Puskesmas Johar Baru
   2. Departemen Ilmu Kesehatan Anak, Fakultas Kedokteran Universitas Airlangga/Rumah Sakit Soetomo, Surabaya / Dr. Dominicus Husada, dr., Sp.A(K)
      Fieldsites: Puskemas Grogol, Puskesmas Tiron, Puskesmas Tarokan (Kediri), Puskesmas Manyar, Puskesmas Balongpanggang, Puskesmas Cerme (Gresik), Puskesmas Kanor, Puskesmas Balean, Puskesmas Kalitidu (Bojonegoro), Puskesmas Kauman, Puskesmas Ngantru, Puskesmas Kalidawir (Tulungagung)
   3. Departemen Ilmu Kesehatan Anak, Fakultas Kedokteran Universitas Udayana/*Rumah* Sakit Sanglah, Denpasar / Dr. I Gusti Ayu Trisna Windiani, dr., Sp.A(K)
      Fieldsites: Puskesmas I Denpasar Selatan, Puskesmas I Denpasar Barat
5. Sponsor / ORK : PT. Bio Farma
6. Persetujuan Etik :
   1. No. KET-1231/UN2.F1/ETIK/PPM.00.02/2019 tanggal 11 November 2019 dan No. ND-1663/UN2.F1/ETIK/PPM.00.02/2019 tanggal 30 Desember 2019 dari Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Indonesia.

2. No. 239/EC/KEPK/FKUA/2019 tanggal 19 Agustus 2019 dan No. 13/EC/KEPK/FKUA/2020 tanggal 8 Januari 2020 dari Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Airlangga.
3. No. 2018/UN14.2.2. VII.14/LP/2019 tanggal 4 Juli 2019 dan No.3021/UN14.2.2.VII.14/LP/2019 tanggal 26 Desember 2019 dari Komisi Etik Penelitian Fakultas Kedokteran Universitas Udayana/Rumah Sakit Umum Pusat Sanglah, Denpasar.

7. Desain Uji Klinik :
- *Main study I: Randomized, observer blinded, lot to lot consistency and noninferiority to PQed thypoid conjugate vaccine*
- *Main study II: Randomized, observer-blind, noninferiority to Vi polysaccharide vaccine*
- *Main study III: Randomized, double blind lot to lot consistency and safety study*

8. Jumlah Subjek : *3071 subjects (6 months – 60 years old)*

9. Tujuan Uji Klinik : ***Primary objectives:***

To evaluate seroconversion following vaccination with one dose of Vi-DT (Bio Farma) in adults, children and infants

Secondary objectives:
- *To describe antibody response following vaccination with one dose of Vi-DT in adults, children and infants for each lot.*
- *To evaluate the percentage of subjects that achieve anti-Vi IgG levels equal to or above predefined threshold values.*
- *To assess the safety following vaccination with one dose of Vi-DT in adult, children and infants.*
- *To compare the safety and immunogenicity of Vi-DT (Bio Farma) to PQed typhoid conjugate vaccine in each age group (6 months-45 years old).*
- *To compare the safety and immunogenicity between three lot of Vi-DT (Bio Farma).*
- *To compare the safety and immunogenicity of Vi-DT (Bio Farma) to Vi polysaccharide vaccine in group 46-60 years old.*
- *To evaluate the safety and immunogenicity of Vi-DT co-administered with MR vaccine in subject ≥ 9 months -23 months old (sub study)*

10. Kriteria Eligibilitas : ***Inclusion criteria***
1. *Healthy*
2. *Subjects/parents/legal guardian(s) have been informed properly regarding the study and signed the informed consent form*
3. *Subjects/parents/legal guardian(s) will commit themselves to comply with intructions of the investigator and the schedule of the trial*

Exclusion criteria
1. *Subject concomitantly enrolled or scheduled to be enrolled in another trial*
2. *Evolving mild, moderate and severe illness, especially infectious diseases or fever (axilarry temperature ≥ 37.50C)*
3. *Known history of allergy to any component of the vaccines*
4. *History of uncontrolled coagulopathy or blood disorders contraindicating intramuscular injection*

