IRB Study Number: 20210641
Version #4, Date: October 26, 2021

Protocol Title: **A Single-Blind, Randomized, controlled trial comparing BNT162b2 vs JNJ-78436735 vaccine as a booster dose after completion of BNT162b2 vaccine in Solid Organ Transplant Recipients.**

Protocol Number: 20210641

Protocol Version number: 5

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1) **Objectives***

The purpose of this study is to investigate the efficacy of the vaccines as a booster dose for COVID-19 in solid organ transplant recipients. The aims and objectives of this study is to check the immunogenicity after booster dosing of adenovirus vector vs. mRNA vaccine as a third dose. We are also going to investigate the safety of the third dosing after completion of two doses of mRNA vaccine.

Hypothesis of this study:
Booster dosing with mRNA vaccine should result in a higher rate of immunogenicity, defined as positive IgG, as compared to Adenovirus vector vaccine in solid organ transplant recipients who completed two doses of mRNA vaccine series.

2) **Background***

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiology behind the coronavirus disease 2019 (COVID-19) worldwide pandemic, has resulted in significant mortality rates worldwide. Among immunocompromised hosts, such as solid organ transplant (SOT) recipients, several reports have indicated a significantly higher hospital admission rate and mortality[1,2]; hence the need to provide robust protection in this vulnerable population.

Since the beginning of the pandemic, several vaccines have been developed that have demonstrated a significant response in the general population in terms of immunogenicity and efficacy[3,4]. This has been developed to hopefully revolutionize the fight against the COVID-19 pandemic[5,6].
It is well known from prior studies that vaccine immunogenicity in other viruses, such as influenza, is diminished in SOT recipients due to immunosuppressive medications[7], as compared to general population. Thus, there have been several attempts to improve vaccine efficacy and/or immunogenicity in this special population, such as use of high dose vaccines[8] and boosted doses[9].
Even though a high efficacy of COVID-19 vaccines has been documented in the general population, there is some concern of low immunogenicity among SOT recipients of the SARS-CoV-2 vaccines[10]. At the same time, several reports have already documented breakthrough infection after vaccination in SOT recipients[11]. Thus, we need to develop a better way to protect this vulnerable population with an efficient vaccine strategy.
Already, there are several reports of increased immunogenicity with additional dosing of vaccination[12]. Randomized controlled trial comparing placebo vs. other mRNA vaccine as a booster dose study showed some benefit[13]. However, as of now, there is no comparison study between mRNA and adenovirus vector vaccine. This time, we are conducting single center randomized controlled trial comparing mRNA vs. Adenovirus vector vaccine as a third dose after completion of two doses of mRNA vaccine in solid organ transplant recipients.

3) Inclusion and Exclusion Criteria*

Inclusion Criteria:

- *Patients 18 years of age and older*
- *Patients who had received a solid organ (kidney, liver, lung, heart, and pancreas) transplant patient from living or deceased donors.*
- *Patients with active graft with at least one immunosuppressive medication*
- *Completed two doses of BNT162b2 vaccination at least 28 days ago*

Exclusion Criteria:

- *Patient with non-active graft*
- *Any significant side effect with previous COVID-19 vaccination*
- *Within 28 days of BNT162b2 vaccine completion*
- *Already received more than and equal to three doses of COVID-19 vaccination*
- *Previously received COVID-19 vaccine other than BNT162b2 vaccine*
- *Previously received monoclonal Antibody treatment that are specifically directed against the spike protein for SARS-CoV-2 such as Mab, Bamlanivimab, etesevimab, Casirivimab, imdevimab, Sotrovimab and/or any combination.*

- *Thrombocytopenia (listed as a medical diagnosis or less than 50,000 per microliter 30 days prior vaccination)*
- *History of Capillary Leak Syndrome*
- *Adults unable to consent*
- *Individuals who are not yet adults (younger than 18 year old)*
- *Vulnerable patients (prisoners)*
- *Pregnant women*

4) **Evaluation**

Evaluation will be conducted as below schedule.

