**RINGKASAN HASIL EVALUASI**
**PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK**
**VAKSIN *Mycobacterium tuberculosis* (Mtb) M72/AS01$_{E-4}$**
**BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE**

**Informasi Umum**

1. Vaksin M72/AS01E-4 merupakan vaksin tuberculosis dengan *platform recombinant fusion protein* yang dikembangkan oleh GlaxoSmithKline Biologicals, SA (GSK). Vaksin ini mengandung M72 antigen dan adjuvant AS01E-4. Pada tahun 2020, Bill & Melinda Gates Medical Research Institute (Gates MRI) melisensikan vaksin ini untuk melanjutkan pengembangannya.
2. PT. IQVIA selaku Organisasi Riset Kontrak mengajukan persetujuan pelaksanaan uji klinik fase 3 *randomized, double-blind, placebo-controlled* untuk mengevaluasi efikasi, imunogenisitas dan keamanan vaksin M72/AS01E-4 pada subjek remaja usia 15-17 tahun dan dewasa usia 18-44 tahun. Uji klinik akan dilaksanakan *multicenter* di Vietnam, Afrika Selatan, Malawi, Kenya, Mozambik, Zambia, dan Indonesia. Uji klinik akan mengikutsertakan 2.500 subjek Indonesia dari total 20.000 subjek.

**Informasi Uji Klinik**

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| 1. | Judul Protokol | : | ***A Phase 3, randomized, double-blind, placebo-controlled, multicenter, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of the investigational M72/AS01E-4 Mycobacterium tuberculosis (Mtb) vaccine when administered intramuscularly on a 0,1-month schedule to adolescents and adults***<br>No. protokol Gates MRI-TBV02-301 Versi 2, Tanggal 8 Januari 2024 |
| 2. | Produk Uji | : | M72 antigen (10 mcg) direkonstitusi dengan AS01$_{E-4}$ adjuvant (25 mcg MPL dan 25 mcg QS-21) dalam 0,5 mL diberikan 2 kali pada hari ke-1 dan hari ke-29 secara intramuskular. |
| 3. | Produk Pembanding | : | Plasebo berupa NaCl 0.9% dalam 0,5 mL diberikan 2 kali pada hari ke-1 dan hari ke-29 secara intramuskular |
| 4. | Peneliti Koordinator | : | Prof. Dr. dr. Erlina Burhan, Sp.P(K), MSc |
| 5. | *Center* / Peneliti | : | RSUP Persahabatan / Dr. dr. Fathiyah Isbaniah, M.Pd.Ked., Sp.P(K) |
| 6. | Sponsor / ORK | : | Bill & Melinda Gates Medical Research Institute / PT IQVIA RDS Indonesia |
| 7. | Persetujuan Etik | : | No. 141.A.1/KEPK-RSUPP/04/2024 tanggal 4 April 2024 dari Komisi Etik Penelitian Kesehatan Rumah Sakit Umum Pusat Persahabatan |
| 8. | Desain Uji Klinik | : | *Phase 3, randomized, double-blind, placebo-controlled, multicenter, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of the investigational M72/AS01E-4 Mtb vaccine when administered intramuscularly on a 0,1-month schedule to adolescents and adults (15 to 44 years of age).*<br>*The trial will include 2 groups (M72/AS01E-4 group and placebo group). Participants will receive 2 doses of either M72/AS01E-4 or placebo based on randomization, administered intramuscularly (IM) in the deltoid muscle, preferably in the nondominant arm, given approximately one month apart.* |



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9. Jumlah Subjek : ***Number of participants:*** *Approximately 20,000*
*Indonesia will follow the IGRA-Positive and IGRA-Negative Cohort, in total 2.500 subjects.*

10. Tujuan Uji Klinik : ***Primary Objective***
*To evaluate the vaccine efficacy (VE) of M72/AS01E-4 in the prevention of laboratory-confirmed pulmonary TB among IGRA-positive participants without HIV infection (IGRA-Positive Cohort) in the per-protocol (PP) analysis set.*

