RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
***ROTAVIRUS RV3 VACCINE* FASE III PRODUSEN BIO FARMA**

Informasi Umum

1. Vaksin Rotavirus RV3 fase III merupakan rangkaian uji klinik dalam rangka obat pengembangan baru yang dikembangkan oleh PT. Bio Farma. Uji klinik fase I telah dilaksanakan dengan hasil yang secara umum dapat diterima.
2. Uji klinik fase III yang diajukan mengikutsertakan 1400 subjek bayi usia 0 – 5 hari. Pengajuan uji klinik ini didukung dengan uji klinik fase I yang telah dilakukan sebelumnya pada 100 subjek dewasa, anak dan bayi.

Informasi Uji Klinik

1.	Judul protokol	:	***Efficacy, Safety and Immunogenicity of Rotavirus RV3 Vaccine (Bio Farma) in Neonates, Lot to Lot Consistency and Antigen Interference with Co-Administered EPI Vaccines (Phase III)*** Nomor protokol RV 0319 versi 3.1 tanggal 11 September 2020
2.	Produk Uji	:	Vaksin Rotavirus RV3 yang diberikan 3 (tiga) kali secara oral Produsen : PT. Bio Farma
3.	Produk Pembanding	:	Placebo Vaksin Oral yang mengandung Sukrosa yang diberikan 3 (tiga) kali secara oral. Produsen : PT. Bio Farma
4.	Center/Peneliti	:	Koordinator Studi: dr. Jarir At-Thobari, PhD 1. *Center for Child Health* Universitas Gadjah Mada, Yogyakarta (CCH-PRO UGM) / Dr. dr. Titis Widowati, Sp.A(K) 2. *Pediatric Research Center* Universitas Sebelas Maret (PRC-UNS) / dr. Hary Wahyu N, M.Kes., Sp.A(K)
5.	Sponsor/ ORK	:	PT. Bio Farma (Persero), Bandung / IQVIA Indonesia
6.	Persetujuan Etik	:	1. No. KE/FK/1055/EC/2020 tanggal 22 September 2020 dari *Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing* Universitas Gadjah Mada, Yogyakarta untuk *Center for Child Health* Universitas Gadjah Mada *(CCH-PRO UGM)* Yogyakarta. 2. No. 931/VII/HREC/2019 tanggal 23 Januari 2020 dari Komisi Etik Penelitian Kesehatan Rumah Sakit Umum Daerah Dr. Moewardi Surakarta untuk *center Pediatric Research Center* Universitas Sebelas Maret (PRC- UNS)
7.	Desain Uji Klinik	:	*Randomized, double-blind, placebo-controlled study*
8.	Jumlah subjek	:	1400 subjek
9.	Tujuan uji klinik	:	***Primary Objective:*** *To assess the efficacy of three doses of Rotavirus RV3 vaccine (Bio Farma) against severe acute rotavirus gastroenteritis, up to 18 months of age.* ***Secondary Objectives:*** *1. To assess the efficacy of three doses of Rotavirus RV3 vaccine (Bio Farma) compared with placebo and the outcomes reported in the Indonesian efficacy study (IIb) of the RV3-BB vaccine produced by MCRI, in regards to:* - *Rotavirus gastroenteritis of any severity* - *All-cause gastroenteritis*

2. *To assess serum immune response (sIgA) 28 days after the third dose of Rotavirus RV3 vaccine (Bio Farma) administered in a neonatal schedule.*
3. *To compare Rotavirus RV3 vaccine (Bio Farma) to the outcomes reported in the Indonesian efficacy study (IIb) of the RV3-BB vaccine produced by MCRI, in regards to:*
   - *Serum immune response (sIgA) 28 days after the third dose of Rotavirus RV3 vaccine (Bio Farma)*
   - *The incidence of stool excretion of RV3 on days 3 to 5 following each dose of Rotavirus RV3 vaccine (Bio Farma)*
   - *Cumulative serum immune response (cumulative sIgA following dose 1/ dose 2/ dose 3) of Rotavirus RV3 vaccine (Bio Farma)*
4. *To compare Rotavirus RV3 vaccine (Bio Farma) to placebo with respect to:*
   - *Serum immune response (sIgA) 28 days after the third dose of Rotavirus RV3 vaccine (Bio Farma) or placebo*
   - *The incidence of stool excretion of RV3 on days 3 to 5 following each dose of Rotavirus RV3 vaccine (Bio Farma) or placebo*
   - *Cumulative serum immune response (cumulative sIgA after dose 1/dose 2/dose 3) of Rotavirus RV3 vaccine (Bio Farma) or placebo*
5. *To evaluate lot-to-lot consistency using 3 batches of Rotavirus RV3 vaccine (Bio Farma) by assessment of serum immune response (sIgA) 28 days after the third dose of vaccine.*
6. *To describe the safety, tolerability and reactogenicity of Rotavirus RV3 Vaccine (Bio Farma) compared to placebo, between batches and co-administration with EPI vaccine, with respect to:*
   - *Solicited and unsolicited adverse events, from randomisation to 28 days following last dose*
   - *Serious adverse events, from randomisation to 28 days following last dose*
   - *Comparison number and percentage of subject with adverse event and Serious Adverse Events (SAE) compare to placebo, between batches, and co-administration with EPI vaccine*
   - *ALT/AST 28 days following dose 1 [in a subset of 200 immunogenicity participants]*
7. *To describe the serum immune response after the first dose of Rotavirus RV3 Vaccine (Bio Farma) [subset of 200 immunogenicity participants] as follows:*
   - *To describe the proportion of participants with a serum immune response (sIgA) 28 days following the first dose of Rotavirus RV3 Vaccine (Bio Farma)*
   - *To compare the serum immune response (sIgA) after 1 doses of Rotavirus RV3 vaccine (Bio Farma) or placebo*
8. *8. To describe the serum immune response after the second dose of Rotavirus RV3 vaccine (Bio Farma) [subset of 200 immunogenicity participants] as follows:*
   - *To describe the proportion of participants with a serum immune response (sIgA) 28 days following the second dose of Rotavirus RV3 Vaccine (Bio Farma)*
   - *To compare the serum immune response (sIgA) and cumulative serum immune response after 2 doses of Rotavirus RV3 vaccine (Bio Farma) or placebo*
9. *To assess immune interference between Rotavirus RV3 Vaccine (Bio Farma) co-administered with EPI vaccines compared to placebo [subset of 200 immunogenicity participants]:*