Procedures	Screening	Enrollment/Baseline Visit 1, Day 1	Phone Call Visit 2 48-96 hours	Phone Call Visit 3 6-8 days	Study Visit 4 Day 28 +/-7 day	Study Visit 5 Month 6 (+/-7 days)	Study Visit for Sub study only At Month 6 (+/- 30 days)
Informed consent	X	X					
Demographics	X	X					
Medical history	X	X					
Randomization	X	X					
Blood sample collection		X			X		X*
Vaccine Administration		X					
Symptom checker		X	X	X	X		
Phone call follow up			X	X	X	X	

* 50 optional participants only

Blood samples will be obtained from all patients at the time of enrollment (Day 1) and day 28 to test IgG and IgM against SARS-CoV-2 spike protein.

At month 6, 50 optional patients will join to participate in the sub-study which will consist of blood sample collection to measure long term immunogenicity (IgG and IgM).

5) **Sample Size calculation**

The primary outcome of this study is IgG positivity after 28 (21-35) days of the booster dose of the either vaccine. This IgG should be antibody against spike protein, and reported as RBD, measured by Dr. Pallikuh's lab. We put alfa of 0.05 and beta of 0.2. The IgG positivity in JNJ-78436735 should be assumed as 80% and BNT162b2 as 60%.

6) **Number of Subjects***

The Number needed in this study should be 93 per one arm, which is 186 in total. We assume 5-10% follow-up lost so we are going to enroll 200 patients in total.
For sub study to measure long term immunogenicity, we will enroll 50 patients among 200 participants.
The participants will be contacted via phone call in 6 months for monitoring.

7) **Description of the study**

This is the patient-blinded randomized controlled trial. To monitor patient reporting side effect properly, we are going to conduct the patient-blinded. Study team member will be aware after randomization, at the time of giving vaccination. This is not observer blinded. Also, to minimize bias, Dr. Pallikuh lab members will not be notified which vaccine each participant receives. Randomization will be conducted via excel by Dr. Natori. Adult transplant recipients will be recruited from outpatient clinics. Transplant patients will be randomized in a 1:1 ratio.

8) **Randomization of vaccine**

A randomization schedule will be created using Microsoft Excel. Dr. Natori will randomly select 100 numbers out of 200 using excel. The selected number patients will receive JNJ-78436735 vaccine. The rest will receive BNT162b2 vaccine. Those randomized result will put into 200 envelopes. On top of each envelope, only study ID, from 001 to 200, will be written. The envelope will be filed in each patient's research chart. Charts will be located at the research office located at the Elliot Building. Only the study team will have access to the building.

After obtaining consent, study team member, other than Dr. Natori, will open the envelope to identify which vaccine to give. Each participant should be randomized and will receive one time dosing of either JNJ-78436735 or BNT162b2. After vaccination, those patients will need to stay Miami Transplant Institute outpatient clinic waiting area for 15minutes (+/- 2 minutes) to be monitored.

9) **Discontinuation of patients:**

- Patients may be discontinued under the following circumstances:
- A patient desire for discontinuation for any reason

- Lost to follow up (every effort must be made to contact the patient)
- Death
- An Investigator's opinion that continuing the patient in the study is not appropriate

10) **Study Timelines***

After consent is obtained, the blood draw for all patients will be done at the outpatient clinic phlebotomy room. After that, the participants will receive either vaccine. After vaccination, those patients will stay in the clinic for 15mins and if they have any symptoms, those patients will notify the research team. In the event of any severe reaction, the principal investigator will be notified immediately. Medical intervention will be address based on each case.

On visit 2, 48-96 hours after administration of the vaccine, the research team will call the patient to collect the side effect information. Again, visit 3, 6-8 days after enrollment, the research team will call the patient to collect side effect information. The participants will be back to the Miami Transplant Institute outpatient clinic in 28 (21-35) days from enrollment for follow-up blood collection. Upon follow up blood collection, the study team will ask the patient if they develop any symptoms after booster dosing.

