RINGKASAN HASIL EVALUASI
UJI KLINIK VAKSINASI / REVAKSINASI BCG (POP BCG *TRIAL*)
PRODUKSI SERUM INSTITUTE OF INDIA PVT, LTD, DIDAFTARKAN OLEH PT. BIOFARMA

Informasi Umum

1. Uji klinik merupakan kerjasama antara tim peneliti *Research Center for Care and Control Infectious Disease* Universitas Padjadjaran (UNPAD) dengan University of Otago, New Zealand sebagai Sponsor. Uji klinik yang diajukan adalah studi pendahuluan *(Proof of Principle/PoP)* vaksin BCG yang akan diberikan pada subjek mahasiswa kedokteran dan keperawatan yang berisiko tinggi terinfeksi tuberkulosis saat memasuki masa pendidikan di rumah sakit.
2. Vaksin yang digunakan dalam uji klinik yaitu vaksin Bacillus Calmette Guerin (BCG)-*Freeze-dried (live attenuated)* telah mendapatkan izin edar di Indonesia dengan indikasi untuk memberikan perlindungan terhadap tuberkulosis (TB).
3. Uji klinik diajukan oleh pendaftar pada tanggal 2 Februari 2023, evaluasi dilakukan terhadap aspek scientific validity, kepatuhan regulatori dan etik, Badan POM telah menerbitkan surat permintaan tambahan data pada tanggal 17 Februari 2023 dan persetujuan pada tanggal 21 Maret 2023

Informasi Uji Klinik

1.	Judul Protokol	:	***BCG Vaccination/Revaccination for Prevention of Mycobacterium Tuberculosis Infection in Healthcare Students Entering Clinical Training: A Randomised Placebo-Controlled Proof of Principle Trial (PoP BCG Trial)*** ***Protocol No. 1, version 3.0, 24 October 2022***
2.	Produk Uji	:	*BCG Freeze-dried vaccine (Live attenuated BCG Vaccine (Bacillus Calmette Guerin strain)),* setiap 0.1 ml vaksin mengandung 2 x 10^5 sampai 8 x 10^5 C.F.U.. Vaksin diberikan 1 kali dengan dosis 0,1 mL secara injeksi intradermal.. Produksi: Serum Institute of India Pvt, Ltd yang diimpor dan didaftarkan oleh PT. Bio Farma (Persero).
3.	Produk Pembanding	:	Sodium Chloride 0,9% diberikan 1 kali secara injeksi intradermal. Produksi: PT. Otsuka Indonesia
4.	Center/ Peneliti	:	*Research Center for Care and Control Infectious Disease Universitas Padjadjaran*/ dr. Lika Apriani, MSc, Ph.D
5.	Sponsor/ ORK	:	University of Otago, New Zealand
6.	Persetujuan Etik	:	Nomor: 143/UN6.KEP/EC/2020 tanggal 30 Januari 2020 dan Perpanjangan Persetujuan Etik Nomor: 101/UN6.KEP/EC/2022 tanggal 24 November 2022 dari Komisi Etik Penelitian Universitas Padjadjaran Bandung
7.	Desain Uji Klinik	:	*A proof of principle randomized control trial of BCG vaccination/revaccination versus placebo in medical and nursing students*

8.	Jumlah Subjek	:	*150 subjects*
9.	Tujuan Uji Klinik	:	***Primary objectives:*** *To assess acceptability of the BCG vaccination/revaccination, adverse events, and completeness of follow up.* ***Secondary objectives:*** 1. *To assess if there is an indication of a trend towards protection by BCG against new M. tuberculosis infection (which is defined by IGRA test conversion).* 2. *To assess whether BCG vaccination/revaccination induces innate immune cell and cytokine changes consistent with trained immunity.* 3. *To define an epigenetic signature associated with BCG vaccination/revaccination* *To establish a bio-repository for further testing*
10.	Kriteria Eligibilitas	:	***Inclusion criteria*** 1. *Medical or nursing students who start their clinical training at Hasan Sadikin Hospital Ability to take oral medication.* 2. *Age > 18 years on study day 0* 3. *Tested IGRA negative at screening* 4. *Tested HIV negative at screening* 5. *Completed the written informed consent* ***Exclusion criteria*** 1. *Retraining nursing students (retraining to transform their nursing qualification into a degree)* 2. *A positive prior tuberculin skin test (TST) and/or IGRA* 3. *A history of treatment for TB disease or latent TB infection* 4. *A history or evidence of TB disease* 5. *For female students: currently pregnant or lactating/nursing; or positive urine pregnancy test during screening* 6. *History of autoimmune disease or immunosuppression or used immunosuppressive Medication*
11.	*L*uaran Uji Klinik/ *Endpoint*	:	***Primary endpoints:*** 1. *Acceptability of the intervention: the proportion of participants who consent and accepted to be given the intervention (BCG vaccine or placebo) over the total number of eligible participants in the study. This will be assessed using a questionnaire after vaccination.*

2. *Adverse events: the proportion of participants who experience any adverse event.*
3. *Completeness of the study: the proportion of participants who complete follow-up, including all tests.*

Secondary endpoints:

1. *IGRA test conversion: the key endpoint will be cumulative IGRA test conversion, defined as IGRA test conversion at any time point during the study (at 3, 6, 9 or 12 months). IGRA test conversion will be defined as a change from a negative to a positive test plus a minimum 30% increase in TB1 minus Nil or TB2 minus Nil over the baseline value.*

   Secondarily, we will assess persistent IGRA conversion defined as at least two consecutive IGRA tests over follow-up. Exploratory analyses will consider various combinations of IGRA test results across the four follow-up points. A sensitivity analysis will re-analyse the data based on a definition of IGRA test conversion that simply requires a change from a negative to a positive test.
2. *Induction of trained immunity: the primary readout for immune cell function will be cytokine production of Peripheral blood mononuclear cell (PBMCs) in response to BCG, M. tuberculosis and a range of unrelated microbial stimuli; the increase of ex-vivo monocyte-derived and lymphocyte-derived pro-inflammatory cytokine production capacity following BCG vaccination/revaccination will be used as an established marker of trained immunity. The secondary read outs will be epigenetic changes associated with BCG vaccination/revaccination and immunophenotype of innate and adaptive immune cells.*
3. *Changes in whole blood DNA methylation associated with BCG vaccination/revaccination: Targeted DNA methylation will be measured at baseline and one or two follow-up timepoints (3 months, 6 months, 9 months, or 12 months). This will be an exploratory analysis.*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik vaksinasi / revaksinasi BCG *(PoP BCG Trial)*, yang didukung oleh tim ahli melalui rapat pada tanggal 10 Februari 2023 dengan hasil sebagai berikut:

1. Uji klinik akan mengevaluasi akseptabilitas vaksinasi/revaksinasi BCG, *adverse events,* dan penyelesaian *follow up* yang dilakukan menggunakan vaksin BCG yang telah mendapatkan izin edar di Indonesia.
2. Uji klinik dilakukan dengan vaksin yang telah mendapatkan izin edar di Indonesia dan secara umum vaksin dapat ditoleransi dengan baik
3. Desain uji klinik sebagai *Proof of Principle (PoP)* 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 surat Nomor B-RG.01.06.32.323.06.21.311 tanggal 21 Maret 2023.