Cover Page

Release Date: May 5, 2025

ClinicalTrials.gov ID: NCT06959563

Unique Protocol ID: IND 169135

Brief Title: Early Phase Clinical Trial About Therapeutic Biological Product Mix for Treating HPV (9vHPV-BCG)

Official Title: Conducting an Early Phase Clinical Trial to Assess for HPV Antigen Presentation Therapeutic Biological Product Mix Activity That Suggests the Potential for Clinical Benefits of HPV Patients.

Secondary IDs: IND 169135 [Registry ID: FDA, Investigational New Drug Application (IND)]
NPI-1831468511 [Registry ID: HHS, Health Care Provider Individual]
NPI-1023387701 [Registry ID: HHS, Health Care Provider Organization]
FWA00015357 [Registry ID: HHS, Human Protections Administrator]
IORG0007849 [Registry ID: HHS, IORG]
IRB00009424 [Registry ID: HHS, IRB]

Human APCs treat HPV antigen into small fragments, and then clear HPV in vivo.

6. Protocol [21 CFR 312.23(a)(6)]
6a. Study protocol *[21 CFR 312.23(a)(6)]*

Contents

It is my **commitment** that our Institutional Review Board (IRB) (IRB00009424) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in my proposed clinical investigation and that the sponsor-investigator (me i.e. Han Xu, M.D., Ph.D.) will report to our IRB (IRB00009424) the proposed changes in my research activity in accordance with the requirements of part 56.

I write the **statement** with respect to each clinical study involving human subjects that it either will be conducted in compliance with the institutional review board regulations in part 56 or will not be subject to the regulations under §56.104 or §56.105; and that it either will be conducted in compliance with the informed consent regulations in part 50 or will not be subject to the regulations under §50.23 and §50.24.

21 CFR§312.23 (a)(6)
Protocols.

(i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with § 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation - an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose - and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

The protocol for the planned IND 169135 Phase 1 clinical study NCT06959563:
In general, protocols for Phase 1 studies may be less detailed and more flexible. Phase 1 protocol of the planned IND 169135 clinical study NCT06959563 will be directed primarily at providing an outline of the clinical investigation NCT06959563 as follows:

- **An estimate of the number of patients to be involved:**
  - 20 Cervical HPV Infection Patients
- **A description of participant inclusions:**
  - Positive testing HPV by standard PCR assay
  - HPV infection without symptoms
  - No clinical signs indicative of oncology
  - TB negative participant is negative IGRA blood test with TB antigens.
- **A description of safety exclusions:**
  - Pregnant
  - Thrombosis
  - Allergy
  - TB positive participant is positive IGRA blood test with TB antigens.
  - Symptoms of HPV infection.
  - Clinical signs suggestive of other infection
  - Symptoms suggestive of other infection
  - Clinical signs indicative of oncology
  - Evidence of critical illness
- **A description of the dosing plan:**
  - **Duration:** 4-weeks = 28-days
  - **Dose:**
    - 2 x Dose i.e., 2 x 0.5 mL = 1 mL 9vHPV Vaccine like as following:
      https://dailymed.nlm.nih.gov/dailymed/
      LABEL: GARDASIL 9 - human papillomavirus 9-valent vaccine, recombinant injection, suspension
      NDC *0006-4119-03*
      BLA *125508*
      Packager: Merck Sharp & Dohme LLC
      - Each 0.5-mL dose contains human papillomavirus L1 protein of each type adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant as follows: Type 6 (30 mcg), Type 11 (40 mcg), Type 16 (60 mcg), Type 18 (40 mcg), Type 31 (20 mcg), Type 33 (20 mcg), Type 45 (20 mcg), Type 52 (20 mcg), Type 58 (20 mcg).
      - GARDASIL 9 - Each 0.5-mL dose x 2 = 1 mL

- ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
- 1 Dose i.e., 50 mg wet weight organism i.e., 1 Intact Vial of lyophilized powder like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: BCG VACCINE - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
  NDC *0052-0603-02*
  BLA *103050*
  Packager: Merck Sharp & Dohme Corp.
  Active Ingredient(s) and Strength(s) like as following:
  BCG VACCINE contains live bacteria. BCG VACCINE for percutaneous use is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis. The TICE® strain used in this BCG VACCINE preparation. The TICE® BCG organism is grown for preparation of freeze-dried cake.
  - ✓ Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis
  - ✓ 1 to 8 × 10^8 colony forming units (CFU) of BCG (equivalent to approximately 50 mg wet weight)
  - ✓ Merck TICE® BCG organism 50 MG wet weight

✧ **The method to be used in determining dose:**

✧ Purchased below FDA approved biological products according to labels:

- 2 x Dose i.e., 2 x 0.5 mL = 1 mL 9vHPV Vaccine like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: GARDASIL 9 - human papillomavirus 9-valent vaccine, recombinant injection, suspension
  NDC *0006-4119-03*
  BLA *125508*
  Packager: Merck Sharp & Dohme LLC
- ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
- 1 Dose i.e., 50 mg wet weight organism i.e., 1 Intact Vial of lyophilized powder like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: BCG VACCINE - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
  NDC *0052-0603-02*
  BLA *103050*
  Packager: Merck Sharp & Dohme Corp.

✧ We will specify in detail only those elements of the IND 169135 Phase 1 clinical study NCT06959563 that are critical to safety, such as necessary monitoring of vital signs and blood chemistries.

- **The vital signs of safety exclusions:**
  - ✓ Pregnant
  - ✓ Thrombosis
  - ✓ Allergy
  - ✓ TB positive participant is positive IGRA blood test with TB antigens.
  - ✓ Clinical signs indicative of oncology
  - ✓ Evidence of critical illness

✧ Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

21 CFR § 312.30

(a) ***New protocol.*** Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met:

(1) The sponsor has submitted the protocol to FDA for its review; and

(2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

Phase 1 protocols will be directed primarily at providing an outline of the investigation:

- **An estimate of the number of patients to be involved:**
  - ✓ 20 Cervical HPV Infection Patients
- **A description of safety exclusions:**
  - ✓ Pregnant
  - ✓ Thrombosis
  - ✓ Allergy
  - ✓ TB positive participant is positive IGRA blood test with TB antigens.
  - ✓ Symptoms of HPV infection.
  - ✓ Clinical signs suggestive of other infection
  - ✓ Symptoms suggestive of other infection
  - ✓ Clinical signs indicative of oncology
  - ✓ Evidence of critical illness
- **A description of the dosing plan for duration:**
  - ✓ Our trial duration will be 4-week duration.
- **A description of the dosing plan for dose:**
  - ✓ 9vHPV Vaccine 1.0 mL plus BCG Vaccine 50 MG Mix
- **A description of the dosing plan for method to be used in determining dose:**
  - ✓ **LABEL: GARDASIL 9** - human papillomavirus 9-valent vaccine, recombinant injection, suspension
    NDC *0006-4119-03*
    BLA *125508*
    Packager: Merck Sharp & Dohme LLC
  - ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
  - ✓ **LABEL: BCG VACCINE** - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
    NDC *0052-0603-02*
    BLA *103050*
    Packager: *Merck Sharp & Dohme Corp.*

- The elements of the study that are critical to safety:
  - **The necessary monitoring of vital signs:**
    - ✓ TB positive participant is positive IGRA blood test with TB antigens.
    - ✓ Positive testing HPV by standard PCR assay

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

The IND 169135 Phase 1 clinical study need not describe Phases 2 and 3 protocols.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.

1. Treat Infection of Multiple HPV Virus Strains.
2. Activate human HPV Antigen Presentation Reaction.
3. The human antigen presenting cells (APCs) can treat the HPV virus protein antigens into small peptide fragments, and then clear HPV virus in vivo.

Statement

The objectives and purpose of the IND 169135 Phase 1 clinical study will be 2 doses of the biological product, **9vHPV VACCINE** add into 1 dose of the biological product, **BCG VACCINE** and mix above them **before 5 minutes** to take the percutaneous use and treat the Infection of Multiple HPV Virus Strains.