We will also collect the blood test at 6 months (20-28 weeks) time period for those who are enrolled in the sub-study (50 patients will be enrolled)

11) **Study Endpoints***

Primary endpoint is the anti-spike protein of SARS-CoV-2 virus IgG positive rate in one month after vaccination. Secondary endpoint includes the incidence rate of COVID-19 and the severity of COVID-19.

Safety endpoints includes side effect (i.e. pain at injection site, size of indwelling, fever, fatigue, and joint pain) at day 2 and 7 after vaccination. We also follow up to 6 months for any symptoms. This could also be gathered from the Jackson Health System medical record.

12) **Procedures Involved***

This is a single center single blinded (patient blinded) randomized controlled trial comparing BNT162b2 and JNJ-78436735vaccine as a third dose after completion of two doses of BNT162b2 vaccine in Solid Organ Transplant Recipients.

Once informed consent is obtained , 10 ml of blood from the participants will be obtained at day 0 and day 28(21-35) to monitor IgG and IgM against SARS-CoV-2 spike protein. Then, a Jackson transplant nurse and/or medical assistant will intramuscularly inject either vaccine to the participants. The source of clinical information will be collected through Jackson Health System electronical medical record.

Blood test will be analyzed Dr. Pallikuh's lab in University of Miami.

As an optional sub study for 50 participants, we will collect 10 ml of blood again at 6months (20-28 weeks) time to monitor IgG and IgM.

After vaccination, those patients will need to stay Miami Transplant Institute outpatient clinic waiting area for 15minutes (+/- 2 minutes) to be monitored.

Unblinding Process:

The vaccine given at the time of enrollment will be unblinded upon patient's request at Day 28. However, if an emergency, the vaccine will be unblinded immediately for the patient.

A potential early unblinding event could occur if the patient's healthcare provider, including Jackson, provides the vaccine records from Florida Shot.

However, the early unblinding event should only affect the study secondary outcomes and will not affect primary outcome, i.e. serology data.

13) **Data and Specimen Banking***

Blood specimen will be stored in Dr. Pallikuh's lab for 5 years. For sub-study, we will also obtain PBMC and this should also be stored in 5 years. Only the research team member will have an access to those specimen.

For clinical data, we will use a unique ID for each patient that does not include or derive from any identifiers. Miami Transplant Institute will retain the key to these IDs subject to local IRB review.

14) **Data Management***

1.1.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data for electronic CRFs will be entered into Velos. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Velos, a HIPAA AND 21 CFR Part 11-compliant data capture system provided by the University of Miami. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study Records Retention

All records and documents relating to research studies and participants must be kept confidential to the extent permitted by law; however, records and documents shall be available in a timely manner to the University authorized employees or other agents authorized by the University including IRB members and HSRO staff and appropriate governmental agencies including but not limited to DHHS, OHRP and the FDA.

Although principal investigators are responsible for the creation and maintenance of research records and documents, such records and documents (including data collected pursuant to research) are the property of the University. Until the temporal requirements for record/document retention are met, investigators or others may not remove or destroy research records or documents (or copies of such records or documents) without written permission from the Vice Provost of Research. This permission requirement extends to investigators leaving the University even if they plan to continue the research at another institution.

The sample size was based on previous studies, which had indicated a response rate of approximately 50% and 70% to each vaccine.

