Cover Page

Release Date: March 11, 2022

ClinicalTrials.gov ID: NCT02403505

Unique Protocol ID: IND 28299

Brief Title: Early Phase Clinical Trial About Therapeutic Biological Product Mix for Treating COVID-19 (AD26-BCG)

Official Title: Conducting an Early Phase Clinical Trial to Assess for COVID-19 Antigen Presentation Therapeutic Biological Product Mix Activity That Suggests the Potential for Clinical Benefits of COVID-19 Patients.

Secondary IDs: FWA00015357 [Registry ID: Federal-wide Assurance (FWA) DHHS OHRP]
IORG0007849 [Registry ID: Institution or Organization (IORG) DHHS OHRP]
IRB00009424 [Registry ID: Institutional Review Board (IRB) DHHS OHRP]
IND28299 [Registry ID: Investigational New Drug Application (IND) FDA]
NDA217392 [Registry ID: New Drug Application (NDA) FDA]
BLA761321 [Registry ID: Biologics License Applications (BLA) FDA]

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

Contents

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.

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 Lighter Than Mild COVID-19 Patients
- **A description of safety exclusions:**
  - ✓ PPD positive participant is 10 TU skin test reading > 5 mm induration at 48 hours
  - ✓ Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
  - ✓ Clinical signs suggestive of moderate illness with COVID-19
  - ✓ Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
  - ✓ Clinical signs indicative of severe systemic illness with COVID-19
  - ✓ Evidence of critical illness
  - ✓ Respiratory failure
  - ✓ Shock
  - ✓ Multi-organ dysfunction / failure
- **A description of the dosing plan for duration:**
  - ✓ Our trial duration will be 4-week duration
- **A description of the dosing plan for dose:**
  - ✓ Ad26 COVID-19 Spike Organism 1.0 mL plus Merck TICE® BCG Organism 50 MG Mix
- **A description of the dosing plan for method to be used in determining dose:**
  - ✓ **LABEL:** JANSSEN COVID-19 VACCINE - ad26.cov2.s injection, suspension
    NDC *59676-580-15*
    Packager: *Janssen Products, LP*
  - ✓ **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:**
    - ✓ PPD positive participant is 10 TU skin test reading > 5 mm induration at 48 hours

- ✓ Clinical signs indicative of moderate severity
- ✓ Clinical signs indicative of severe severity
- ✓ Clinical signs indicative of critical severity

➢ **The necessary monitoring of blood chemistries:** Blood Saturation of Oxygen (SpO2)

(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 Gene Mutation COVID-19 Virus Strains.
2. Activate human COVID-19 Antigen Presentation Reaction.
3. The human antigen presenting cells (APCs) can treat the COVID-19 virus antigens into small peptide fragments, and then kill COVID-19 virus directly.

(*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 subinvestigator (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, IORG 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, IORG Director
Health Care Provider - Individual (NPI - 1831468511)
The address of investigator: (Virtual / Mobile / Telehealth / Telemedicine)
➢ 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, IORG Director
- ➢ **The address of the investigator: (Virtual / Mobile / Telehealth / Telemedicine)**
- ✓ 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, IORG Director
- ✓ Health Care Provider - Individual (NPI - 1831468511)
- ✓ Health Care Provider - Research Clinic/Center (Code - 261QR1100X)
- ✓ ClinicalTrials.gov ID: NCT02403505

(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 - Research Clinic/Center (Code - 261QR1100X)

- **The address of research facility: (Virtual / Mobile / Online)**
  - ✓ 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: (Virtual / Mobile / Online)**
  - ✓ 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: (Virtual / Mobile / Online)**
  - ✓ 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;

21 § 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the **requirements** *contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.*

(*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 (NCT02403505) 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;

21 CFR § 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator **(Han Xu, M.D. Ph.D., FAPCR)**, the Food and Drug Administration should waive any of the requirements contained in these regulations, including the requirements for IRB (IRB00009424) review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

(*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 (NCT02403505) 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.

21 CFR § 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB (IRB00009424) review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Commitment

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

On the application of a sponsor or sponsor-investigator **(Han Xu, M.D., Ph.D., FAPCR)**, the Food and Drug Administration should waive any of the requirements contained in these regulations, including the requirements for IRB (IRB00009424) review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

(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

(*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:

- ✓ Lighter Than Mild COVID-19 Patients
- ✓ Positive testing COVID-19 by standard RT-PCR assay
- ✓ COVID-19 infection without symptoms
- ✓ Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea
- ✓ No clinical signs indicative of Moderate, Severe, or Critical Severity
- ✓ PPD negative participant is 10 TU skin test reading < 5 mm induration at 48 hours.

