RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
RECOMBINANT NONAVALENT *HUMAN PAPILLOMAVIRUS VACCINE* PRODUKSI
BEIJING HEALTH GUARD BIOTECHNOLOGY, INC (BHGB) CHINA

Informasi Umum

1. Vaksin *Recombinant Nonavalent Human Papillomavirus* ***(****HPV)* dikembangkan oleh Beijing Health Guard Biotechnology, Inc China. Uji klinik di Indonesia bekerja sama dengan sponsor PT. Etana Biotechnologies Indonesia. Tipe HPV vaksin uji adalah HPV 6/11/16/18/31/33/45/52/58 sama dengan vaksin Gardasil®9 yang merupakan vaksin pembanding dalam uji klinik yang diajukan.
2. Telah tersedia uji non klinik untuk uji toksisitas (akut dan dosis berulang) dan uji imunogenisitas pada tikus dan macaca serta uji klinik fase I dan fase II yang telah dilakukan di China.

Informasi Uji Klinik

1. Judul protokol	:	***A Randomized, Observer Blinded, Active Controlled Phase 3 Study to Evaluate the Immunogenicity and Safety of Candidate Recombinant Nonavalent (types 6/11/16/18/31/33/45/52/58) Human Papillomavirus (HPV) Vaccine (Escherichia coli) Administered Intramuscularly According to Different Vaccination Schedules in Healthy Female Participants Aged 9 to 45 Years*** *Protocol number: KLWS-V502-05* versi 1.1 tanggal 3 Oktober 2022
2. Produk Uji	:	Nama: Recombinant human papillomavirus 9-valent (Type 6/11/16/18/31/33/45/52/58) Vaccine diberikan 3 kali (bulan ke 0, 2 dan 6) secara intramuskular. Produsen : Beijing Health Guard Biotechnology Inc.
3. Produk pembanding	:	Nama: Vaksin Gardasil 9 (human papillomavirus 9-valent (Type 6/11/16/18/31/33/45/52/58) diberikan 3 kali (bulan ke 0, 2 dan 6) secara intramuskular. Produsen: Merck
4. Center/	:	1. Rumah Sakit M. Djamil Padang / dr. Asrawati, M.Biomed, Sp. A(K). 2. Rumah Sakit Universitas Muhammadiyah Malang / Prof. DR. dr. Djoni Djunaedi, Sp.PD-KPTI, FINASIM 3. Rumah Sakit Universitas Udayana / Dr. dr. I Gusti Ayu Trisna Windiani, SpA (K)
5. Sponsor/ ORK	:	PT. Etana Biotechnologies Indonesia dan *Beijing Health Guard Biotechnology Inc* (sponsor)/ PT. Equilab International (ORK Indonesia)
6. Persetujuan Etik	:	1. Persetujuan Etik No. UM.01.05/5.7/61/2022 tanggal 21 Desember 2022 dari Komite Etik Penelitian dan Kesehatan dari RSUP Dr. M.. Djamil Padang 2. Persetujuan Etik No. E.5.a/276/KEPK-UMM/XII/2022 tanggal 29 Desember 2022 dari Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Muhammadiyah Malang 3. Persetujuan Etik Rumah Sakit Universitas Udayana belum tersedia karena masih dalam proses evaluasi tim Komite Etik.

7. Desain Uji Klinik : *Randomized, observer blinded, active controlled, multicenter clinical study*
8. Jumlah subjek : 2.880 subjek wanita sehat
9. Tujuan uji klinik : ***Primary Objectives**:*

1. *To evaluate that the immune response induced by the nonavalent HPV study vaccine administered with 2-dose schedule is non-inferior to those induced by GARDASIL® 9 administered with 2-dose schedule in female participants aged 9-14 years old.*
2. *To evaluate that the immune response induced by the nonavalent HPV study vaccine administered with 3-dose schedule is non-inferior to those induced by GARDASIL® 9 administered with 3-dose schedule in female participants aged 15-45 years old.*

***Secondary Objectives**:*

1. *To evaluate the immune response (IgG antibodies) induced by the nonavalent HPV study vaccine administered with 2-dose schedule in female participants aged 9-14 years old;*
2. *To evaluate the immune response (IgG antibodies) induced by the nonavalent HPV study vaccine administered with 3-dose schedule in female participants aged 15-45 years old;*
3. *To evaluate the persistence of immune response to the nonavalent HPV study vaccine;*
4. *To evaluate the safety of the nonavalent HPV study vaccine*

Exploratory objectives:

To evaluate that the immune response induced by 1st dose of nonavalent HPV study vaccine in female participants aged 9-14 years old.