(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each sub-investigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

Contact Person: Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, Medical Director
Contact Company: Medicine Invention Design Incorporation
Contact Address: 5545 Burnside Drive, Rockville, MD 20853, USA
Contact Call: 001-301-222-7143
Contact Fax: 001-866-458-0099
Contact Email: hanxumdphd@midinc.us

The name of investigator:
- Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, Medical Director

Health Care Provider - Individual (NPI - 1831468511)
The address of investigator: (Online Clinical Trial Site)
- 5545 Burnside Drive, Rockville, MD 20853, USA

The statement of the qualifications of investigator:
21 CFR 312.53(c)(1)
A signed investigator statement (Form FDA-1572) containing:
(i) The name and address of the investigator:
- The name of the investigator:
  - ✓ Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, Medical Director
- **The address of the investigator: (Online Clinical Trial Site)**
  - ✓ 5545 Burnside Drive, Rockville, MD 20853, USA

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator:
- ✓ Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, Medical Director
- ✓ Health Care Provider - Individual (NPI - 1831468511)
- ✓ Health Care Provider - Health Maintenance Organization (Code - 302R00000X)
- ✓ **IND Number:** IND 169135
- ✓ **ClinicalTrials.gov ID:** NCT06959563

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted:
- The name of research facility:
  - ✓ Medicine Invention Design Incorporation
  - ✓ Medicine Invention Design Incorporation (FWA00015357)
  - ✓ Medicine Invention Design Incorporation (IORG0007849)
  - ✓ Health Care Provider - Group/Organization (NPI - 1023387701)
  - ✓ Health Care Provider - Health Maintenance Organization (Code - 302R00000X)
  - ✓ Health Care Provider - Research Clinic/Center (Code - 261QR1100X)

- **The address of research facility: (Online Clinical Trial Site)**
  - ✓ 5545 Burnside Drive, Rockville, MD 20853, USA

(iv) The name and address of any clinical laboratory facilities to be used in the study:

- The name of clinical laboratory facility:
  - ✓ Medicine Invention Design Incorporation
  - ✓ Medicine Invention Design Incorporation (FWA00015357)
  - ✓ Medicine Invention Design Incorporation (IORG0007849)
  - ✓ Health Care Provider - Clinical Medical Laboratory (Code - 291U00000X)
- **The address of clinical laboratory facility: (Online Clinical Trial Site)**
  - ✓ 5545 Burnside Drive, Rockville, MD 20853, USA

(v) The name and address of the IRB that is responsible for review and approval of the study(ies):

- The name of the IRB:
  - ✓ Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424)
- **The address of the IRB: (Online Clinical Trial Site)**
  - ✓ 5545 Burnside Drive, Rockville, MD 20853, USA

(vi) A commitment by the investigator that he or she:

(*a*) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

21 CFR 312.55(a)

Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

Commitment

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator

A commitment by the sponsor-investigator that I:

(*a*) Will conduct the study (NCT06959563) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects.

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part.

(*c*) Will personally conduct or supervise the described investigation(s).

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(*e*) Will report to the sponsor (Han Xu, M.D. Ph.D., FAPCR) adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64.

(*f*) Have read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug.

21 CFR 312.55(a)

Han Xu, Sponsor-Investigator, need not give an investigator brochure containing the information described in § 312.23(a)(5).

(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study (NCT06959563) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

Commitment

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, Medical Director

It is my **commitment** that our Institutional Review Board (IRB) (IRB00009424) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in my proposed clinical investigation and that the sponsor-investigator (me i.e. Han Xu, M.D., Ph.D.) will report to our IRB (IRB00009424) the proposed changes in my research activity in accordance with the requirements of part 56.