The criteria for patient exclusion:

- ✓ PPD positive participant is 10 TU skin test reading > 5 mm induration at 48 hours
- ✓ Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- ✓ Clinical signs suggestive of moderate illness with COVID-19
- ✓ Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- ✓ Clinical signs indicative of severe systemic illness with COVID-19
- ✓ Evidence of critical illness
- ✓ Respiratory failure
- ✓ Shock
- ✓ Multi-organ dysfunction / failure

(*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:** Early 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 Lighter Than Mild COVID-19 Patients
  - ✓ Positive testing COVID-19 by standard RT-PCR assay
  - ✓ COVID-19 infection without symptoms
  - ✓ Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea
  - ✓ No clinical signs indicative of Moderate, Severe, or Critical Severity
  - ✓ PPD negative participant is 10 TU skin test reading < 5 mm induration at 48 hours.

- **Dose:** Janssen Ad26 COVID-19 Spike Organism 1.0 mL plus Merck TICE® BCG Organism 50 MG Mix
- **Route:** Intradermic Injection, ID
- **Duration:** Our trial duration will be 4-week duration.
- **Endpoint:** Negative testing COVID-19 by standard RT-PCR assay after injection 2 weeks.

(*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.

- ✓ **LABEL:** JANSSEN COVID-19 VACCINE - ad26.cov2.s injection, suspension
  NDC *59676-580-15*
  Packager: *Janssen Products, LP*
- ✓ **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.*
- **Dose:** Janssen Ad26 COVID-19 Spike Organism 1.0 mL plus Merck TICE® BCG Organism 50 MG Mix
- **Route:** Intradermic Injection, ID
- **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.

- **Endpoint:** Negative testing COVID-19 by standard RT-PCR assay after injection 2 weeks.

(*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 COVID-19 by standard RT-PCR assay after injection 2 weeks.
- BCG should **not** be given to individuals previously infected with M. tuberculosis. A person given the tuberculin skin test [10 tuberculin units (10 TU) purified protein derivative (PPD)] must return within 48 hours. The positive is skin test reading > 5 mm induration at 48 hours.

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, IORG Director
Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair, IORG Director
Health Care Provider - Individual (NPI - 1831468511)
Health Care Provider - Clinical Ethicist (Code - 174V00000X)
Health Care Provider - Research Study Specialist (Code - 1744R1102X)
Health Care Provider - Clinical Pharmacology (208U00000X)
Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424)
Medicine Invention Design Incorporation (IORG0007849)
Medicine Invention Design Incorporation (FWA00015357)
Health Care Provider - Group/Organization (NPI - 1023387701)
Health Care Provider - Research Clinic/Center (Code - 261QR1100X)
Health Care Provider - Clinical Medical Laboratory (Code - 291U00000X)

Mail: 5545 Burnside Drive, Rockville, MD 20853
Call: 301-222-7143
Fax: 866-458-0099
E-mail: hanxumd@gmail.com

Ad26 COVID-19 Spike plus TICE® BCG Mix for Intradermal Injection to treat COVID-19 Infection

Active Ingredients:

DailyMed - https://dailymed.nlm.nih.gov/dailymed/
LABEL: JANSSEN COVID-19 VACCINE - ad26.cov2.s injection, suspension
NDC *59676-580-15*
Packager: Janssen Products, LP
The replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein is grown in PER.C6 TetR cells, after propagation, the Ad26 COVID-19 Spike virus particles (VP) are processed purification.

- JANSSEN Ad26 COVID-19 Spike organism
- Each 0.5 mL dose is formulated to contain 5×10^10 Ad26 COVID-19 Spike virus particles (VP) X 2
- Janssen Ad26 COVID-19 Spike organism 1 mL

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 the 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

The mechanism of action of Janssen Ad26 COVID-19 Spike organism plus Merck TICE® BCG organism Mix to treat Infection of Multiple Gene Mutation COVID-19 Virus Strains like as following:

- Trained immunity - https://en.wikipedia.org/wiki/Trained_immunity
- Antigen presentation - https://en.wikipedia.org/wiki/Antigen_presentation
- Type IV hypersensitivity - https://en.wikipedia.org/wiki/Type_IV_hypersensitivity
- Immunological memory - https://en.wikipedia.org/wiki/Immunological_memory

The indications for Ad26 COVID-19 Spike plus TICE® BCG Mix for Intradermal Injection to treat Infection of Multiple Gene Mutation COVID-19 Virus Strains via following three processes: 1. Trained Immunity. 2. Antigen Presentation Therapy (**It is Key**). 3. Delayed Type Hypersensitivity (DTH) Memory.

1. Trained Immunity: BCG activate monocytes and macrophages, COVID-19 virus antigens ligate the pattern recognition receptors (PRRs) of the monocytes and macrophages can undergo epigenetic modifications. The trained immunity is mediated mostly by epigenetic modifications, i.e., alterations in gene expression and cellular function without changes to the original DNA sequence, at monocytes and macrophages.

2. Antigen Presentation Therapy: It is Key. BCG can activate macrophages, a kind of antigen presenting cells (APCs), treat COVID-19 virus antigen into small peptide fragments, and then kill COVID-19 virus directly.

