

# Establishment Inspection Report

Jose F. Cardona, M.D.  
Hialeah, FL 33012

FEI: 3008031588  
EI Start: 11/10/2020  
EI End: 11/17/2020

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## SUMMARY (b) (6), (b) (7)(C)

This is a comprehensive FY 2021, High Priority, Surveillance, PDUFA, Clinical Investigator Inspection Assignment for IND # 19736 for an RNA-Based COVID-19 vaccine (BNT162). This inspection was conducted as requested by the Center for Biologics Evaluation and Research (CBER), Office of Compliance and Biologics Quality (OCBQ) under MARCS # 179758, and the assignment memorandum dated 10/21/20 (**Attachment # 2**). The assignment requested to conduct

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an inspection according to Compliance Program 7348.811, Bioresearch Monitoring Clinical Investigators and Sponsor-Investigators. The clinical study covered was Protocol C4591001 entitled, "A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study To Evaluate The Safety, Tolerability, Immunogenicity, And Efficacy Of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 In Healthy Adults," sponsored by Pfizer, Inc. located in Collegeville, PA and BioNTech RNA Pharmaceuticals GmbH, located in Mainz, Germany. We reviewed 127 subjects randomized in the protocol.

Dr. Jose F. Cardona has one previous FDA inspection, which closed in June 2019 and was classified as NAI and no FDA 483, Inspectional Observations, was issued.

The current inspection covered the authority and administration of the clinical trial, the protocol, the IRB documentation, subject records, financial disclosures, investigational product controls, and the monitoring of the study. The inspection included the review of all available relevant records as follows: informed consents, protocols, signed investigator agreements, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, clinical source data, study test article accountability, concomitant medication, subject diaries, and sponsor monitoring activities.

The following are the subject numbers:

- Screened: 643
- Randomized: 611
- Screen Failed: 32
- Completed: 0
- Withdrew Consent/ Early Termination: 18
- Source Reviewed:
  - o ICF: 127 of 643 Screened Subjects
  - o Source: 127 of 611 Randomized Subjects
  - o ECRFs: 127 of 611 Randomized Subjects

The study is ongoing; however, according to Dr. Cardona, new enrollment has now closed.

There were no significant objectionable conditions for the current inspection and no FDA 483, Inspectional Observations, was issued. Three discussion items were presented related to:

1. Failure to complete the investigation in accordance with the investigational plan. One subject who reported COVID-19 symptoms did not complete the Unplanned Potential COVID-19 Illness Visit (COVID Visit). Two subjects who reported COVID-19 symptoms did not complete a nasal swab during the COVID Visit.

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- 2. Failure to contact subjects with reported COVID-19 symptoms in their e-diary in a timely manner. 12 subjects were initially contacted at least 4 days after they reported COVID-19 symptoms in their e-diary.
- 3. Failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Five subjects did not have all adverse events recorded in the electronic data capture (EDC) system at the time of our inspection beginning on 11/10/2020.

Investigator [REDACTED] informed Dr. Cardona that the discussion items made may be determined, upon further review by the Agency, to be violations of the FD&C Act and that administrative actions, injunction, fines, and prosecution are all options available to FDA. Dr. Cardona acknowledged the discussion items.

No samples were collected, and no refusals were encountered.

**ADMINISTRATIVE DATA** (b) (6), (b) (7)(C)

Inspected firm: Jose F. Cardona, M.D.  
 Location: 3700 W 12th Avenue, Suite 300  
 Hialeah, FL 33012  
 Phone: 305-825-6588  
 FAX: 305-825-6598  
 Mailing address: 3700 W 12th Avenue, Suite 300  
 Hialeah, FL 33012  
 Email address: jcardona@indagoresearch.org  
 Dates of inspection: 11/10-13/2020; 11/16-17/2020  
 Days in the facility: 6  
 Participants: (b) (6), (b) (7)(C) Investigator  
 (b) (6), (b) (7)(C) Investigator  
 (b) (6), (b) (7)(C) Investigator

On 11/10/2020, we presented our credentials and issued a FDA 482, Notice of Inspection, to Dr. Jose F. Cardona, Clinical Investigator, (**Attachment #1**) who identified himself as the most responsible person for the conduct of the study.

