Cover Page

Release Date: September 12, 2025

ClinicalTrials.gov ID: NCT07182838

Unique Protocol ID: IND 179135 Research

Brief Title: Proof-of-Concept Clinical Pharmacology Trial for HIV Antigen Presentation Therapeutic Biologic Mix (HIVGP-BCG)

Official Title: Conducting an Initial Small, Controlled Clinical Pharmacology Trial to Assess for Therapeutic Biologics Activity (Proof-of-Concept) that Suggests the Potential for Clinical Benefits of HIV (+) Patients

Secondary IDs: FWA00015357 [Registry ID: DHHS, OHRP]
IRB00009424 [Registry ID: IRB, DHHS]
IORG0007849 [Registry ID: IORG, DHHS]
NPI-1831468511 [Registry ID: HHS, Health Care Provider Individual]
NPI-1023387701 [Registry ID: HHS, Health Care Provider Organization]
IND 179135 [Registry ID: IND, FDA]

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

4. General Investigational plan *[21 CFR 312.23(a)(3)]* … (including **Statistical Analysis Plan**)

Contents

21 CFR 312.23 (a)(3)

Introductory statement and general investigational plan.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: ……. (including **Statistical Analysis Plan**)

My investigation will use commercially available lawfully marketed prescription biological products by US Pharmacy as follows:

https://www.antibodies-online.com/
HIV-1 gp160 Protein
Catalog No. ABIN1111556
0.1 mg x 1mL
ANTIBODIES-ONLINE INC.

Before 5 minutes for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:

DailyMed - 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.

- 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)
- TICE® BCG organism 50 MG

- Mix above FDA approved biological products to take the percutaneous use and treat the Infection of Multiple HIV-1 Virus Strains.
- The IND 179135 Phase 1 clinical investigation NCT07182838 will use 1 dose of the biological product, **HIV-1 gp160 Protein** add into 1 dose of the biological product, **BCG VACCINE** and mix above them to take the percutaneous use and treat the Infection of Multiple HIV-1 Virus Strains.

(*a*) The rationale for the drug or the research study.

The rationale for the clinical research study of HIV-1 gp160 Protein plus BCG Vaccine Mix to treat Infection of Multiple HIV-1 Virus Strains via following three processes: 1. Trained Immunity. 2. Antigen Presentation Therapy **(It is Key).** 3. Innate immune memory.

1. Activate the Trained Immunity Reaction to HIV-1 Protein Antigen (Pharmacology)

- Trained immunity - https://en.wikipedia.org/wiki/Trained_immunity

Trained immunity is the modification of cells in the innate immune system (the one with which an organism is born) to create a "memory" of a pathogen. Trained immunity creates no antibodies in preparation for a second encounter. Instead, the immunity is mediated mostly by epigenetic modifications -- alterations in gene expression and cellular function without changes to the original DNA sequence. The resulting immunity lasts up to several months and is usually unspecific because there is no production of specific antibodies or receptors. The term "innate immune memory" can be used as a synonym for the term “trained immunity”. Monocytes/macrophages can undergo epigenetic modifications after a ligation of their pattern recognition receptors (PRRs). This ligation with HIV-1 virus antigens may prepare these cells for a second encounter with the training pathogen HIV-1 virus. The secondary response may be heightened not only against the training pathogen, but also against different pathogens **(Multiple HIV-1 Virus Strains)** whose antigens can be recognized by the same PRRs. This effect has also been observed when stimulating cells by vaccination against tuberculosis with a vaccine containing **BCG**.