(viii) A list of the names of the sub-investigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

Not available right now

The name of the research facility:

- Medicine Invention Design Incorporation (MIDI)
  - ✓ Medicine Invention Design Incorporation (FWA00015357)
  - ✓ Medicine Invention Design Incorporation (IORG0007849)
  - ✓ Health Care Provider - Group/Organization (NPI - 1023387701)
  - ✓ Health Care Provider - Research Clinic/Center (Code - 261QR1100X)

The address of the research facility: (Virtual / Mobile / Online)

- 5545 Burnside Drive, Rockville, MD 20853, USA

The name of Institutional Review Board:

- Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424)
- Health Care Provider - Individual (NPI 1831468511)
- Health Care Provider - Clinical Ethicist (Code - 174V00000X)

The address of Institutional Review Board: (Virtual / Mobile / Online)

- 5545 Burnside Drive, Rockville, MD 20853, USA

21 CFR 312.53(c)(2)

Curriculum vitae. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

The statement of the qualifications of sponsor-investigator:

The education, training, and experience that qualifies the sponsor-investigator as an expert in the IND 169135 Phase 1 clinical investigation of FDA approved biological products for the use under the IND 169135 Phase 1 clinical investigation:

The information about medical and scientific training of sponsor-investigator (SI)
Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, IORG Director

INSTITUTION / UNIVERSITY	DEGREE / TRAINING	Start Date MM/YYYY	End Date MM/YYYY	FIELD OF STUDY
Beijing Medical University (BMU) School of Basic Medical Sciences (SBMS)	B.S.	0719/86		Basic and Clinical Medicines
Beijing Medical University (BMU) School of Basic Medical Sciences (SBMS) Department of Medicine	Internship	09/1984	08/1985	Clinical Medicines
Beijing Medical University (BMU) School of Basic Medical Sciences (SBMS)	Internship	09/1985	07/1986	Basic Medicines
Beijing Friendship Hospital (BFH) Beijing Clinical Research Institute (BCRI)	Residency Physician	07/1986	06/1991	Internal Medicine
NIH-NCI accepted my degree obtained in BMU like as USA equivalent doctorate titles	M.D. Ph.D.	07/1986		Basic and Clinical Medicines
National Institutes of Health (NIH) National Cancer Institute (NCI)	Visiting Scholar	12/1995	03/2000	Basic and Clinical Research

The information about medical and scientific experience of sponsor-investigator (SI)

- **Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, IORG Director**
- 1980-1986 - M.D., Ph.D. accepted by NIH; Beijing Medical University School of Basic Medical Science; Beijing, China

  Dr. Han Xu received clinical education and clinical training in 1980-1986.
- 1986-1995 - Principal Investigator (PI), Clinical Attending Physician, Beijing Clinical Research Institute, Beijing Friendship Hospital; Beijing, China

  Dr. Han Xu received clinical training and had clinical experience in 1986-1995.
- 1995-2000 - M.D., Ph.D. accepted by NIH; Visiting Scholar, NCI-Frederick, National Cancer Institute (NCI), National Institutes of Health (NIH); Frederick, Maryland

  Dr. Han Xu received clinical investigator training in 1995-2000
- 2000-2006 - Principal Investigator (PI) / Program Director (PD), Pharm1 Incorporation - Beijing Office; Beijing, China
- **2006 - Sponsor-Investigator (SI) / IRB Chair (Study Chair, SC) / IORG Director (Study Director, SD) / Medical Monitor (MM) / Safety Officer (SO), Medicine Invention Design Incorporation (MIDI); Rockville, Maryland**
- 2013 - Director Member, Medicine Invention Design Incorporation (MIDI) (IORG0007849) - Institution or Organization (IORG) of Registration at U.S. Department of Health and Human Services (HHS)
- 2013 - Board Member and Chair, Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424) - Institutional Review Board (IRB) of Registration at U.S. Department of Health and Human Services (HHS)
  Dr. Han Xu had already been Sponsor-Investigator (SI) approved by IRB00009424.
- 2020 - Active Member, Fellow of the APCR (FAPCR), Academy of Physicians in Clinical Research (APCR) - APCR Membership Eligibility - Physician Investigator
  - Certificate of Fellow of Academy of Physicians in Clinical Research (FAPCR)
  - Academy of Physicians in Clinical Research (APCR)
    - ✧ **PI (Principal Investigator) in clinical trials**
    - ✧ **Medical Director of Clinical Research Site**
- 2023 - FDA Pre-Assignment - My IND has been granted. My pre-assigned number is 169135.
  - Individual **Sponsor**: HAN XU
  - Organization **Sponsor**: Medicine Invention Design Incorporation
- 2023 update - **ClinicalTrials.gov ID:** NCT06959563 under **42 CFR Part 11**
  - Responsible Party **(Sponsor-Investigator)**
  - Study Principal Investigator [**Principal Investigator (PI)**]
  - Study Director (Medical Director)
  - Study Chair (IRB Chair)