Present at the opening meeting were Dr. Cardona, (b) (6), Clinical Research Supervisor, (b) (6), Clinical Research Coordinator (CRC), and (b) (6), Project Manager/Owner. During the opening meeting, we explained the purpose of the inspection and the records and information we would be reviewing.

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Dr. Cardona, (b) (6), and (b) (6) provided all the information contained within this report.

At the conclusion of the inspection on 11/17/20, We met with Dr. Cardona, (b) (6), (b) (6), Regulatory Specialist, and Ms. Maria Vicky Perez, Owner, to close out the inspection and answer any questions that they had.

Post-inspectional correspondence should be directed to Dr. Cardona at the address listed in the ADMINISTRATIVE DATA section of this report.

This report was written by Investigators, (b) (6), (b) (7)(C), (b) (6), (b) (7)(C). Sections are labeled with the initials of the writer.

Investigators (b) (6), (b) (7)(C) were present for the entire inspection. Investigator (b) (6), (b) (7)(C) was present during the inspection from 11/10-13/2020.

### HISTORY (b) (6), (b) (7)(C)

Dr. Cardona has been conducting research at Indago Research and Health Center, Inc. (Indago) since June 2015 and has been practicing medicine since 1988. Dr. Cardona works full-time at Indago as a contractor and also maintains a private practice at MDR Medical Center located at 7951 SW 40<sup>th</sup> Street, Suite 212, Miami, FL 33155. Dr. Cardona is licensed to practice medicine in Florida and is Board Certified in Emergency Medicine.

Dr. Cardona stated that all study procedures took place at Indago, including all nasal (midturbinate) swabs.

(b) (6) provided the CV for Dr. Cardona (**Exhibit #1**).

Dr. Cardona's email address is jcardona@indagoresearch.org.

(b) (6) provided a current organizational chart for Indago (**Exhibit #39**).

### INTERSTATE (I.S.) COMMERCE (b) (6), (b) (7)(C)

Dr. Cardona was the Principal/Clinical Investigator and as such was not involved in the distribution or marketing of regulated products. Investigational product for the protocol was sent to the clinical site from (b) (4) on behalf of the sponsor Pfizer, Inc./BioNTech RNA Pharmaceuticals GmbH.

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**JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)** (b) (6), (b) (7)(C)

Dr. Cardona is the clinical investigator for Protocol C4591001 entitled, “A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study To Evaluate The Safety, Tolerability, Immunogenicity, And Efficacy Of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 In Healthy Adults,” an FDA regulated human clinical trial involving an investigational product conducted under IND #19736.

**INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED** (b) (6), (b) (7)(C)

**Dr. Jose F. Cardona, Clinical Investigator (CI):** Dr. Cardona was the clinical investigator and most responsible person for the study based on the signed FDA 1572s (**Exhibit # 3**). Dr. Cardona’s main responsibilities during the study included: oversight of the clinical trial, evaluating adverse events, conducting patient assessments, reviewing medical history, evaluating inclusion/exclusion criteria, and training staff on the protocol. He stated that he received training for the study at the Site Initiation Visit (SIV), online modules, and during monitoring visits. Dr. Cardona stated that he works full-time as an independent contractor at Indago, the site of the study, and has no hire/fire authority and no ownership stake in the company. He stated that he does not have a formal written contract with Indago, but he is aware of his regulatory responsibilities as the Clinical Investigator. He reports to Maria Vicky Perez, an Owner of Indago. Dr. Cardona was available throughout the inspection and provided information contained in this report.

**(b) (6), Sub-Investigator:** (b) (6) was the Sub-Investigator based on the Delegation of Authority log and FDA 1572s (**Exhibit # 3**). (b) (6) main responsibilities during the study included: conducting physical exams and evaluating inclusion/exclusion criteria. (b) (6) received training for the study at monitoring visits, through online modules, and by Dr. Cardona throughout the study. (b) (6) is an independent contractor at Indago, the site of the study, and has no hire/fire authority and no ownership stake in the company. (b) (6) reports to Maria Vicky Perez, an Owner of Indago, and Dr. Cardona who has delegated (b) (6) authorities as a Sub-Investigator for the study. We met (b) (6) briefly during our tour of the facility and (b) (6) provided limited information contained in this report.