2. Activate the Antigen Presentation Reaction to HIV-1 Proteins (Pharmacology)

- Antigen presentation - https://en.wikipedia.org/wiki/Antigen_presentation

BCG can activate macrophages, a kind of antigen presenting cells (APCs), treat HIV-1 virus protein antigens into small peptide fragments, and then clear HIV-1 virus in vivo. In the antigen presentation process, these HIV-1 virus antigen proteins are mainly degraded into small peptides by cytosolic proteases in the proteasome, but there are also other cytoplasmic proteolytic pathways. APCs can internalize exogenous HIV-1 virus antigens by endocytosis, but also by pinocytosis, macro-autophagy, endosomal micro-autophagy or chaperone-mediated autophagy. After internalization, the HIV-1 virus antigens can be enclosed in vesicles called endosomes. There are three compartments involved in this antigen presentation pathway: early endosomes, late endosomes or endolysosomes and lysosomes, where the HIV-1 virus antigens can be hydrolyzed by lysosome-associated enzymes (acid-dependent hydrolases, glycosidases, proteases, lipases). This process is favored by gradual reduction of the pH. The main proteases in endosomes are cathepsins and the result is the degradation of the antigens into oligopeptides.

3. Produce the Innate immune memory to HIV-1 virus (Pharmacology):

- Innate immune memory - https://en.wikipedia.org/wiki/Immunological_memory

Trained Immunity is also Innate Immune Memory for unspecific. Innate immune memory (trained immunity) is defined as a long-term functional reprogramming of innate immune cells evoked by exogenous or endogenous insults and leading to an altered response towards a second challenge after returning to a non-activated state. When innate immune cells receive an activation signal, for example, through recognition of BCG with Pattern recognition receptors (PRRs), they start the expression of proinflammatory genes, initiate an inflammatory response, and undergo epigenetic reprogramming. After the second stimulation, the transcription activation is faster and more robust. Innate immunological memory was reported in monocytes, macrophages, and some others, changing their epigenetic state and respond differently after priming insult. Additionally, cellular metabolism doesn't return to the state before stimulation, and trained cells remain in a prepared state. This status can last from weeks to several months and can be transmitted into daughter cells. Secondary stimulation induces a new response, which is faster and stronger. The secondary response may be heightened not only against the training pathogen, but also against different pathogens (Multiple HIV-1 Virus Strains) whose antigens can be recognized by the same PRRs.

4. Produce the Type IV hypersensitivity as side effect risk (Toxicology)

- Type IV hypersensitivity - https://en.wikipedia.org/wiki/Type_IV_hypersensitivity

Type IV hypersensitivity, often called delayed-type hypersensitivity, is a type of hypersensitivity reaction that takes several days to develop. It is a type of cell-mediated response. This response involves the interaction of T cells, monocytes, and macrophages. This reaction is caused when CD4+ Th1 cells recognize foreign antigen **(including HIV-1 protein antigen mix BCG)** in a complex with MHC class II on the surface of antigen-presenting cells. These can be macrophages that secrete IL-12, HIV-1 which stimulates the proliferation of further CD4+ Th1 cells. CD4+ T cells secrete IL-2 and interferon gamma (IFN-γ), inducing the further release of other Th1 cytokines, thus mediating the immune response. Activated macrophages produce hydrolytic enzymes and, on presentation with certain intracellular pathogens, transform into multinucleated giant cells. The overreaction of the helper T cells and overproduction of cytokines damage tissues, cause inflammation, and cell death. An example of a tuberculosis (TB) infection that comes under control: M. tuberculosis organisms are engulfed by macrophages after being identified as foreign pathogens, but due to an immuno-escape mechanism peculiar to mycobacteria, TB bacteria are able to block the fusion of their enclosing phagosomes with lysosomes which would destroy TB bacteria. Thereby TB organisms can continue to replicate within macrophages. After several weeks, the immune system ramps up and, on stimulation with IFN-gamma, the macrophages become capable of killing M. tuberculosis organisms by forming phagolysosomes and nitric oxide radicals. The hyper-activated macrophages secrete TNF-α which recruits multiple monocytes to the site of infection. These monocyte-macrophage system cells differentiate into epithelioid cells which wall off the infected cells but result in significant inflammation and local damage. **BCG can produce similar but lighter damage.** Type IV hypersensitivity can usually be resolved with trigger avoidance. In the IND 179135 Phase 1 clinical investigation NCT07182838, **TB negative participant is negative IGRA blood test with TB antigens.**

(*b*) the indication(s) to be studied.