Therefore, for an alpha of 0.05 and a power of 80%, a sample size of 93 evaluable patients in each study group should be required. As we assume 10% of the patients will not be back, we have that margin and going to enroll 200 patients in total. The immunogenicity analysis will be only performed in those who received a vaccine dose and returned for follow-up serum (per-protocol population). The safety analysis will be performed in all patients who received the study vaccine regardless of whether they returned for follow-up serum. Demographics will be analyzed using descriptive statistics. Differences in vaccine response rates between the 2 arms will be compared using $\chi 2$ test. Pre- and post-vaccination titers will be compared using Wilcoxon rank-sum test. Univariate analyses will be performed to determine significant factors affecting seroconversion using $\chi 2$ test for categorical variables and Mann-Whitney U test for continuous variables. We will develop multivariate model to determine the factor of positive IgG post booster dosing. For multivariate analysis, a model should be developed using variables that had a P value < 0.2 on univariate analysis. Multivariate analysis will be performed using

binary logistic regression. Statistical significance was defined as a P value < 0.05. Statistical analysis will be performed using IBM SPSS version 26.0.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects*

Study Auditing and Monitoring

This study will be monitored (as applicable) and may be audited according to the University of Miami requirements. See also http://research.med.miami.edu/clinical-research/crors/monitoring

Clinical Research Operations & Regulatory Support CRORS will provide internal study monitoring compliance. Following the monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by, government regulatory authorities, of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities.

Quality Assurance and Quality Control

In addition to the Clinical Monitoring component of this protocol, Quality Assurance (QA) will be implemented to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

Publication and Data Sharing

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The financial disclosure information will be completed prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.
The Sponsor-Investigator will register the trial on www.clinicaltrials.gov. In addition, Sponsor-Investigator will publish the results of the trial.

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16) **Risks to Subjects***

COVID-19 vaccination itself is routine practice at our institution however this study includes additional dosing. The major risk would be immediate local and systemic reactions. The third dose is not well assessed yet even in general population so difficult to foresee. However, given immunosuppressive state of the patients, these side effect, which is due to immune reaction, should be low.

RISK OF BLOOD DRAW
Risks and discomforts associated with having a needle placed in your arm for blood sampling include pain, bruising or bleeding at the puncture site, temporary light-headedness, and in rare cases, fainting or site infection. If faintness is felt, you should lie down as soon as possible to avoid possible injury caused by falling and tell study staff.

WHAT ARE THE RISKS OF THE JANSSEN COVID-19 VACCINE?

Side effects that have been reported with the Janssen COVID-19 Vaccine include:

• Injection site reactions: pain, redness of the skin and swelling.

• General side effects: headache, feeling very tired, muscle aches, nausea, and fever.

There is a remote chance that the Janssen COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Janssen COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

• Difficulty breathing,

• Swelling of your face and throat,

• A fast heartbeat,

• A bad rash all over your body,

• Dizziness and weakness.

These may not be all the possible side effects of the Janssen COVID-19 Vaccine. Serious and unexpected effects may occur. The Janssen COVID-19 Vaccine is still being studied in clinical trials.

WHAT ARE THE RISKS OF THE PFIZER-BIONTECH COVID-19 VACCINE?
There is a remote chance that the Pfizer-BioNTech COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Pfizer-BioNTech COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Dizziness and weakness

Side effects that have been reported with the Pfizer-BioNTech COVID-19 Vaccine include:

- severe allergic reactions
- non-severe allergic reactions such as rash, itching, hives, or swelling of the face
- injection site pain
- tiredness
- headache
- muscle pain
- chills
- joint pain
- fever
- injection site swelling
- injection site redness
- nausea
- feeling unwell
- swollen lymph nodes (lymphadenopathy)
-
- diarrhea
- vomiting
- arm pain

17) **Potential Benefits to Subjects***

The results of this trial have the potential for immediate knowledge translation and could lead to early and tangible benefits for transplant patients. If our hypothesis is correct and the novel booster vaccine strategy is safe and effective, it could even be implemented for transplant patients. In addition, the results could signal a paradigm shift for vaccination strategies in other populations of immunocompromised patients and lay the groundwork for future similar studies in these groups. Since this will be the largest yet reported sample size to assess this, the results will alleviate fears among some transplant physicians and improve vaccine uptake.

18) **Sharing of Results with Subjects***

The laboratory result will be requested directly to the principal investigator. The results will be shared with the patient at the end of the study period.