**Daniel A. Pineda, Clinical Research Supervisor:** Mr. Pineda has been conducting research at Indago since 2015. His main responsibilities during the study included: serving as the unblinded coordinator, prepared and administered the investigational product (IP) to subjects, and maintained IP accountability. Mr. Pineda was trained by Dr. Cardona and the monitors during the study and at the Site Initiation Visit. Mr. Pineda is an employee of Indago and has no hire/fire authority. He reports to Ms. Perez and the other owners. Mr. Pineda was available during the inspection and provided information contained in this report. He was the main contact throughout the inspection.

**(b) (6), Clinical Research Coordinator:** (b) (6) has been conducting research at Indago since 2/2019. (b) (6) main responsibilities during the study included: serving as the main

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blinded coordinator, conducting the informed consent process, taking vitals, monitoring subjects after they received IP, scheduling subject visits, and following up with subjects regarding e-diary compliance, as well as reported COVID-19 symptoms. (b) (6) was trained by Dr. Cardona and the monitors during the study and at the SIV. (b) (6) is an employee of Indago and has no hire/fire authority. (b) (6) reports to Mr. Pineda. (b) (6) was available during the inspection and provided information contained in this report.

**Maria Vicky Perez, Owner, Clinical Research Coordinator:** Ms. Perez is one of the owners of Indago and also was delegated study tasks by Dr. Cardona based on the Delegation of Authority Log. She served as a backup coordinator but was not heavily involved in the day to day duties for this protocol. As one of the owners of Indago, she has hire/fire authority. We met Ms. Perez briefly during our tour of the facility and she provided limited information contained in this report.

### CLINICAL SITE TRAINING (b) (6), (b) (7)(C)

The Site Initiation Visit (SIV) for the protocol took place virtually on 8/3/20 and was conducted by (b) (6) a monitor from (b) (4), the Contract Research Organization (CRO) hired by the sponsor (**Exhibit #4, page 13**).

Dr. Cardona stated he provided training throughout the study on topics such as: the protocol and amendments, Informed Consent Form (ICF), adverse events (AE) and serious adverse event (SAE) procedures, and other clinical procedures. Dr. Cardona stated that he and the staff were trained by the monitors throughout the study. We reviewed the training records for the research personnel involved in the conduct the protocol and no observations were found.

### AUTHORITY AND ADMINISTRATION (b) (6), (b) (7)(C)

Dr. Cardona is the clinical investigator responsible for the conduct of the study since its initiation per the Form FDA 1572s (**Exhibit #3**) and our review of the study procedures. He is aware of the status of the test article(s), nature of the protocol and his obligations as the investigator. The authority for the conduct of the various aspects of the study is delegated appropriately per the Delegation of Authority Log (**Exhibit #5**).

Dr. Cardona stated that all study subjects were seen at Indago.

(b) (6) provided a list of studies Dr. Cardona had conducted over the past five years (**Exhibit #2**).

The monitor, (b) (4), provides training and continuous information related to any updated safety information and general study updates to Dr. Cardona by teleconference, in person visits, and email. Please refer to the **Clinical Site Training** section of this report for additional information.

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The site maintains the FDA 1572 forms on file (**Exhibit #3**).

The initial 1572 was signed by Dr. Cardona on 6/17/20. Additional 1572s were signed on 7/22/20, 8/3/20, 8/11/20 (two were completed), 10/6/20, and 11/4/20. The additional 1572s were created in order to add an additional clinical laboratory facility and to update the sub-investigators.

The first subject was screened, signed the informed consent form (ICF), and randomized on 8/19/20.

The first and last subjects were randomized and received the investigational product on 8/19/20 and 10/30/20 respectively.

The study is still ongoing; however, Dr. Cardona stated that enrollment is now closed.

Dr. Cardona stated that the subjects were recruited through Indago's database, IRB approved advertisements, and word of mouth.