- *To assess immunogenicity of Oral Polio vaccine co-administered with Rotavirus RV3 Vaccine (Bio Farma)*
- *To assess immunogenicity of Rotavirus RV3 vaccine (Bio Farma) co-administered with Oral Polio vaccine*

10. *To describe the Geometric mean titre (GMT) of serum IgA 28 days after each dose of Rotavirus RV3 vaccine (Bio Farma).*
11. *To describe Serum neutralising antibodies in 80 participants.*

10. Kriteria Eligibilitas : ***Inclusion Criteria***

1. *Neonate 0-5 days of age at the time of first dose.*
2. *Neonate is in good health as determined by clinical judgment, including a medical history and physical exam, which confirms the absence of a current or past disease state considered significant by the investigator.*
3. *The neonate was born full term (minimum of 37 completed weeks and maximum of 42 completed weeks gestation).*
4. *Neonate birth weight 2500-4000 g inclusive.*
5. *Parent or guardian has been informed properly regarding the study and signed the informed consent form.*
6. *Parent or guardian commits to comply with the instructions of the investigator and the schedule of the trial.*

Exclusion Criteria

1. *Subject concomitantly enrolled or scheduled to be enrolled in another trial.*
2. *The subject has direct relatives with relationship with the study team.*
3. *The subject has evolving mild, moderate or severe illness, especially infectious diseases or fever (body temperature 37.5C) within the 48 hours preceding enrollment.*
4. *Subject with known or suspected history of allergy to any component of the vaccines (based on anamnesis).*
5. *Subject with a biological mother with a known or suspected human immunodeficiency virus (HIV) or Hepatitis B infection.*
6. *Subject with known or suspected major congenital malformations or genetically determined disease.*
7. *Subject with intussusception.*
8. *Subject with a known or suspected disease of uncontrolled coagulopathy or blood disorders contraindicating for phlebotomy.*
9. *Subject with a known or suspected disease of the immune system or who has received immunosuppresive therapy, including immunosuppresive courses of systemic corticosteroid.*
10. *Subject who have ever received any blood products, including immunoglobulin, or for whom receipt of any blood product is anticipated during the course of study.*
11. *Any abnormality or chronic disease which according to the investigator might interfere with the assessment of the trial objectives.*
12. *Subject immunized with non-EPI vaccines.*
13. *Gastroenteritis in the 24 hours preceding dosing (temporary exclusion criteria).*
14. *Subject planning to move from the study area before the end of study period.*

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

Episodes of severe rotavirus gastroenteritis (defined as a modified Vesikari score ≥11 and rotavirus antigen detected in stool by ELISA) from 2 weeks after three doses of investigational product to 18 months of age.