***Secondary Objectives***
***Secondary Efficacy Objectives***
1. *To evaluate the VE of M72/AS01E-4 in the prevention of Mtb infection among the IGRA-Negative Cohort in the PP analysis set.*
2. *To evaluate the VE of M72/AS01E-4 in the prevention of laboratory- confirmed pulmonary TB among the IGRA-Negative Cohort in the PP analysis set.*
3. *To evaluate the VE of M72/AS01E-4 in the prevention of laboratory- confirmed pulmonary TB among the HIV Cohort in the PP analysis set.*
4. *To evaluate the VE of M72/AS01E-4 in the prevention of less stringently defined laboratory-confirmed pulmonary TB among the IGRA- Positive Cohort in the PP analysis set.*

***Secondary Safety Objectives***
*To evaluate the safety and reactogenicity following administration of M72/AS01E-4 vaccine or placebo.*
***Secondary Immunogenicity Objectives***
*To assess the humoral immunogenicity of M72/AS01E-4 vaccination.*

***Exploratory Objectives***
1. *To further explore the VE of M72/AS01E-4 in the prevention of laboratory-confirmed pulmonary TB as defined for the primary endpoint, among the IGRA-Positive Cohort in the mITT analysis set.*
2. *To explore the effect of potential covariates on the VE of M72/AS01E-4 in the prevention of laboratory-confirmed pulmonary TB as defined for the primary endpoint, among the IGRA-Positive Cohort in the PP analysis set.*
3. *To explore the VE of M72/AS01E-4 in the prevention of laboratory-confirmed pulmonary TB, where sputum was collected up to 28 days after treatment initiation among IGRA-positive, IGRA-negative, and HIV Cohorts, respectively, in the mITT analysis set.*
4. *To explore the VE of M72/AS01E-4 in the prevention of clinical TB (including extrapulmonary TB) defined as a participant for whom a clinician has diagnosed TB, and has initiated TB treatment, in the absence of laboratory-confirmed pulmonary TB, among IGRA-positive, IGRA-negative, and HIV Cohorts, respectively, in the mITT analysis set.*
5. *To explore the VE of M72/AS01E-4 in the prevention of subclinical TB, defined as a participant with a positive result from Xpert Ultra or similar assay (excluding "trace positive") from a single sputum sample at the EoT visit, in the absence of signs or symptoms of pulmonary TB, among IGRA-positive, IGRA-negative, and HIV Cohorts, respectively, in the mITT analysis set.*

6. *To assess the cellular immunogenicity of M72/AS01E-4 vaccination using M72-specific CD4+ and CD8+ T-cell responses measured by co-expression of 2 or more cytokines using intracellular cytokine staining (ICS).*
7. *To further explore the cellular immunogenicity of M72/AS01E-4 vaccination using M72-specific CD4+ and CD8+ T-cell responses measured by co-expression of multiple functional markers by ICS.*
8. *To confirm candidate CoP and CoR if identified in the M72 Immune Correlates Program and to explore new candidate CoP and CoR.*
9. *To explore characteristics of Mtb isolates, including drug susceptibility profiles and genetic diversity.*

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

***Age***

1. *Participants must be 15 to 44 years of age (inclusive), at the time of signing the consent or assent.*

***Type of Participant and Disease Characteristics***

2. *Capable of giving informed consent or informed assent (as appropriate). For participants below the age of consent, the participant's parent, or legally authorized representative (LAR) will be required to sign a statement of informed consent, in addition to the minor's signed statement of assent.*
3. *In the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of diary cards as applicable, and return for follow-up visits).*
4. *Agree to actively stay in contact with the trial site for the duration of the trial for the participants' own safety.*
5. *Agree to provide updated contact information as necessary, and have no current plans to relocate from the trial area for the duration of the trial.*
6. *Healthy, or with preexisting stable disease, as established by medical history and physical examination and as determined by the investigator. Preexisting stable disease is defined as not requiring significant change in therapy or hospitalization for worsening disease during the 28 days before enrollment.*
7. *Negative sputum Xpert Ultra or similar assay result at screening*
8. *Both males and females are included. Females are included with restrictions. Females must either be of non-childbearing potential, defined as pre-menarche, have a history of either current tubal ligation, hysterectomy, or ovariectomy, or post-menopause,* ***or****, if she is of childbearing potential, she has practiced abstinence from penile-vaginal intercourse or adequate contraception for 28 days prior to vaccination, has a negative pregnancy test on the day of screening and the day of first vaccination, and agrees to continue abstinence or adequate contraception until 2 months after the second dose of trial intervention.*
9. *HIV-negative test result at screening (IGRA-Positive Cohort and IGRA-Negative Cohort only)*
10. *HIV Cohort only: Participants with documented* HIV infection who fulfill all of the following criteria:*