No safety laboratories were required by the protocol for phase 3 which, according to Dr. Cardona, all subjects were enrolled into. The laboratory used for COVID testing was Pfizer Vaccines Research Laboratories located in Pearl River, NY. Dr. Cardona stated that all nasal swabs were performed at the site and sent to the Pfizer Laboratory.

Immunogenicity labs were sent to (b) (4) located in (b) (4)

Both laboratories are listed on the firm's Form FDA 1572s.

The site maintained the laboratory's certificates, including the CLIA certification, in the regulatory binders.

The Screening Log was collected as **Exhibit #6**. We confirmed the Screening Log accurately reflects the number of subjects screened and randomized for the study.

**CLINICALTRIALS.GOV REQUIREMENTS** (b) (6), (b) (7)(C)

The protocol has been registered on clinicaltrials.gov; however, results are not currently posted as the study's estimated primary completion date is 6/13/21.

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Dr. Cardona stated that he has no agreement with the sponsor to update any information on [clinicaltrials.gov](https://clinicaltrials.gov).

### PROTOCOL (b) (6), (b) (7)(C)

Protocol C4591001 entitled, “A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study To Evaluate The Safety, Tolerability, Immunogenicity, And Efficacy Of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 In Healthy Adults,” was conducted with the following objectives:

#### Primary Efficacy Objectives for Phase 2/3:

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination

#### Primary Safety Objective for Phase 2/3:

- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3

Multiple protocol amendments were used for the conduct of the study at Dr. Cardona’s site beginning with Amendment 5 dated 6/24/20. Amendment 9 dated 10/29/20 is currently being utilized (**Exhibit #7**). Numerous changes spanning the protocol amendments included: adding secondary phase 2/3 endpoints, clarifying endpoint and interim analyses, expanding the age range of subjects to include subjects as young as 12 and as old as 85, and clarifying protocol definitions.

The protocols found onsite matched the protocols provided in the background materials, with the exception of Amendment 9 which is included in this report as **Exhibit #7**. All protocol amendments were approved by the IRB prior to implementation.

Our review of the source documents found that Subject (b) (6) who reported COVID-19 symptoms did not complete the Unplanned Potential COVID-19 Illness Visit (COVID Visit) as required by the protocol. Subjects (b) (6) who reported COVID-19 symptoms did not complete a nasal swab during the COVID Visit as required by the protocol.

Please see the **General Discussion with Management** section for additional information.

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No other discrepancies were discovered regarding the investigator following study related procedures to include: subjects meeting inclusion/exclusion criteria, number of subjects enrolled, blinding procedures, required study procedures, storage of investigational product, administration of investigational product, and data collection.

A protocol deviation log provided by the monitor was reviewed and protocol deviations were reported to the IRB and Monitor as necessary.

**INSTITUTIONAL REVIEW BOARD (b) (6), (b) (7)(C)**

The Institutional Review Board (IRB) used was (b) (6), (b) (7)(C) IRB which is located at (b) (4), (b) (4). The IRB was chaired by (b) (6).

Regulatory binders were well maintained with the required regulatory correspondence including the initial review and approval of the study. Required communications were reported promptly to the IRB.

The important dates for protocol can be found in the following table:

Document	Approval Date	Exhibit #8 page #
IRB approval (investigator, protocol dated 4/15/20, ICF English dated 7/29/20, advertisements, (b) (4) Directions )	7/29/20	1
IRB approval (amendment 5 dated 7/24/20, ICF English ver. 3)	7/31/20	4
IRB approval (ICF Spanish ver. 3)	8/7/20	6
IRB approval (amendment 6 dated 9/8/20, ICF Spanish/English ver. 4)	9/11/20	10
IRB approval (ICF English ver. 4.1)	10/8/20	12
IRB approval (amendment 7 dated 10/6/20, ICF English ver. 5)	10/10/20	14
IRB approval (amendment 8 dated 10/15/20)	10/16/20	18
IRB approval (ICF Spanish ver. 5)	10/23/20	20
IRB approval (amendment 9 dated 10/29/20)	11/5/20	24

Important IRB approvals were collected as **Exhibit #8**.

According to Dr. Cardona, IRB approved advertisements were used to recruit subjects for the study.

A list of IRB approvals for advertisements was collected as **Exhibit #8, page 1**.