- **The qualifications of sponsor-investigator:**
  - ✧ **Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, Medical Director, IRB Chair**
  - ✧ NPI 1831468511 - Individual
  - ✧ Clinical Ethicist - (Code - 174V00000X)
  - ✧ Specialist Research Study - (Code - 1744R1102X)
  - ✧ **ClinicalTrials.gov ID:** NCT06959563 [Responsible Party (**Sponsor-Investigator**)]
  - ✧ FWA00015357 (Human Protections Administrator)
- **Medicine Invention Design Incorporation (MIDI) (IORG0007849)**
- **Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424)**
- **Federal-wide Assurance (FWA) for the Protection of Human Subjects (FWA00015357)**
  - ✧ NPI 1023387701 - Organization
  - ✧ Research Clinic/Center - (Code - 261QR1100X)
  - ✧ Clinic/Center Health Services - (Code - 261QH0100X)
  - ✧ Clinic/Center Multi-Specialty - (Code - 261QM1300X)
  - ✧ Clinic/Center Medical Specialty - (Code - 261QM2500X)
  - ✧ Clinical Medical Laboratory - (Code - 291U00000X)
  - ✧ Health Maintenance Organization - (Code - 302R00000X)
  - ✧ Pharmacy Mail Order Pharmacy - (Code - 3336M0002X)

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

The criteria for patient selection:
- ✓ Cervical HPV Infection Patients
- ✓ Positive testing HPV by standard PCR assay
- ✓ HPV infection without symptoms
- ✓ No clinical signs indicative of oncology
- ✓ TB negative participant is negative IGRA blood test with TB antigens.

The criteria for patient exclusion:
- ✓ Pregnant
- ✓ Thrombosis
- ✓ Allergy
- ✓ TB positive participant is positive IGRA blood test with TB antigens.
- ✓ Symptoms of HPV infection.
- ✓ Clinical signs suggestive of other infection
- ✓ Symptoms suggestive of other infection.
- ✓ Clinical signs indicative of oncology
- ✓ Evidence of critical illness

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

- **Study Type:** Interventional
- **Primary Purpose:** Treatment
- **Study Phase:** Phase 1 Clinical Trial
- **Interventional Study Model:** Single Group Assignment / Single Usage / Single Dosage
- **Number of Arms:** 1 / single-arm study
- **Masking:** None (Open Label)
- **Allocation:** N/A
- **Enrollment:**

- ✓ 20 Cervical HPV Infection Patients
- ✓ Positive testing HPV by standard PCR assay
- ✓ HPV infection without symptoms
- ✓ No clinical signs indicative of oncology
- ✓ TB negative participant is negative IGRA blood test with TB antigens.

➢ **Dose:** 9vHPV Vaccine 1.0 mL plus BCG Vaccine 50 MG Mix

- 2 x Dose i.e., 2 x 0.5 mL = 1 mL 9vHPV Vaccine like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: GARDASIL 9 - human papillomavirus 9-valent vaccine, recombinant injection, suspension
  NDC *0006-4119-03*
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- ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
- 1 Dose i.e., 50 mg wet weight organism i.e., 1 Intact Vial of lyophilized powder like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: BCG VACCINE - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
  NDC *0052-0603-02*
  BLA *103050*
  Packager: Merck Sharp & Dohme Corp.

➢ **Route:** Percutaneous Use with Multiple Puncture Device
➢ **Duration:** Our trial duration will be 4-week duration.
➢ **Endpoint:** Negative testing HPV by standard PCR assay after percutaneous use 21 days.