- *have reactive anti-HIV antibody at screening*
- *have been on ART for at least 3 consecutive months at screening and agree to remain on ART throughout the trial*
- *have documented HIV RNA <200 copies/mL at screening*
- *have CD4+ cell count ≥200 cells/µL at screening*
- *have had TPT in the past and are not receiving TPT at the time of screening, according to the judgment of the investigators*
- *have an IGRA-positive or negative result at screening.*

**Note that 'documented' refers to documentation from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*

***Exclusion criteria***

***Medical Conditions***

1. *Current TB, or history of TB or treatment for TB disease*
2. *Clinical suspicion of pulmonary TB at screening, defined as a participant presenting with one or more of the following signs or symptoms: unexplained cough, unexplained fever, night sweats, unintentional weight loss, hemoptysis, pleuritic chest pain*
3. *Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol, or that will interfere with the assessments or the safety of the participant*
4. *Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., invasive, or malignant cancers), other than HIV infection in the HIV Cohort*
5. *Known bleeding disorder that is considered a contraindication to intramuscular injection or phlebotomy.*

***Prior/Concomitant Therapy***

6. *Any cytotoxic drugs or administration of medications known to have a major impact on the immune system, as determined by the investigator, within 90 days prior to Day 1. These include immune globulin, blood, or blood products, potent immunosuppressants and immunomodulators, and systemic corticosteroids (exceeding 20 mg/day prednisone equivalent). Inhaled, topical, and intra-articular corticosteroids are allowed.*

***Prior/Concurrent Clinical Trial Experience***

7. *Planned receipt of blood, or blood products during the trial period*
8. *Receipt or planned receipt of any vaccine in the period starting 28 days before, and ending 28 days after, each dose of the trial vaccine*
9. *History of previous administration of an experimental Mtb vaccine including M72/AS01E in a previous trial*
10. *History of allergy or hypersensitivity to the trial intervention, excipients, or related substances*

***Diagnostic assessments***

11. *An indeterminate IGRA test result at screening*
12. *Female participants with any one of the following conditions: currently pregnant or lactating; having positive serum*

*pregnancy test during the screening window, positive urine pregnancy test on Day 1, planning a pregnancy within 2 months after completion of the vaccination series*

13. *Only in the HIV Cohort: Safety laboratory values at screening that are of concern, based on investigator's judgment. Note that preexisting stable chronic disease will not necessarily lead to exclusion, especially if laboratory values are graded as mild.*

***Other Exclusions***

14. *Participation in an interventional clinical trial in which the participant has been or will be exposed to an investigational product (pharmaceutical product or device), within 28 days prior to signing consent or assent, or during the trial period.*
15. *Individuals who are acting as personnel for this trial, or who have immediate family members (brother, sister, child, parent, or the spouse/partner) who are acting as personnel for this trial.*
16. *Child in Care, defined as a child who is under the care (control or protection) of an agency, organization, institution or entity by the courts, the government body, acting in accordance with powers conferred in them by law or regulations. The definition of a child in care can include a child who is cared for by foster parents or living in a care home or institution, provided that the arrangements fall within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed LAR.*
17. *Participants who had a Tuberculin Skin Test (TST) within 6 months prior to Day 1.*

12. *Endpoint* Uji Klinik : ***Primary Endpoints:***

*Laboratory-confirmed pulmonary TB over a period starting 1 month post Dose 2 and lasting up to End of Trial (EoT) where a laboratory-confirmed pulmonary TB case is defined as a participant with:*

