RINGKASAN HASIL EVALUASI
PERMOHONAN PERSETUJUAN PELAKSANAAN UJI KLINIK
VAKSIN SARS-COV-2 VEKTOR VIRUS INFLUENZA
(DelNS1-2019-nCoV-RBD-OPTI) INTRANASAL
PRODUKSI BEIJING WANTAI BIOLOGICAL PHARMACY ENTERPRISE CO LTD.

Informasi Umum

1. Vaksin COVID-19 Vektor Virus Influenza (DelNS1-2019-nCoV-RBD-OPTI) dengan *platform viral vector (replicating)* dikembangkan oleh University of Hong Kong, Xiamen University dan Beijing Wantai Biological Pharmacy Enterprise Co Ltd, China. Vaksin ini mengandung virus influenza yang dilemahkan yang disisipkan gen RBD SARS-CoV-2 menggantikan site NS-1.
2. Telah dilakukan uji non klinik antara lain *challenge protection* pada hamster, uji imunogenisitas-imunopersisten pada BALB/c mice dan *cynomolgus monkey*; imunitas seluler pada mice, serta uji toksisitas pada rat, *cynomolgus monkeys, guinea pigs.* Uji klinik fase I pada 63 subjek dan uji klinik fase II pada 724 subjek telah dilakukan di China untuk mengevaluasi keamanan dan imnunogenisitas vaksin.
3. Uji klinik yang diajukan adalah uji klinik fase III, akan dilakukan multicenter dan multinasional di Indonesia dan 9 negara lainnya (Philippines, Thailand, Vietnam, Peru, Colombia, South Africa, Ghana, Rwanda dan Uganda). Subjek yang akan direkrut secara global sebanyak 32.000 – 40.000 subjek dan 6.000 diantaranya direncanakan direkrut di Indonesia.

Informasi Uji Klinik

1	Judul Protokol	:	***A Global, Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Clinical Trial to Evaluate the Protective Efficacy and Safety of Influenza Virus Vector COVID-19 Vaccine for Intranasal Spray (DelNS1-2019-nCoV-RBD-OPT1) in Adults Aged 18 Years and Older*** No protokol: COVID-19-PRO-003, version 2.0 tanggal 10 Agustus 2021
2	Produk Uji	:	*Influenza Virus Vector COVID-19 Vaccine for Intranasal Spray* Sediaan cair 0.2 mL/vial mengandung paling sedikit 6.3 lg *Cell Culture Infectious Dose* (CCID50). Vaksin diberikan pada hari ke-0 dan hari ke-14 secara *intranasal spray* (0,1 ml untuk setiap hidung). Produksi: Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China.
3	Produk Pembanding	:	*Placebo of Influenza Virus Vector COVID-19 Vaccine for Intranasal Spray* Sediaan cair 0,2 ml/vial mengandung *Sodium chloride, trehalose, sucrose, glycine, arginine, sodium glutamate, histidine, urea, dextran 40, hydrochloric acid, human serum albumin.* Vaksin diberikan pada hari ke-0 dan hari ke-14 secara *intranasal spray* (0,1 ml untuk setiap hidung). Produksi: Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China.
4	Center / Peneliti	:	a. RSGM Universitas Jember - RS Paru Jember/ dr. Ulfa Elfiah, M.Kes., Sp.BP-RE(K)

b. Rumah Sakit Universitas Sebelas Maret, Surakarta/ Prof. Dr. Hartono, dr, M.Si
c. Rumah Sakit Husada Utama, Surabaya/ dr. Didi D. Dewanto, Sp.OG
d. Rumah Sakit Universitas Kristen Krida Wacana, Jakarta/ dr. Wiliam., Sp.FK
e. Rumah Sakit Sri Pamela, Sumatera Utara/ Dr. Hj. Sake Juli Martina, Sp.FK
f. Rumah Sakit Universitas Indonesia/ Dr. dr. Astuti Giantini, Sp.PK(K), MPH
g. Fakultas Kedokteran dan Ilmu Kesehatan Universitas Katolik Indonesia Atma Jaya (FKIK Unika Atma Jaya) dan RS Atma Jaya - Dr. dr. Linawati Hananta, Sp.FK
h. RSUD Dr. Soeselo Kab. Tegal/ dr. Yuki Fitria Maastisya, Sp.N

5	Sponsor / ORK	:	Beijing Wantai Biological Pharmacy Enterprise Co., Ltd/ PT Tigermed Consulting Indonesia
6	Persetujuan Etik	:	Protokol sedang dievaluasi oleh Komite Etik Penelitian Kesehatan RSUD Dr. Soetomo, Surabaya dan Komite Etik Penelitian Universitas Sumatera Utara
7	Desain Uji Klinik	:	*Case-driven, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of DELNS1-2019-nCoV-RBD-OPT1*
8	Jumlah Subjek	:	*32,000~40,000 subjects (global), 6000 subjects in Indonesia*
9	Tujuan Uji Klinik	:	***Primary objective***

Efficacy

To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 for preventing virologically confirmed (RT-PCR-positive) symptomatic COVID-19.

