RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN DTP-HB-Hib FASE III
PRODUKSI PT. BIO FARMA

Informasi Umum

1. Vaksin DPT-Hb-Hib (Pentabio) telah terdaftar di Indonesia dan telah digunakan sebagai vaksin untuk imunisasi program nasional. Uji klinik dilakukan dikarenakan adanya perubahan *vendor* bulk Vaksin Hepatitis B (Inactive HbsAg) yang semula berasal dari *The Jannsen Vaccine Corp* menjadi *Serum Institute of India (SII).* Uji klinik ini bertujuan untuk melihat apakah imunogenisitas dan safety vaksin dengan *vendor* baru similar dengan yang telah teregistrasi sebelumnya dan untuk melihat apakah ada interaksi dengan vaksin lain (mengingat Pentabio merupakan vaksin kombinasi).
2. Uji klinik Vaksin Rekombinan Hepatitis B telah dilakukan pada subjek usia di atas 10 tahun. Hasil uji klinik ini akan dijadikan sebagai data dukung dalam rangka registrasi variasi perubahan *vendor* zat aktif Vaksin Rekombinan Hepatitis B dan Pentabio. Diharapkan kedua hasil studi mendukung posologi Vaksin Rekombinan Hepatitis B yang dapat diberikan kepada semua kelompok usia.

Informasi Uji Klinik

1.	Judul Protokol	:	***Comparison of Immunogenicity and Safety of DTP-HB-HIB (Bio Farma) with Pentabio® vaccine Primed with Recombinant Hepatitis B at Birth dose (using different source of Hepatitis B), in Indonesian Infants*** No. protokol Penta BS19, versi 2 tanggal 16 Maret 2020
2.	Produk Uji	:	Hepatitis B rekombinan (HbsAg 10 mcg) dalam 0,5 mL single dose uniject pada usia hari ke 0/+3 secara intramuscular DTP-HB-Hib (Purified diphtheria toxoid > 30 IU, Purified tetanus toxoid > 60 IU, Inactivated Bordetella pertussis > 4 IU, HbsAg 10 mcg) dalam 0.5 ml, diberikan 3 kali pada usia 6-11 minggu, 28 hari setelah penyuntikan pertama, dan 28 hari setelah penyuntikan kedua, secara intramuskular Produsen : PT. Bio Farma
3.	Produk Pembanding	:	Hepatitis B rekombinan (HbsAg 10 mcg) dalam 0,5 mL single dose uniject pada usia hari ke 0/+3 secara intramuscular Pentabio (Purified diphtheria toxoid > 30 IU, Purified tetanus toxoid > 60 IU, Inactivated Bordetella pertussis > 4 IU, HbsAg 10 mcg) dalam 0.5 ml, diberikan 3 kali pada usia 6-11 minggu, 28 hari setelah penyuntikan pertama, dan 28 hari setelah penyuntikan kedua, secara intramuskular Produsen : PT. Bio Farma
4.	*Center*/Peneliti	:	Bagian Ilmu Kesehatan Anak RS Hasan Sadikin/Fakultas Kedokteran Universitas Padjadjaran, Bandung / Dr. dr. Eddy Fadlyana, Sp.A(K),M.Kes. *Field sites*: Puskesmas Garuda, Puskesmas Ibrahim Adjie, dan Puskesmas Puter
5.	Sponsor / ORK	:	PT. Bio Farma
6.	Persetujuan Etik	:	No. 17/UN6.KEP/EC/2020 tanggal 27 Maret 2020 dari Komisi Etik Penelitian Universitas Padjadjaran Bandung
7.	Desain Uji Klinik	:	*Randomized, double-blind, bridging study, prospective intervention study*
9.	Jumlah Subjek	:	*n = 220 infants, 0-3 days old*
10.	Tujuan Uji Klinik	:	***Primary Objective*** *To evaluate protectivity of DTP-HB-Hib Vaccine (Bio Farma) using different source of Hepatitis B bulk.*

Secondary Objectives

1. *To describe the antibody response to diphteri, pertussis, tetanus, hepatitis B and PRP-TT when the antigens are presented in the form of DTP-HB-Hib liquid vaccine using different source of Hepatitis B bulk.*
2. *To describe the antibody response to diphtheria, pertussis, tetanus, hepatitis B and PRP-TT in Pentabio® vaccine.*
3. *To assess the safety of DTP-HB-Hib using different source of Hepatitis B bulk.*
4. *To assess the safety of Recombinant Hepatitis B using different source of Hepatitis B bulk at birth dose.*
5. *To evaluate immunogenicity and safety after primary series of investigational product compare to control.*