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

Participants must meet all the following inclusion criteria:

1. **Healthy female participants, aged between 9 years and 45 years as of the 1st dose of vaccination (9 years ≤ age < 46 years).*
2. *Prior to enrolment, written informed consent obtained from the participants or Parent(s)/legally acceptable representative (s) (LARs); If appropriate, participants ≤17 years old are also required to sign an Informed Assent Form (IAF) per local law.*
3. **Participants must be either of non-childbearing potential, or if of childbearing potential, they must be abstinent or have practiced adequate contraception for 14 days prior to 1st vaccination, and agree to continue such precautions for 1 month after full vaccination. [Effective contraception includes oral contraceptives, injectable or implantable contraception, extended-release topical contraceptives, hormonal patches, intrauterine devices (IUDs), sterilization, abstinence, condoms (for males), diaphragms, cervical caps, etc.]; WOCBP participants have a negative urine pregnancy test before the 1st dose.*
4. *Participants and/or participants' parent(s)/ legally acceptable representative (s) (LARs) are able to comply with study protocol, including all scheduled visits, vaccinations, laboratory tests, and other study procedures.*

Note: For items with an asterisk (*), If the subject does not meet the criteria, the visit may be rescheduled when the criteria are met.

Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study.

1. ** Participant has fever (axillary temperature ≥ 37.3℃) within 24 hours prior to the 1st dose of vaccination;*
2. *Participant has vaccinated previously or plans to vaccinate with other HPV vaccines during the study period;*
3. *Participant is participating or plans to participant in other clinical studies during the period of this study;*
4. *Participant has a history of a positive test for HPV, or a history of an abnormal Pap test result showing atypical squamous cells - undetermined significance (ASC-US), atypical squamous cells - cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical glandular cells. Participant has a history of an abnormal cervical biopsy result showing cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ or cervical cancer;*
5. *Participant has a history of HPV-related genital diseases (e.g., genital warts, VIN, VaIN, vulvar cancer, vaginal cancer or anal cancer), a history of venereal disease (e.g., syphilis, gonorrhea, genital chlamydial infection, genital herpes, chancroid, lymphogranuloma venereum, inguinal granuloma, etc.);*
6. *Participant has a history of allergy to any component of the study vaccine or severe allergic reaction to vaccine (including but not limited to anaphylaxis, allergic laryngeal edema, anaphylactic purpura, thrombocytopenic purpura, or localized allergic necrosis (Arthus reaction), severe urticaria, dyspnea, angioneurotic edema, etc.);*
7. *Immunocompromised participant or participant that has been diagnosed with congenital or acquired immunodeficiency, human immunodeficiency virus (HIV) infection, lymphoma, leukemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), inflammatory bowel disease, or other autoimmune condition;*
8. *Participant who has/had epilepsy, excluding a history of febrile seizures under 2 years of age, or alcoholic epilepsy within 3 years prior to alcohol withdrawal;*
9. *Participant who has severe liver and kidney disease, severe cardiovascular disease, diabetes, malignant tumors, severe infectious diseases (e.g., tuberculosis, chronic hepatitis B/C, syphilis, etc.), is unsuitable to participate in this study based on the investigator's judgment;*
10. *Participant who has thrombocytopenia or any coagulopathy that is not suitable for intramuscular injection;*
11. *Asplenia or functional asplenia, complete or partial splenectomy from any cause;*
12. *Participant who is receiving or has received prolonged use (>14 days) of immunosuppressive or other immunomodulatory drugs (e.g., corticosteroids, ≥20 mg/d prednisone or equivalent; however, topical medications such as ointments, eye drops, inhalants or nasal sprays are permitted) within 6 months prior to the 1st dose of vaccination, or plans to receive them during the period from 1st dose of vaccination to 30 days after full vaccination;*
13. *Participant has received immunoglobulin or other blood products within 3 months prior to the 1st dose of vaccination*

or plans to receive them during the period from the 1st dose of vaccination to 30 days after full vaccination;

14. **Participant who has acute illness or in acute exacerbation of chronic diseases or use antipyretic, analgesic and anti-allergic drugs (e.g., paracetamol, ibuprofen, aspirin, loratadine, cetirizine, etc.) within 3 days prior to vaccination;*
15. **Participant who has vaccinated with inactivated/recombinant/nucleic acid vaccines (non attenuated vaccines) within 14 days before enrollment or attenuated vaccines within 28 days before enrollment, or plans to administrate vaccine(s) from the 1st dose of vaccination to 30 days after the full vaccination of investigational vaccine.*
16. **Participant who donated blood or lost blood ≥ 450 mL within one week before enrollment, or plans to donate blood during the period from the 1st dose of vaccination to 30 days after full vaccination of investigational vaccine;*
17. *Participant who cannot comply with the requirements of the study due to psychological conditions, and has a history of mental diseases or currently suffer from mental diseases;*
18. *Participant, who is unsuitable for participation in this study based on the investigator's judgment.*

Note: For items with an asterisk (*), if the participant meets these exclusion criteria, the visit may be rescheduled for a time when these criteria are not met. In addition to the examination items set forth in the protocol, other medical history, surgical history and medication history may be obtained in the form of inquiry.