5. *Subject who has received in the previous 4 weeks a treatment likely to alter the immune response (intravenous immunoglobulin's, blood derived products, corticosteroid therapy and other immunosuppressant)*
6. *Any abnormality or chronic disease which according to the investigator might interfere with the assessment of the trial objectives*
7. *Pregnancy and lactation (adults) based on first day of the last menstruation period and test pack*
8. *Individuals who has previously receive any vaccines against typhoid fever*
9. *Subject already immunized with any vaccine within 1 month prior and expect to receive other vaccines within 1 month following immunization, except MR vaccine*
10. *Individuals who have a previously ascertained typhoid fever by laboratory confirmation (blood culture/new rapid test) at any time*
11. *Subject planning to move from the study area before the end of study period*

11. Luaran Uji Klinik*/Endpoint* : ***Primary Endpoints***

Number and percentage of subjects with four-fold increasing antibody 28 days after vaccination compare to baseline.

Secondary Endpoints

Immunogenicity

- *Geometric Mean Titre of anti-Vi IgG in each group*
- *Number and percentage of subjects that achieve anti-Vi IgG levels equal to or above predefined threshold values (≥ 2.0 ug/mL) one month after vaccination compared to baseline.*
- *Comparison of GMT, seroconversion between each lot number of Vi-DT (Bio Farma) vaccine in each group*
- *Comparison of GMT, seroconversion between Vi-DT (Bio Farma) and PQed typhoid conjugate vaccine in each group (6 months – 45 years old)*
- *Comparison of GMT, seroconversion between Vi-DT and Vi-polysaccharide vaccine in group 46 – 60 years old*
- *Serological response to Meales vaccine in infants group (≥9 months – 23 months); percentage of subjects with anti-Measles IgG titer ≥8 (1/dil) 28 days after one dose of MR Vaccine (seroprotection rate), GMT and seroconversion rate.*
- *Serological response to Rubella vaccine in infants group (≥9 months – 23 months); percentage of subjects with anti-Rubella IgG titer ≥8 (1/dil) 28 days after one dose of MR Vaccine (seroprotection rate), GMT and seroconversion rate.*

Safety

- *Number and percentage of adults, children and infants with at least one adverse event. Solicited or unsolicited, within 30 minutes 72 hours, and 28 days after vaccination.*
- *Number percentage of subjects with serious adverse event from inclusion until 28 days after vaccination*

- *Number and percentage of subjects with serious adverse event from inclusion until 6 months after the last dose (Main study I dan II)*
- *Comparison of safety data between Vi-DT and PQed thypoid conjugate vaccine in each age group*
- *Comparison of adverse events between each lot number of Vi-DT*
- *Comparison of safety data between Vi-DT and Vi-polysaccharide vaccine in group 46 – 60 years old.*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol yang diajukan yang didukung oleh tim ahli melalui rapat pada tanggal 13 November 2019 dengan hasil sebagai berikut:

1. Berdasarkan hasil uji klinik fase I dan II, Vaksin Konjugat Vi-DT aman dan memberikan respon imun yang baik pada dewasa, anak dan bayi. Terdapat perubahan dosis vaksin, fase I menggunakan 2 dosis sedangkam fase II dan III menggunakan 1 dosis. Hal ini dikarenakan berdasaran hasil uji klinik fase I, imunogenisitas setelah vaksinasi dosis pertama tidak berbeda bermakna dengan setelah vaksinasi dosis kedua.
2. Desain uji klinik fase 3 yang diajukan dapat diterima, yang mencakup studi noninferiority terhadap Vi-TT (PQ WHO), Vi-polisakarida (yang terdaftar di Indonesia) dan studi konsistensi antar lot.
3. Vaksin memenuhi persyaratan mutu.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas disetujui melalui penerbitan Persetujuan Pelaksanaan Uji Klinik (PPUK) No. RG.01.06.321.01.20.0161 tanggal 20 Januari 2020.