19) **Setting**

- *Research will be done at the following locations:*

- *1. MTI Highland Professional building (Clinic) 1801 NW 9th Ave*
- *2. Jackson Memorial Hospital 1611 NW 12 Ave Miami, FL 33136*

20) **Resources Available**

This study will be overseen by Doctor Yoichiro Natori, Shweta Anjan, and Giselle Guerra. They are physicians managing the care of solid organ transplant patients at the Miami Transplant Institute.

The research office consists of five research coordinators.

All of them have more than three years' experience conducting transplant clinical studies. Besides the extended experience, coordinators attend Research Compliance and Quality Assurance training frequently.

21) **Recruitment Methods**

Principal Investigator and/or co-investigators will review medical records to assess if subject can be consented. Assessment will be done during regular clinic evaluation.

Transplant care provider will refer those patients during their clinical visits and notify the investigators. Investigators will evaluate their patients. If patient is a good candidate, then they discuss the study purpose, procedures, benefits and risks.

If patient agrees, an informed consent form will be signed.

Bilingual staff will approach to our Spanish-speaking patients to inform patients about the study.

Flyer will be posted in the MTI clinics as well as that, all MTI transplant physicians will be aware of this study prior to initiation.

22) **Confidentiality**

Data will be stored in an electronic password protected database. Patient will be identified with a study number and it will be linked to the subject's JHS MRN. This will be kept in a separate location and locked in the research office.

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Choose the statements below that are applicable to this research:

26(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☒ Yes (If checked go to 26(b))

☐ No (If checked, go to Section 27)

26(b). Check the box next to the correct statement below

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB. *(If checked, complete Section 17 below)*

26(c). How will the research store the data? *(See Section 26(e) below)*

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☐ On a cloud-based storage system that is approved by the University of Miami

☒ On the secured JHS SharePoint environment *(required for protected health information or identifiable information collected from JHS records without a waiver of authorization from an IRB.)*

☐ Other, specify: Click here to enter text.

26(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed in the instructions for Section 26 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

26(e) Additional requirement for Jackson Health System Data:

☐ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☒ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and

the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

27. Biospecimens

☐ Not applicable. No biospecimens will be collected

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☒ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

23) **Compensation for Research-Related Injury**

If the patient gets sick because of being in this study, treatment will be available in most cases. The patient's insurance may or may not pay for these costs. If the patient have insurance, or if the patient's insurance company refuses to pay, patient will need to pay.

24) **Consent Process**

Informed consent will be obtained from subjects who are willing to participate in the study. The study team will approach to potential subjects during clinical visits. Clinical visits are done at Highland Professional Building. Participants will be given sufficient time to consider taking part in the study. They may take home a consent tor review. Due to our population, Spanish speaking subjects will also be enrolled in the study. All research coordinators are bilingual and they will approach to these subjects. Prior consenting, all ICFs will be translated by the certified translator and approval will be obtained from the IRB.

Process to Document Consent in Writing Consents are included with this submission.

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25) **Authorization for Use and Disclosure of Protected Health Information (HIPAA)**

If the research team will access patient medical records or other identifiable health information for this research, you must obtain a waiver of the requirement for written authorization from the patients to access their medical records.

Type of Request:
☒ Waiver of Authorization for access to medical record for subject identification/recruitment.
☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.
☒ ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.
☒ ***I confirm***

If you are collecting health information from JHS under a waiver of authorization, you must read the paragraph below and sign the signature block to indicate your agreement:
☐ Not applicable. This research will not collect data from JHS record under a waiver of authorization

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

_____
PI Signature Date

26) **Drugs: Pfizer COVID-19 and Janssen COVID-19 Vaccines**

Both vaccines will be provided by the Jackson Health System through the Department of Health.

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EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 12 years of age and older.

*The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered **as a series of two** doses (0.3 mL each) 3 weeks apart.*

The FDA has authorized the emergency use of the Janssen COVID-19 Vaccine to prevent COVID-19 in individuals 18 years of age and older under an Emergency Use Authorization (EUA).