The methods to be used to minimize bias on the part of subjects, investigators, and analysts:

21 CFR 312.53(c)(1)

(vi) A commitment by the investigator that he or she:

(a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(c) Will personally conduct or supervise the described investigation(s);

(d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

21 CFR 312.55(a)

Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

Commitment

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator

A commitment by the sponsor-investigator that I:
(*a*) Will conduct the study (IND 169135) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects.
(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part.
(*c*) Will personally conduct or supervise the described investigation(s).
(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;
(*e*) Will report to the sponsor (Han Xu, M.D. Ph.D., FAPCR) adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64.
(*f*) Have read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug.
21 CFR 312.55(a)
Han Xu, Sponsor-Investigator, need **not** give an investigator brochure containing the information described in § 312.23(a)(5).
(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the clinical study (IND 169135) are informed about their obligations in meeting the above commitments.

21 CFR 312.53(c)(1)
(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

Commitment

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator

It is my **commitment** that our Institutional Review Board (IRB) (IRB00009424) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in my proposed clinical investigation and that the sponsor-investigator (me i.e. Han Xu, M.D., Ph.D.) will report to our IRB (IRB00009424) the proposed changes in my research activity in accordance with the requirements of part 56.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

- **The method for determining the single dose to be administered:**
  - 2 x Dose i.e., 2 x 0.5 mL = 1 mL 9vHPV Vaccine like as following: https://dailymed.nlm.nih.gov/dailymed/
    LABEL: GARDASIL 9 - human papillomavirus 9-valent vaccine, recombinant injection, suspension
    NDC *0006-4119-03*
    BLA *125508*
    Packager: Merck Sharp & Dohme LLC

- ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
- 1 Dose i.e., 50 mg wet weight organism i.e., 1 Intact Vial of lyophilized powder like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: BCG VACCINE - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
  NDC *0052-0603-02*
  BLA *103050*
  Packager: Merck Sharp & Dohme Corp.

➢ **The planned maximum dosage:**

- 2 x Dose i.e., 2 x 0.5 mL = 1 mL 9vHPV Vaccine like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: GARDASIL 9 - human papillomavirus 9-valent vaccine, recombinant injection, suspension
  NDC *0006-4119-03*
  BLA *125508*
  Packager: Merck Sharp & Dohme LLC
  Active Ingredient(s) and Strength(s) like as following:
  - ➢ Each 0.5-mL dose contains human papillomavirus L1 protein of each type adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant as follows:
    Type 6 (30 mcg), Type 11 (40 mcg), Type 16 (60 mcg), Type 18 (40 mcg), Type 31 (20 mcg), Type 33 (20 mcg), Type 45 (20 mcg), Type 52 (20 mcg), Type 58 (20 mcg).
  - ➢ GARDASIL 9 - Each 0.5-mL dose x 2 = 1 mL
- ⊙ **Before 5 minutes** for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:
- 1 Dose i.e., 50 mg wet weight organism i.e., 1 Intact Vial of lyophilized powder like as following:
  https://dailymed.nlm.nih.gov/dailymed/
  LABEL: BCG VACCINE - bacillus calmette-guerin substrain tice live antigen injection, powder, lyophilized, for solution
  NDC *0052-0603-02*
  BLA *103050*
  Packager: Merck Sharp & Dohme Corp.
  Active Ingredient(s) and Strength(s) like as following:
  BCG VACCINE contains live bacteria. BCG VACCINE for percutaneous use is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis. The TICE® strain used in this BCG VACCINE preparation. The TICE® BCG organism is grown for preparation of freeze-dried cake.
  - ✓ Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis
  - ✓ 1 to 8 × 10^8 colony forming units (CFU) of BCG (equivalent to approximately 50 mg wet weight)
  - ✓ Merck TICE® BCG organism 50 MG wet weight

➢ **The duration of individual patient exposure to the drug:** 4-weeks = 28-days

➢ **Duration:** Our trial duration will be 4-week duration.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

- **The observations and measurements to be made to fulfill the objectives of the study:**
  - ✧ Positive testing HPV by standard PCR assay before the study.
  - ✧ TB negative participant is negative IGRA blood test with TB antigens before the study.
  - ✧ Negative testing HPV by standard PCR assay after 21 days of dosage
  - ✧ HPV protein derivative will be positive with 1/10 Dose of 9vHPV Vaccine by IGRA blood test to take the IGRA blood test with 9vHPV antigens after the percutaneous use 3 weeks of the biological product mix dosage.