- *Suspected pulmonary TB as defined as a participant presenting with one or more of the following signs or symptoms:*
    - o *unexplained cough, unintentional weight loss, hemoptysis, unexplained fever, night sweats, pleuritic chest pain*

*who has*

*At least 2 positive Mtb test results (positive Mtb culture and/or positive test result from Xpert Ultra or similar assay, excluding "trace positive"), from the same or from different sputum samples collected during the 3 suspected TB visits, preferably within a 7-day time frame, before initiation of TB treatment .*

***Secondary Endpoints***

***Secondary Efficacy Endpoints:***

1. *Sustained QuantiFERON®-TB Gold Plus assay (or similar) conversion (i.e., initial conversion and IGRA-positive test result at next attended scheduled visit) over a period starting 1 month post dose 2 and lasting up to EoT*
2. *Laboratory-confirmed pulmonary TB over a period starting 1 month post Dose 2 and lasting up to EoT, where a laboratory-confirmed pulmonary TB case follows the same definition as the primary endpoint*

3. *Laboratory-confirmed pulmonary TB over a period starting 1 month post Dose 2 and lasting up to EoT, where a laboratory-confirmed pulmonary TB case follows the same definition as the primary endpoint*
4. *Laboratory-confirmed pulmonary TB over a period starting 1 month post Dose 2 and lasting up to EoT, where a laboratory-confirmed pulmonary TB case is defined less stringently as a participant with:*
    - Suspected pulmonary TB as defined for the primary efficacy endpoint, and
    - At least 1 positive *Mtb* culture or at least 1 positive result from Xpert Ultra or similar assay (excluding "trace positive"), from the same or from different sputum samples collected during the 3 suspected TB visits, preferably within a 7-day time frame, before initiation of TB treatment

***Secondary Safety Endpoint***

1. *Occurrence of solicited AEs during the 7 days following each vaccination (starting on day of vaccination and 6 subsequent days after each vaccine dose), Safety analysis set*
2. *Occurrence of unsolicited AEs during the 28 days following each vaccination (starting on day of vaccination and 27 subsequent days after each vaccine dose), Safety analysis set*
3. *Occurrence of all serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs) from Day 1 through Month 13, Safety analysis set*
4. *Occurrence of SAEs related to trial participation through trial end, Safety analysis set*

***Secondary Immunogenicity Endpoint***

*Geometric mean concentration (GMC) and seropositivity of M72-specific antibodies at Day 1, Month 1, Month 2, Month 7, Month 13, Month 37, and Month 49 among each of the IGRA-Positive Cohort, IGRA-Negative Cohort, and HIV Cohorts in the per-protocol for immunogenicity (PPI) analyses set.*

**Ringkasan Hasil Evaluasi**

Badan POM telah melakukan evaluasi protokol uji klinik vaksin Mycobacterium tuberculosis (Mtb) M72/AS01E-4, yang didukung oleh tim ahli melalui rapat pada tanggal 5 Oktober 2023 dengan hasil sebagai berikut:

1. Hasil uji non-klinik toksikologi, farmakologi, *post-exposure,* dan studi eksploratori pada hewan model mencit, tikus Wistar, kelinci, dan *cynomolgus macaques* dengan dosis yang setara yang akan digunakan pada manusia, menunjukkan produk yang akan digunakan dalam uji klinik memiliki (i) profil keamanan yang masih dapat ditoleransi dengan baik, (ii) menginduksi respon imun seluler maupun humoral, dan (iii) tidak menyebabkan percepatan *disease progression* atau peningkatan *relapse rate*.
2. Uji klinik yang telah dilaksanakan sebelumnya yang menjadi pendukung dilaksanakannya uji klinik fase 3 ini antara lain uji klinik fase 2 (TB-009, TB-017, Gates MRI TBV02-202) dan fase 2b GSK TB-018 menunjukkan (i) profil keamanan yang memadai, (ii) meningkatkan imunogenisitas subjek (GMC Anti-M72 antibody), dan (iii) memiliki *vaccine efficacy* yang potensial.
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 RG.01.06.32.321.4.2024.3959 tanggal 19 April 2024.



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