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The ICFs were approved by the IRB and contained all the required basic elements, including the clinicaltrials.gov statement as required by 21 CFR 50.25(c).

### SUBJECTS' RECORDS (b) (6), (b) (7)(C)

The following are the subject numbers:

- Screened: 643
- Randomized: 611
- Screen Failed: 32
- Completed: 0
- Withdrew Consent/ Early Termination: 18
- Source Reviewed:
  - o ICF: 127 of 643 Screened Subjects
  - o Source: 127 of 611 Randomized Subjects
  - o ECRFs: 127 of 611 Randomized Subjects

No minors were screened or randomized.

We conducted an in-depth review of 127 out of 613 enrolled subjects in the protocol. The records consisted of ICFs, medical histories, patient diaries, patient assessments, vital signs, physical examinations, concomitant medications, adverse events (AEs), investigational product usage, and progress notes. Our review of the data in the source documents found that they were mostly entered by Dr. Cardona and (b) (6).

Subjects were identified at screening by an (b) (4) digit number. The first (b) (4) digits refer to the (b) (4) number (b) (4) and the last (b) (4) numbers correspond (b) (4). The initial subject number for the protocol was (b) (4).

We reviewed 127 out of 643 signed informed consent forms (ICFs) for subjects screened in the protocol and found that the ICFs were obtained by the delegated study personnel to include Ms. (b) (6), CRC. The ICFs were written in English and Spanish. According to Dr. Cardona, the clinical site performed the consenting procedure for each subject in a private area; giving the subject time to read the ICF and ask any questions. According to Dr. Cardona, all informed consent procedures were done in person and subjects were required to wear personal protective equipment (PPE) and maintain social distancing while present at the site. Subjects were provided with a copy of the signed ICF for their records. No study procedures were performed prior to the ICF being obtained.

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Subject (b) (6) was the only subject consented using an electronic ICF, which was done in person using a tablet. The form was subsequently printed out with the audit trail and included in the source documents.

Copies of the most recent ICF versions were collected as **Exhibit #9**.

The source documents were compared to the eCRFs provided by the site as finalized data has not yet been submitted to the Agency. We compared the handwritten adverse event logs filed in the subject source documents to the log created in the eCRF and found that five subjects did not have all adverse events recorded in the electronic data capture (EDC) system at the time of our inspection, beginning on 11/10/2020.

Please see the **General Discussion with Management** section for additional information.

No further discrepancies between the source documents and data entered into the eCRFs were uncovered.

We reviewed the subject (b) (4) electronic diaries using printouts of the “All Questionnaires” tab found in the (b) (4) program. We also reviewed a printout from the (b) (4) system, provided by the site, which listed the subjects and dates of positive COVID-19 symptoms reported by subjects in the e-diaries over approximately the last two months (**Exhibit #10**). We also reviewed the email notifications sent by the (b) (4) program to the site which indicate when subjects report a positive COVID-19 symptom in their e-diary (**Exhibit #11**).

Our review of this documentation found that 12 subjects were initially contacted by the site at least 4 days after they reported COVID-19 symptoms in their e-diary.

Please see the **General Discussion with Management** section for additional information.

Our review of the subject diaries via the (b) (4) printouts found that some subjects were not completing diary entries weekly (subjects at this site were not enrolled in the reactogenicity portion of the protocol per Dr. Cardona). We asked (b) (6), CRC, how (b) (6) reviews subject compliance, and (b) (6) stated that (b) (6) uses the (b) (4) program every (b) (4) to identify subjects who did not complete the COVID-19 Illness diary in over a week. (b) (6) stated that (b) (6) and the study staff will call subjects and remind them to fill out the diary at least weekly and also ask them to report any possible COVID-19 symptoms that they may have missed. (b) (6) stated that these contacts were not always documented in the source documents or in the (b) (4) program. We reminded Dr. Cardona and the study staff that e-diary compliance should be assessed frequently and any contact with the subject should be documented. Dr. Cardona agreed that the documentation should be improved, and Mr. Pineda provided a written procedure of how subject compliance will be assessed and documented moving forward (**Exhibit #12**).