The indications for HIV-1 gp160 Protein plus BCG Vaccine Mix for Percutaneous Use to treat Infection of Multiple HIV-1 Virus Strains like as following:

1. Treat infection of multiple HIV-1 virus strains.
2. Activate human trained immunity reaction via the pattern recognition receptors (PRRs) of immune cells litigated with HIV-1 protein antigens.

3. Activate human HIV-1 protein antigen presentation reaction.
4. The human antigen presenting cells (APCs) treat HIV-1 virus target protein antigen into small peptide fragments, and then clear HIV-1 virus in vivo.
5. BCG activate APCs presenting HIV-1 virus antigens to Memory T Cells and the Trained Immunity is also Innate Immune Memory.
6. The secondary response of trained immunity may be heightened not only against the training pathogen, but also against different pathogens (Multiple HIV-1 Virus Strains) whose antigens can be recognized by the same PRRs.

(*c*) the general approach to be followed in evaluating the drug; …

My investigation will use commercially available lawfully marketed prescription biological products by US Pharmacy as follows:

https://www.antibodies-online.com/
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Catalog No. ABIN1111556
0.1 mg x 1mL
ANTIBODIES-ONLINE INC.

Before 5 minutes for the percutaneous route with the multiple puncture device, above biologic will be added into following biologic:

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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.

- **Study Type:** Interventional
- **Primary Purpose:** Treatment
- **Study Phase:** Phase 1 / Clinical Biological Pharmacology
- **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 HIV-1 Infection Patients with controlled cancers
  - ✓ Positive testing HIV-1 by standard PCR assay
  - ✓ HIV-1 infection without symptoms
  - ✓ TB negative participant is negative IGRA blood test with TB antigens.
- **Dose:** HIV-1 gp160 Protein 0.1 mg x 1.0 mL plus BCG Vaccine 50 MG Mix
- **Route:** Percutaneous Use with Multiple Puncture Device
- **Duration:** Our trial duration will be 4 weeks.
- **Endpoint:** Negative testing HIV-1 by standard PCR assay after percutaneous use 21 days.

(*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate);

Our planned duration will be 4 weeks.

(*e*) the estimated number of patients to be given the drug in those studies; and

20 HIV-1 Infection Patients with controlled cancer [Positive testing by standard PCR assay]

(*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

- **The safety exclusions:**
  - ✧ Pregnant
  - ✧ Thrombosis
  - ✧ Allergy
  - ✧ TB positive participant is positive IGRA blood test with TB antigens.
  - ✧ AIDS Symptoms
  - ✧ Clinical signs suggestive of other infection
  - ✧ Symptoms suggestive of other infection
  - ✧ Evidence of critical illness

BCG should **not** be given to individuals previously infected with M. tuberculosis. A person will give the IGRA blood test with TB antigens. TB patients who are positive on the IGRA blood test with TB antigens **cannot** participate.

Type IV hypersensitivity, often called delayed-type hypersensitivity, is a type of hypersensitivity reaction that takes several days to develop. It is a type of cell-mediated response. This reaction can be caused by antigen-presenting cells. These monocyte-macrophage system cells differentiate into epithelioid cells which wall off the infected cells but result in significant inflammation and local damage. **BCG can produce similar but lighter damage.**

Table of procedures …… (including Statistical Analysis Plan)

Procedure	**Online Enrollment**	**V 1 M 1 W 1 D 1**	**V 2 M 1 W 1 D 3**	**V 3 M 1 W 4 D 3**	**M 1 W 4 D 5**	**Online Notification**	**V 4 M 2**	**V 5 M 3**
Medical history *	√	√	√	√	√	√	√	√
Test HIV by standard PCR **		√		√		√		
IGRA blood test with TB antigens ***		√		√		√		
IGRA blood test with HIV GP160 antigens ****				√		√		
Review Results			√		√	√		
Biological Product Mix (Percutaneous Use)			√			√		
Online Interview & Online Questionnaire For every day in 3 months	√	√	√	√	√	√	√	√

* This includes online reporting on symptoms every day for up to 30 days.