3. Delayed Type Hypersensitivity (DTH) Memory: BCG can activate APCs. DTH reaction to COVID-19 virus is caused when CD4+ Th1 cells recognize COVID-19 virus antigen in complex with MHC II on the surface of APCs. BCG activate macrophages to stimulate CD4+ Th1 cells mediating DTH immune response. BCG activate APCs presenting COVID-19 virus antigens to Memory T Cells and Trained Immunity is also Innate Immune Memory.

Ad26 COVID-19 Spike plus TICE® BCG Mix for Intradermal Injection

The biologics is administered percutaneously utilizing a sterile, single-use multiple puncture device. The multiple puncture device consists of a plastic holder for a thin, wafer-like stainless steel plate from which 36 points protrude (Figure 1). After the biologics is prepared, the skin site is cleansed with an alcohol or acetone sponge and allowed to dry thoroughly.

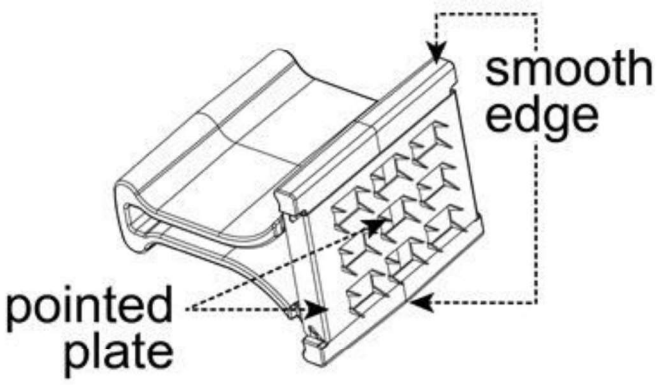

Figure 1

1. Administer the biologics in the deltoid region (Figure 2). Position the arm to maintain a horizontal surface where the biologics is to be placed.

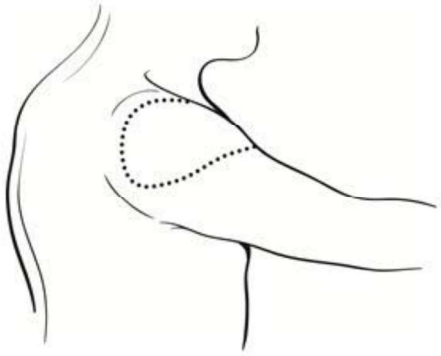

Figure 2

2. Drop the dose of 1 mL of the biologics from the syringe and needle onto the cleansed surface of the skin (Figure 3) and spread over a 1" by 2" area using the smooth edge of the multiple puncture device (Figure 4).

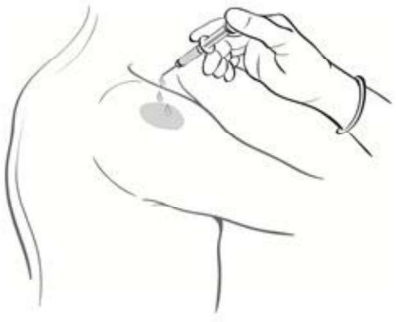

Figure 3

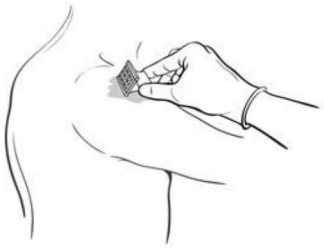

Figure 4

3. Grasp the arm firmly from underneath, tensing the skin. Center the multiple puncture device over the biologics and apply firm downward pressure such that the device points are well buried in the skin (Figure 5).

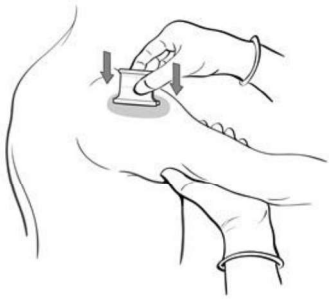

Figure 5

4. Maintain pressure for 5 seconds. Do not "rock" the device. Release the pressure underneath the arm and remove the device. In a successful procedure the points puncture the skin. If the points do not puncture the skin, the puncture procedure must be repeated.

5. After successful puncture, spread the biologics as evenly as possible over the puncture area with the smooth edge of the device (Figure 4). An additional 1–2 drops of the biologics may be added to ensure a very wet vaccination site.

6. Use the multiple puncture device once and discard in a standard biohazardous sharps container.

7. Loosely cover the site and keep dry for 24 hours.

8. Advise the patient that the biologics contains live organisms. Although the biologics will not survive in a dry state for long, infection of others is possible.

- BCG should not be given to individuals previously infected with M. tuberculosis.
- **The biologics can use <u>Needle-Free Jet Injector</u> or <u>Needle-Free Syringe</u>**