- **Endpoint:** Negative testing HPV by standard PCR assay after percutaneous use 21 days.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

- Negative testing HPV by standard PCR assay after percutaneous use 21 days.
- BCG should **not** be given to individuals previously infected with M. tuberculosis. A person will give the IGRA blood test with TB antigens. TB positive participant is positive IGRA blood test with TB antigens.
- BCG can activate the human antigen presenting cells (APCs) to treat HPV virus target protein antigen into small peptide fragments and to clear HPV virus antigens in vivo. So, the related allergen in vivo will decrease gradually.

The clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the biological product mix in human subjects and to minimize risk like as follows:

- **The clinical procedures to be taken to minimize risk:**
  - ✓ To take the percutaneous use can minimize risk.
  - ✓ 2 doses of the biological product, **9vHPV VACCINE** add into 1 dose of the biological product, **BCG VACCINE** and mix above them **before 5 minutes** to take the percutaneous use.
  - ✓ BCG can activate the human antigen presenting cells (APCs) to treat HPV virus target protein antigen into small peptide fragments and to clear HPV virus antigens in vivo. So, the related allergen in vivo will decrease gradually.

- **The clinical and laboratory tests to be taken to monitor the effects of the biological product mix in human subjects:**
  - ✓ Positive testing HPV by standard PCR assay before the study.
  - ✓ Negative testing HPV by standard PCR assay after 21 days of dosage
  - ✓ HPV protein derivative will be positive with 1/10 Dose 9vHPV Vaccine by the IGRA blood test to take the IGRA blood test with 9vHPV antigens after the percutaneous use 3 weeks of the biological product mix dosage.

- **The clinical and laboratory tests to be taken to minimize risk:**
- The risk exclusions like as following:

✧ Pregnant
✧ Thrombosis
✧ Allergy
✧ TB positive participant is positive IGRA blood test with TB antigens.
✧ Symptoms of HPV infection
✧ Clinical signs suggestive of other infection
✧ Symptoms suggestive of other infection
✧ Clinical signs indicative of oncology
✧ Evidence of critical illness

21 CFR 312.10(a)
A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND.
[21 CFR 312.10(a)(3)]
Other information justifying a waiver.

According to 21 CFR 312.10(a), the sponsor (Han Xu, M.D., Ph.D., FAPCR) needs to request FDA to waive applicable requirement under this part which means 21 CFR Part 312. Therefore, my investigation must waive the requirements of 21 CFR 312.53(c). In particular, my investigation must waive the requirements of 21 CFR 312.53(c)(1). Also, my clinical investigation must waive the requirements of 21 CFR §312.305 (c)(1) and 21 CFR §312.305 (c)(3). Although I am not a licensed physician, I still can be a qualified sponsor-investigator for my IND Phase I clinical investigation.

21 CFR 312.53(c)(1)(vi)(*d*)
Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

I write the **statement** with respect to each clinical study involving human subjects that it either will be conducted in compliance with the institutional review board regulations in part 56 or will not be subject to the regulations under §56.104 or §56.105; and that it either will be conducted in compliance with the informed consent regulations in part 50 or will not be subject to the regulations under §50.23 and §50.24.

21 CFR 312.53(c)(1)(vii)
A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

It is my **commitment** that our Institutional Review Board (IRB) (IRB00009424) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in my proposed clinical investigation and that the sponsor-investigator (me i.e. Han Xu, M.D., Ph.D.) will report to our IRB (IRB00009424) the proposed changes in my research activity in accordance with the requirements of part 56.

To minimize potential bias resulting from orally verbal voice administration of assessments, the sponsor (Han Xu, M.D., Ph.D., FAPCR) will consider using automated virtual interviewers to administer the assessments remotely. According to similar principles, the formal pre-IND review will be conducted in the format -- written response only (WRO) by email.

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