Secondary Evaluation Criteria

1. *Efficacy of Rotavirus RV3 vaccine (Bio Farma) compare to placebo and MCRI Phase IIb study, from 2 weeks after three doses of investigational product to 18 months of age, in regards to:*
   - *Severity rotavirus gastroenteritis; defined as a modified Vesikari score ≥11 and rotavirus antigen detected in stool by ELISA*
   - *Episode of gastroenteritis: three or more stools in a 24-hour period, that are looser than normal for that child*
2. *Serum immune response (sIgA): Number and percentage of subjects with ≥3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the third dose of Rotavirus (Bio Farma) vaccine.*
3. *Comparison between Rotavirus RV3 vaccine (Bio Farma) with MCRI Phase IIb, in regards to:*
   - *Serum immune response (sIgA): Number and percentage of subjects with ≥ 3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the third dose*
   - *Stool excretion: detectable RV3 excretion in stool (by PCR) any day from day 3 to day 5 following each dose*
   - *Cumulative serum immune response defined as cumulative serum anti-rotavirus IgA (sIgA) after any doses of IP (dose 1 or dose 2 or dose 3)*
4. *Comparison between Rotavirus RV3 vaccine (Bio Farma) with placebo, in regards to:*
   - *Serum immune response (sIgA): Number and percentage of subjects with ≥3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the third dose*
   - *Stool excretion: detectable RV3 excretion in stool (by PCR) any day from day 3 to day 5 following each dose*
   - *Cumulative serum immune response defined as cumulative serum anti-rotavirus IgA (sIgA) after any doses of IP (dose 1 or dose 2 or dose 3)*
5. *Evaluation of lot-to-lot consistency: Number and percentage of subjects with ≥ 3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the third dose of rotavirus vaccine (Bio Farma).*
6. *Description of the safety, tolerability and reactogenicity of Rotavirus RV3 Vaccine (Bio Farma) compared to placebo, between batches and co-administration with EPI, with respect to:*
   - *Number and percentage of subjects, number of events with solicited and unsolicited Adverse Events (AE) from randomization to 28 days following last dose*
   - *Number and percentage of subject with Serious Adverse Events (SAE), from randomization to 28 days following last dose, and number of events*
   - *Number and percentage of subject with adverse event and Serious Adverse Events (SAE), from randomization to 28 days following last dose compared to placebo, between batches, and co-administration with EPI vaccine*
   - *Any abnormality detected in routine laboratory evaluation (ALT/AST) that is assessed as probably or definitely related to the dosing*
7. *Description of the serum immune response after the first dose of Rotavirus RV3 Vaccine (Bio Farma) [subset of 200 immunogenicity participants] as follows:*
   - *Serum immune response (sIgA): Number and percentage of subjects with ≥ 3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the first dose*

- *To compare sIgA after 1 doses of Rotavirus RV3 vaccine (Bio Farma) or*

8. *Description of the serum immune response after the second dose of Rotavirus RV3 vaccine (Bio Farma) [subset of 200 immunogenicity participants] as follows:*
   - *Serum immune response (sIgA): Number and percentage of subjects with ≥ 3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the second dose*
   - *To compare the serum immune response (sIgA) and cumulative serum immune response after 2 doses of Rotavirus RV3 vaccine (Bio Farma) or placebo*
9. *Assessment of immune interference between Rotavirus RV3 Vaccine (Bio Farma) co-administered with EPI vaccines compared to placebo [in a subset of 200 immunogenicity participants]:*
   - *To assess immunogenicity of Oral Polio vaccine co-administered with Rotavirus RV3 Vaccine (Bio Farma): number and percentage of subject with reciprocal titre ≥ 1:8 against poliovirus strains 1-3, GMT and percentage subject with transition from seronegative to seropositive and percentage of subject with 4 fold increase of immune response measured 28 days after bOPV4+ IPV vaccination*
   - *To assess immunogenicity of Rotavirus RV3 vaccine (Bio Farma) co-administered with Oral Polio vaccine: number and percentage of subject with ≥ 3 times increase in serum anti-rotavirus IgA (sIgA) from baseline to 28 days after the third dose and GMT*
10. *Geometric mean titre (GMT) of serum IgA 28 days after each dose of Rotavirus vaccine (Bio Farma).*
11. *Serum immune response (serum neutralizing antibodies): Description of serum neutralising antibodies (SNA) level [number and percentage of subjects with positive SNA (≥ 100), two fold and three fold increasing antibodies] from baseline to 28 days after the third dose [in 80 participants].*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik vaksin Rotavirus fase III yang didukung oleh tim ahli melalui rapat pada tanggal 7 November 2019.

Tersedia data uji klinik:

1. Fase I pada bayi usia 0 – 5 hari (3 dosis), anak usia 2-5 tahun (1 dosis) dan dewasa usia 18 – 40 tahun (1 dosis) yang menunjukkan vaksin dapat ditoleransi dengan baik dan memberikan respon imun setelah 28 hari setelah dosis lengkap.
2. Uji klinik fase II tidak dilakukan karena menggunakan data uji klinik fase IIb yang dikembangkan oleh *Murdoch Children's Research Institute* (MCRI) yang mengikutsertakan 1649 subjek bayi usia <6 hari. Vaksin Rotavirus Bio Farma dan MCRI memiliki kesamaan/homolog >99%.

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-RG.01.06.3.32.09.20.795 tanggal 18 September 2020 untuk *center Pediatric Research Center* Universitas Sebelas Maret (PRC- UNS) dan Nomor R-RG.01.06.3.32.10.20.862 tanggal 7 Oktober 2020 untuk *Center for Child Health* Universitas Gadjah Mada *(CCH-PRO UGM)* Yogyakarta.