Safety

To evaluate the safety of DelNS1-2019-nCoV-RBD-OPT1.

Secondary Objectives

Efficacy

1. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against severe COVID-19.*
2. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of any severity in different age groups.*
3. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against virologically -confirmed (RT-PCR-positive) COVID-19 deaths.*
4. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of any severity in patients with chronic diseases.*
5. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against virologically confirmed (RT-PCR positive)*

symptomatic COVID-19 in subjects previously administered with COVID-19 vaccine

Exploratory objective

Efficacy

1. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of any severity at least 14 days after the first vaccination (≥15 days).*
2. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of different severities.*
3. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of any severity in all subjects with symptomatic COVID-19 during the follow-up period.*
4. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 infections of any severity in different clinical study sites (countries).*
5. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 against symptomatic COVID-19 of any severity caused by the variant of concern (VOC).*
6. *To evaluate the protective efficacy of DelNS1-2019-nCoV-RBD-OPT1 for preventing virologically confirmed (RT-PCR-positive) influenza A.*

Safety

To assess the safety of DelNS1-2019-nCoV-RBD-OPT1 from the perspective of vaccine-enhanced disease (VED).

10 Kriteria Eligibilitas **:** Kriteria Inklusi / *Inclusion criteria*

1. *Aged ≥18 years old at the time of enrolment;*
2. *Be able to comply with the requirements of clinical study protocol and complete all trial procedures, and sign informed consent form;*
3. *Subjects who have not received any COVID-19 vaccine (marketed or investigational), those who have received at least one dose of other COVID-19 vaccines (marketed or investigational) with an interval of ≥6 months between the last dose and the date when the subjects sign the informed consent for this study;*
4. *Those who are negative for HIV screening (depending on the relevant policy of the country where the trial is conduct, if qualification for HIV testing is required in the country, this information will be obtained mainly by inquiry while protecting the candidate's privacy);*
5. *Fertile males and females of childbearing potential who are willing to take appropriate contraceptive measures from signing ICF to 3 months after the last dose, including abstinence or effective contraceptive measures (e.g., intrauterine or implantable contraceptive devices, oral contraception, combination of contraceptive diaphragm or condom with contraceptive gel); women of childbearing potential should be negative for pregnancy test on the day of vaccination.*

6. *Healthy people or people with a mild underlying disease that has remained stable without exacerbation (not requiring hospitalization or without major modification of the treatment regimen) within at least 3 months prior to inclusion in the study.*

Kriteria Eksklusi / *Exclusion criteria*

1. *Prior history of COVID-19;*
2. *Positive test of total SARS-CoV-2 specific antibody using colloidal gold reagent [Only applicable to subjects without vaccination history of COVID-19 vaccine (marketed or investigational)];*
3. *Pregnant or lactating women;*
4. *Fever on the day of vaccination or within 3 days prior to vaccination (oral temperature ≥37.5℃/axillary temperature ≥37.3℃);*
5. *Those who had any acute disease in the past 5 days that requires systemic antibiotic or antiviral treatment (including but not limited to the use of anti-influenza virus drugs such as Tamiflu, Relenza, Symmetrel or Flumadine);*
6. *Those who had low immune function caused by immunodeficiency diseases, diseases of important organs, cancer, and immune diseases (e.g. Guillain Barre syndrome, systemic lupus erythematosus, rheumatoid arthritis, alienia or splenectomy caused by any condition, and other immune disease that may affect immune response at the investigator's discretion);*
7. *Long-term use (defined as ≥14 days) of immunosuppressants or other immunomodulators (for glucocorticoids, e.g., ≥10 mg/day prednisone or equivalent dose; inhaled and topical steroids are allowed) within 6 months prior to the first vaccination;*
8. *History of hemorrhagic diseases (e.g., factor deficiency, thrombocytopenia or other coagulation disorders), or hemorrhagic tendency, or continuous requirement of anticoagulants;*
9. *Having received immunoglobulins and/or blood products within 3 months before receiving the investigational vaccine;*
10. *Received subunit or inactivated vaccine within 14 days before vaccination, or received live attenuated vaccine within 28 days before vaccination;*
11. *Participation in a clinical trial of another product within 1 month prior to vaccination, or planning to participate in a clinical trial of another product during the study;*
12. *Having a history of severe allergic reactions or severe adverse reactions from previous immunizations, or allergy to any component of the investigational vaccine;*
13. *Patients deemed by the investigator as unsuitable for using nasal spray (those with severe rhinitis or nasal deformities, etc.);*
14. *Planning to relocate permanently from the current area prior to the completion of the study or to leave the current area for a long period (preventing compliance with the prescribed visit schedule) during the study visits;*
15. *Other conditions that the investigators consider unsuitable for this clinical study.*