11. Kriteria Eligibilitas : ***Inclusion criteria***

1. *Healthy, full term, newborns infants*
2. *Infant born after 37-42 weeks of pregnancy*
3. *Infant weighing 2500 gram or more at birth*
4. *Father, mother or legally acceptable representative properly informed about the study and having signed the informed consent form*
5. *Parents will commit themselves to comply with the indications of the investigator and with the schedule of the trial*

Exclusion criteria

1. *Child concomitantly enrolled or scheduled to be enrolled in another trial*
2. *Child evolving moderate or severe illness, especially infectious disease or fever (axillary temperature ≥ 37.5^{0}C on Day 0)*
3. *Child suspected of allergy to any component of the vaccines (e.g. formaldehyde), based on anamnesis*
4. *Child suspected of uncontrolled coagulopathy or blood disorders contraindicating intramuscular injection, based on anamnesis*
5. *Newborn suspected of congenital or acquired immunodeficiency, based on anamnesis*
6. *Child received orplans to receive any treatment likely to alter the immune response intravenous (immunoglobulins, blood-derived products or long term corticotherapy (> 2 weeks))*
7. *Child received other vaccination with the exception of BCG and poliomyelitis*
8. *Child has any abnormality or chronic disease of which according to the investigator might interfere with the assessment of the trial objectives*
9. *Mother with HbsAg and HIV positive (by rapid test)*
10. *Mother suspected of immunodeficiency disease based on anamnesis*

12. *Endpoint* Uji Klinik : ***Primary Evaluation Criteria:***

Percentage of infants with :

Anti diphtheria titer and anti tetanus titer ≥ 0.01 IU/mL
Anti HBsAg ≥ 10 mIU/mL
Anti PRP-TT ≥ 0.15 ug/mL

28 days after the last injection of DTP-HB-Hib with different source of Hepatitis B bulk vaccine group.

Secondary Evaluation Criteria:

Antibody response in both group with the evaluation criteria:

1. *Serology response to diphtheria toxoid: GMT, percentage of infants with titer ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, percentage of infants with increasing antibody titer ≥ 4 times and/or percentage of infants with transition of seronegative to seropositive.*
2. *Serology response to tetanus toxoid: GMT, percentage of infants with titer ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, percentage of infants with increasing antibody titer ≥ 4 times and/or percentage of infants with transition of seronegative to seropositive.*
3. *Serology response to pertussis component (agglutinins): GMT, percentage of infant with titer ≥ 40, ≥ 80, ≥ 160, and ≥ 320 (1/dil), percentage of infant with increasing antibody titer ≥ 4 times.*
4. *Serology response to hepatitis B: GMT, percentage of infant with titer HbsAg ≥ 10 IU/mL, percentage of infant with increasing antibody titer ≥ 4 times and/or percentage of infants with transition of seronegative to seropositive.*
5. *Percentage of infants with an anti PRP-TT antibody level >= 0.15 mcg/ml, ≥ 1.0 mcg/ml. Geometric mean of anti-PRP-TT antibodies, percentage of infants with increasing antibody titer ≥ 4 times and/or percentage of infants with transition of seronegative to seropositive.*
6. *Comparison of GMT, seroprotection, percentage of subjects with increasing antibody titer ≥ 4 and/or percentage of subjects with transition of seronegative to seropositive following primary series of investigational product compare to control.*

Safety Criteria:

Safety criteria are defined as the percentage of infants with local reaction and/or systemic events after each injection:

1. *Local reaction and systemic events occurring within 30 minutes after immunization.*
2. *Local reaction and systemic events occurring within 72 hours after immunization.*
3. *Local reaction and systemic events occurring after the 72 hours to 28 days following the vaccination will also be reported through.*
4. *Any serious adverse event occurring from inclusion until 28 days after the last dose.*
5. *Comparison of adverse events between investigational product(IP) and control.*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik vaksin DTP-Hb-Hib dengan hasil sebagai berikut:

1. Uji klinik fase 4 Vaksin Pentabio yang digunakan sebagai pembanding aktif ini, menunjukkan profil keamanan yang baik pada 4.000 bayi, tidak terdapat Kejadian Tidak Diinginkan yang Serius (KTDS).
2. Uji klinik fase 2 Vaksin Rekombinan Hepatitis B yang telah dilakukan pada subjek usia 10-40 tahun menunjukkan (i) tidak terdapat perbedaan profil keamanan dan (ii) tidak terdapat perbedaan seroproteksi terhadap Hepatitis B antara bulk *Serum Institute of India (SII)* dengan bulk *The Jannsen Vaccine Corp*.
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 R-RG.01.06.32.321.04.20.313 tanggal 13 April 2020.