*The Janssen COVID-19 Vaccine is administered as a **single dose**, into the muscle*

Safety Reporting / AE / SAE Definition:

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

1.1.2 Relationship to Study Intervention

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes [Definite, Probable, Possible]

There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug or with similar treatments; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re- challenge.

No [Unrelated, Unlikely etc]

Evidence exists that the AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal

Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

1.1.3 Expectedness

The Sponsor-Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

1.1.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs will be captured on the appropriate case report form (CRF) as well as in the Adverse Event reporting section in Velos, a HIPAA AND 21 CFR part 11 compliant database and will be reported to the University of Miami's IRB per institutional requirements.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the

occurrence of AE/SAEs since the last visit. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject, including pregnancy occurring in the partner of a male study subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period. Events will be followed for outcome information until resolution or stabilization.

1.2 Adverse Event Reporting

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

The Sponsor-Investigator, is responsible for reporting adverse events (AEs) to any regulatory agency, to the Sponsor-Investigator's IRB and to the Investigational Drug Sponsor.

1.3 Serious Adverse Event Reporting

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Section 12.2, Definition of Serious Adverse Events.**

SAEs will be captured on the appropriate case report form (CRF) as well as in the Serious Adverse Event reporting section in Velos, a HIPAA AND 21 CFR part 11 compliant database and will be reported to the University of Miami's IRB per institutional requirements.

According to 21 CFR 312.32(c)(1), "the sponsor must notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting… In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

> (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
> (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

> (C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."

Furthermore, according to 21 CFR 312.32(c)(2), "the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

Serious Adverse Events
Serious criteria are applied by the Investigator to each AE as specifically defined below. These criteria are used to determine whether an AE is serious or non-serious. The assessment is made independently of severity assessment. For example, the development of a severe rash that occurs after signing of the ICF may not meet serious criteria as defined below and therefore would be considered a severe, non-serious AE.
Any AE that meets any 1 of the following 6 criteria is considered an SAE:
• The outcome of the AE is death
• The AE is immediately life threatening. Life threatening means that the patient is, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death
• The AE results in persistent or significant disability/incapacity. Disability means a substantial disruption of a person's ability to conduct normal life functions
• The AE requires or prolongs hospitalization Inpatient hospitalization is defined as any stay in the hospital of more than 24 hours, or any admission to a hospital ward or unit as an inpatient.
• The AE is an important medical event. Important medical events may meet serious criteria should the Investigator assess that they may significantly jeopardize the patient, represent a significant hazard, or require medical/surgical intervention.

As below, we will contact to the participants at 48-96 hours and 6-8 days after enrollment. At that time, we will collect below information.

Side effect(day2)
LOCAL
Erythema(y/n)
Induration(y/n)
Tenderness(y/n)

SYSTEMIC
Fever(defined as higher than and equal to 38.3 degrees Celsius)(y/n)
Gastrointestinal(diarrhea or nausea) (y/n)

Arthralgia(y/n)
Fatigue(y/n)
Muscle ache(y/n)

Side effect(day7)
LOCAL
Erythema(y/n)
Induration(y/n)
Tenderness(y/n)

SYSTEMIC
Fever(defined as higher than and equal to 38.3 degrees Celsius)(y/n)
Gastrointestinal(diarrhea or nausea) (y/n)
Arthralgia(y/n)
Fatigue(y/n)
Muscle ache(y/n)

Within 6months post vaccination
Hospitalization(y/n, reason for admission)
COVID-19(y/n, if yes, date of diagnosis, symptom at the time of diagnosis)
Rejection(y/n)(if yes, type of rejection, date)
CMV infection(y/n)
BK infection(y/n)

27) **Protocol Compliance**

The study team shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted, and that data are generated, documented, and reported in compliance with the protocol, ICH, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with the US Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95). The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate competent authority and IEC/IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be discontinued from the study and render that patient non evaluable.

28) **References**

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