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) type* 6/11/16/18/31/33/45/52/58 dikembangkan oleh Beijing Health Guard Biotechnology, Inc (BHGB) China. Uji klinik vaksin HPV ini sebelumnya pernah diajukan namun belum dapat disetujui, saat ini uji klinik diajukan oleh PT. Equilab International yang merupakan Organisasi Riset Kontrak yang ditunjuk oleh sponsor BHGB.
2. Pengajuan uji klinik ini didukung dengan uji non klinik (uji toksisitas dan uji imunogenisitas), uji klinik fase I dan fase III serta data imunogenisitas pada 30 hari setelah vaksinasi uji klinik fase III di China pada subjek wanita usia 20-26 tahun 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 in Healthy Female Participants Aged 18 to 45 Years*** *Protocol version 2.0 date 10 February 2023*
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/Peneliti	:	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	:	*Beijing Health Guard Biotechnology Inc* (sponsor)/ PT. Equilab International (CRO Indonesia)
6.	Persetujuan Etik	:	1. No. UM.01.05/5.7/14/2023 tanggal 24 Agustus 2023 dari Komite Etik Penelitian dan Kesehatan Rumah Sakit Umum Pusat Dr. M. Djamil Padang. 2. No. E.5.a/252/KEPK-UMM/VIII/2023 tanggal 29 Agustus 2023 dari Komite Etik Penelitian Kesehatan (KEPK) Fakultas Kedokteran Universitas Muhammadiyah Malang. 3. No. 2029/UN14.2.2V.1/PT.01.01/2023 tanggal 30 Agustus 2023 dari Komisi Etik Penelitian Kedokteran Universitas Udayana.
7.	Desain Uji Klinik	:	*Randomized, observer blinded, active controlled, multicenter clinical study*

8. Jumlah subjek : 1260 subjek wanita sehat usia 18 – 45 tahun.

9. Tujuan uji klinik : ***Primary Objectives***:

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 18-45 years old.

Secondary Objectives:

1. *To evaluate the immune response (IgG antibodies) induced by the nonavalent HPV study vaccine administered with 3-dose schedule in female participants aged 18-45 years old;*
2. *To evaluate the persistence of immune response to the nonavalent HPV study vaccine;*
3. *To evaluate the safety of the nonavalent HPV study vaccine.*

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

Participants must meet all the following inclusion criteria.

1. **Healthy female participants, aged between 18 years and 45 years as of the 1st dose of vaccination (18 years ≤ age < 46 years).*
2. *Prior to enrolment, written informed consent obtained from the participants.*
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 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

Exclusion criteria for first vaccination :

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 judgement;*
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 judgement.*

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. *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 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.*

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi terhadap protokol uji klinik *Recombinant Nonavalent Human Papillomavirus Vaccine* yang didukung oleh tim ahli melalui rapat pada tanggal 14 November dan 20 Desember 2022. Pengajuan persetujuan uji klinik ini, didukung dengan data sebagai berikut:

1. Uji non klinik berupa uji toksisitas (akut dan dosis berulang) menunjukkan vaksin memiliki profil keamanan yang 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. Uji klinik fase III imunobridging pada subjek 2750 subjek menunjukkan data imunogenisitas 30 hari setelah vaksinasi pada subjek usia 20 – 26 tahun non inferior terhadap vaksin pembanding (Gardasil 9) untuk semua tipe HPV, termasuk HPV tipe 16. Berdasarkan data uji klinik tersebut, maka pengajuan protokol uji klinik fase 3 imunobridging untuk subjek dewasa (usia 18 – 45 tahun) yang diajukan dapat disetujui.

Desain uji klinik memadai dan vaksin yang akan digunakan dalam uji klinik telah memenuhi persyaratan mutu.

Keputusan

Pelaksanaan uji klinik dengan protokol di atas disetujui melalui penerbitan Persetujuan Pelaksanaan Uji Klinik Nomor RG.01.06.1.3.09.23.41 tanggal 29 September 2023.