Criteria for delay of subsequent dose of vaccination:

If the subject has a positive urine pregnancy test result prior to the vaccination, the vaccination should be delayed until 6 weeks after termination of pregnancy and the urine pregnancy test turns negative.

The participate may be vaccinated at a later date, within the time window specified in the protocol, if assessed by the investigator in the following circumstances:

1. *Participant has fever (axillary temperature ≥ 37.3℃) within 24 hours prior to the vaccination;*
2. *Systemic use of immunomodulators (prolonged and heavy use), immunoglobulins, or blood related products during vaccination is at intervals of less than 3 months with subsequent vaccine dose;*
3. *Participant experiences acute diseases or acute exacerbation of chronic diseases or uses antipyretic, analgesic and anti-allergic drugs (such as paracetamol, ibuprofen, aspirin, loratadine, cetirizine, etc.) 3 days before vaccination;*
4. *Participant who has vaccinated with inactivated/recombinant/nucleic acid vaccines (non attenuated vaccines) within 14 days prior to vaccination or vaccinated with attenuated vaccines within 28 days prior to vaccination;*
5. *Participant who donated blood or lost blood ≥ 450 mL within one week before vaccination;*
6. *Other condition, which is necessary to delay vaccination based on the assessment by the investigator*

The 2nd/3rd dose exclusion criteria:

1. *Serious allergic reactions or serious adverse events judged to be related to the administration of the investigational vaccine.*
2. *Participant is pregnant and decides to give birth.*
3. *Participant who has had COVID-19 since last visit is unsuitable to continue in the study based on the investigator's judgment.*
4. *The investigator considers inappropriate for the participants to continue participation in the study.*

11. Luaran Uji Klinik/ Endpoint :

Primary endpoints:

Geometric mean titer (GMT) and Seroconversion Rate (SCR) for anti-HPV type 6/11/16/18/31/33/45/52/58 neutralizing antibodies (pseudo-virus neutralizing assay) 30 days after full vaccination in participants who are seronegative to the relevant HPV type prior to 1st vaccination.

Secondary endpoints:

1. *GMT and SCR of anti-HPV type 6/11/16/18/31/33/45/52/58 IgG antibodies as assessed by enzyme-linked immunosorbent assay (ELISA) 30 days after full vaccination in participants who are seronegative to the relevant HPV type prior to 1st vaccination;*
2. *GMT and SCR of anti-HPV type 6/11/16/18/31/33/45/52/58 neutralizing antibodies and IgG antibodies 6 months, 12 months and 18 months after full vaccination in participants.*
3. *Incidence, severity and duration of each solicited (local and systemic) AE within 7 days after each dose of vaccination;*
4. *Incidence, severity and duration of each unsolicited AE within 30 days after each dose of vaccination;*
5. *Incidence, severity and causality of SAE and incidence of pregnancy events from 1st dose to 18 months after full vaccination.*

Exploratory endpoints:

GMT and SCR of anti-HPV type 6/11/16/18/31/33/45/52/58 neutralizing antibodies and IgG antibodies 30 days after 1st dose in female participants aged 9-14 years old.

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi terhadap protokol uji klinik *Recombinant Nonavalent Human Papillomavirus (HPV) Vaccine* yang didukung oleh tim ahli melalui rapat pada tanggal 14 November dan 20 Desember 2022.

1. Uji non klinik berupa uji toksisitas (akut dan dosis berulang) menunjukkan vaksin dapat ditoleransi dengan baik serta uji imunogenisitas pada tikus dan macaca menunjukkan adanya peningkatan imunitas hewan setelah 3 kali pemberian vaksin.
2. Uji klinik fase I dan II di China menunjukkan vaksin dapat ditoleransi dengan baik namun laporan uji klinik fase II pada 780 subjek menunjukkan data imunogenisitas HPV tipe 16 inferior dibandingkan vaksin pembanding pada pengamatan 7 bulan setelah penyuntikan.
3. Mengingat tipe HPV 16 merupakan tipe HPV yang paling banyak menginfeksi masyarakat Indonesia maka vaksin uji dinilai tidak dapat memberikan perlindungan terhadap tipe HPV 16 apabila diberikan pada subjek Indonesia. Selain itu, tidak tersedia data imunogenisitas dengan pengamatan lebih dari 7 bulan. Mempertimbangkan hal tersebut, maka pengajuan uji klinik *Recombinant Nonavalent Human Papillomavirus (HPV) Vaccine* Fase III di Indonesia tidak dapat disetujui.

4.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas ditolak melalui surat tanggal 3 Mei 2023.