11	*L*uaran Uji Klinik/ *Endpoint*	:	***Primary Endpoint*** *Endpoint Efficacy* *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity that occurs for the first time at least 7 days (≥ 8 days) after the second vaccination.* *Safety* 1. *All serious adverse events (SAEs), other medically attended AEs (MAAEs), and adverse events of special interest (AESIs) from the first vaccination to 12 months after the second vaccination in all subjects;* 2. *All solicited adverse events within 7 days following the first and second vaccinations in all subjects;* 3. *All unsolicited adverse events that occur during the interval between doses and within 30 days after the second vaccination in all subjects.* ***Secondary endpoints*** *Efficacy* 1. *Virologically confirmed (RT-PCR-positive) severe and above COVID-19 cases that occurs for the first time at least 7 days (≥ 8 days) after the second vaccination.* 2. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity that occur for the first time at least 7 days after the second vaccination (≥ 8 days) in subjects aged 18-59 and ≥60 years.* 3. *Virologically confirmed (RT-PCR-positive) death cases resulting from COVID-19 that occur at least 7 days after the second vaccination (≥ 8 days).* 4. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity that occur for the first time at least 7 days after the second vaccination (≥ 8 days) in subjects with a clear chronic disease.* 5. *Virologically confirmed (positive RT-PCR) symptomatic COVID-19 cases of any severity that occurs for the first time at least 14 days (≥ 15 days) after the first vaccination in subjects previously administered with COVID-19 vaccine.* ***Exploratory Endpoint*** *Efficacy* 1. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity that occur for the first time at least 14 days after the first vaccination (≥15 days).* 2. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of different severities that occur for the first time at least 7 days after the second vaccination (≥ 8 days).* 3. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity after the first vaccination, including subjects with symptomatic COVID-19 that occur during the observation period of non-endpoint cases (interval between doses or within 7 days after the second vaccination).* 4. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity that occurs for the first time at least 7 days after the second vaccination (≥ 8 days) in different countries.*

5. *Virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases of any severity caused by the variant of concern (VOC) at least 7 days after the second vaccination (≥ 8 days).*
6. *Virologically confirmed (RT-PCR-positive) influenza A cases of any severity that occur for the first time at least 7 days (≥ 8 days) after the second vaccination.*

Safety

Vaccine-enhanced disease (VED) events experienced by subjects with virologically confirmed (RT-PCR-positive) symptomatic COVID-19 cases throughout the study period

Ringkasan Hasil Evaluasi

Badan POM telah melakukan evaluasi protokol uji klinik Vektor Virus Influenza (DelNS1-2019-nCoV-RBD-OPTI) untuk COVID-19, yang didukung oleh tim ahli melalui rapat pada tanggal 9 Februari 2022 dengan hasil sebagai berikut:

1. Hasil uji non klinik pada *mice* dan *cynomolgus monkey* menunjukkan tidak terdapat peningkatan bermakna untuk respon imun humoral antibody IgG anti-RBD, IgG anti-virus influenza, anti-RBD IgG. Vaksin uji dapat merangsang respon imun seluler (Sel T) namun terjadi penurunan respon imun sel T yang signifikan mulai 14 hari setelah vaksinasi.
2. Dari uji klinik fase I dan II didapatkan hasil bahwa secara umum vaksin dapat ditoleransi dengan baik namun tidak terdapat peningkatan respon imun humoral, seluler ataupun mukosal yang signifikan setelah pemberian vaksin. Hasil studi tersebut dinilai belum dapat mendukung pelaksanaan uji klinik fase III sehingga uji klinik ini tidak *feasible* untuk dilakukan.

Keputusan

Pelaksanaan uji klinik untuk protokol di atas ditolak melalui surat tanggal 22 Februari 2022.