** Test HIV by standard PCR assay.

*** BCG should not be given to individuals previously infected with M. tuberculosis. A person will give the IGRA blood test with TB antigens. TB patients who are positive on the IGRA blood test with TB antigens cannot participate.

**** Take testing IGRA blood test with 1/10 Dose HIV gp160 protein antigens.

Expected Results:

1. **Biological Product Mix for Percutaneous Use:** HIV gp160 Protein 0.1 mg x 1.0 mL plus BCG Vaccine 50 MG
2. Positive HIV testing by standard PCR before Biological Product Mix by Percutaneous Use
3. Negative HIV testing by standard PCR after Biological Product Mix by Percutaneous Use 21 days
   --- Activate human HIV virus antigen-presentation and treat HIV antigen into small peptide fragments
   --- Clear human HIV virus in vivo
4. Negative IGRA blood test with TB antigens before Biological Product Mix by Percutaneous Use
5. Positive IGRA blood test with TB antigens after Biological Product Mix by Percutaneous Use 21 days
6. **Positive IGRA blood test with HIV GP160 antigens** after Biological Product Mix by Percutaneous Use 21 days
   --- Activate human trained immunity i.e. innate immune memory

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

Sponsor (**Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator)** does **not** transfer any obligations for the conduct of any clinical study to a Contract Research Organization (CRO).

The Institutional Review Board (IRB) will be to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. My investigation will be conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50). Our IRB's review of the investigator's qualifications or the sponsor's qualifications, including any institutional requirements for sponsor-investigator studies, will surely abide by 21 CFR Part 56 and 21 CFR Part 50. After ***IRB approval,*** an IND covering the investigations will be **in effect**.

21 CFR § 50.3 (f)
I (sponsor-investigator) will actually conduct, with online referral clinical investigators, the clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

21 CFR § 56.102 (k)
I (sponsor-investigator) will actually conduct, with online referral clinical investigators, the clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

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

- NPI 1831468511 - Individual
  - Clinical Ethicist - (Code - 174V00000X)
  - Specialist Research Study - (Code - 1744R1102X)
  - Pharmacist Clinician (PhC) / Clinical Pharmacy Specialist (Code - 1835P0018X)
- **Medicine Invention Design Incorporation (MIDI) (IORG0007849) ---** IORG Director (IORG0007849)
- **Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424) ---** IRB Chair (IRB00009424)
- **Federal-wide Assurance (FWA) for the Protection of Human Subjects (FWA00015357)**
  - Human Subjects Administrator (FWA00015357)
- NPI 1023387701 - Organization
  - Multi-Specialty Group (Code - 193200000X)
  - Research Clinic/Center - (Code - 261QR1100X)
  - Clinical Medical Laboratory - (Code - 291U00000X)
  - **Health Maintenance Organization - (Code - 302R00000X) ---** Medical Director (D11379922)
  - Managed Care Organization Pharmacy (Code - 3336M0003X)
  - Mail Order Pharmacy - (Code - 3336M0002X)
  - FDA Wholesale Drug Distributor **(Maryland License Number: D11379922)** --- Medical Director (D11379922)
  - Distribute human drug products under own private label **(FDA NDC Labeler Code - 69891)**
  - FDA Establishment Identifier (FEI Number - 300363713)
- FDA Pre-Assignment application - My IND has been granted. My pre-assigned number is IND 179135.
  - Individual Sponsor: HAN XU
  - Organization Sponsor: Medicine Invention Design Incorporation
- **ClinicalTrials.gov ID: NCT07182838** under **42 CFR Part 11**
  - Responsible Party: **Sponsor-Investigator:** Han Xu, M.D., Ph.D., FAPCR
  - Study Principal Investigator [**Principal Investigator (PI)**]: Han Xu, M.D., Ph.D., FAPCR
  - Study Director (**Medical Director**): Han Xu, M.D., Ph.D., FAPCR
  - Study Chair (**IRB Chair**): Han Xu, M.D., Ph.D., FAPCR