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Our review of the source documents found that the site was notified by Pfizer when the results of a COVID-19 nasal swab taken during any of the visits came back positive. Dr. Cardona stated that negative test results were not reported back to the site. He also confirmed that positive or negative nasal swab test results were not required to be entered into the EDC by the site.

During our review we uncovered three subjects who had positive test results reported at either Visit 1, 2 or both (b) (6). These subjects all claimed to be asymptomatic and were able to continue the study.

Dr. Cardona stated that he notifies all subjects who test positive for COVID-19 and encourages them to follow up with their primary care physician to obtain a confirmatory test and abide by CDC guidelines to prevent infecting other people. At the time of the inspection, the site did not have a written procedure of how subjects are notified of their positive tests. (b) (6) provided a site-written procedure during the inspection which details how this will be done in the future (**Exhibit #41**).

All subjects reviewed were screened and enrolled after the IRB approved the site and investigator.

There were no serious adverse events reported for the protocol. Our review of the progress notes did not uncover unreported adverse events in the paper logs kept in the source documents.

The site created the source documentation templates based on the protocol requirements.

All subjects appeared to be alive and available for the duration of their stated participation in the study.

Dr. Cardona stated that other COVID-19 related trials were ongoing at Indago (**Exhibit #2**); however, he stated that the site has an internal scheduling system which prevents subjects from being scheduled in two different studies at Indago. He stated that subjects are asked if they are participating in other studies at other sites and are also reminded that they should not be enrolled in multiple studies at the same time.

The site was notified on 11/2/20 by the aforementioned monitor, (b) (6), from (b) (4) that subject (b) (6) was enrolled at another site (**Exhibit #40, page 1**). On 11/3/20, the site was notified by (b) (6) from Pfizer indicating their identification of the dual enrollment on 9/29/20 at a site in close proximity to Indago (**Exhibit #40, page 3**). A Protocol Deviation Report form was created by the site on 11/2/20, the subject was discontinued from the study on 11/3/20, and the site reported to the IRB on 11/4/20.

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The collected data was entered into the EDC system by trained and properly delegated staff at the site, to include (b) (6)

### OTHER STUDY RECORDS (b) (6), (b) (7)(C)

The site kept copies of study related information to include: correspondence between the site and the sponsor and monitor as well as MedWatch forms sent to the site.

### ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES (b) (6), (b) (7)(C)

No electronic records replaced paper source documents at this site.

Handheld devices were provided by (b) (4) on behalf of the sponsor for entry of symptoms in the COVID-19 Illness Diary using the (b) (4) program. The (b) (4) program was also available by downloading the app on subjects' personal devices. (b) (6) stated that the (b) (4) program required that the subjects enter a unique PIN that each subject created. (b) (6) stated that at the initial visit, subjects were trained on how to use the (b) (4) program and provided written instructions as a reference. (b) (6) provided the written instructions given to the subjects on how to use the (b) (4) program which include screenshots (**Exhibit #13**).

Only Subject (b) (6) was consented using an electronic ICF. The form was subsequently printed out with the electronic signature and audit trail and placed into the subject's source document file. Dr. Cardona stated that the electronic ICF was only available in English when they first started screening subjects and the procedure was cumbersome, so they opted not to use electronic ICFs for any other subjects.

The EDC system was provided by the sponsor.

### INTERVIEWS OF SUBJECTS/PERSONNEL (b) (6), (b) (7)(C)

No subjects were contacted for this study. Please see INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED section for further discussion of personnel duties.

### FINANCIAL DISCLOSURE (b) (6), (b) (7)(C)

Our review of the financial disclosures found that Dr. Cardona and the Sub-investigators had completed the required documentation. None of the investigators had any major disclosures. Dr. Cardona stated that the financial disclosures remained accurate thus far throughout the conduct of the protocol to his knowledge and were reported to the sponsor.

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### CONTROL OF INVESTIGATIONAL PRODUCT (b) (6), (b) (7)(C)

Investigational product (IP) for the protocol was sent to the clinical site from (b) (4) (b) (4) on behalf of the sponsor Pfizer, Inc/BioNTech.

Our review of the shipping documentation found that the site verified and documented the condition of the IP upon receipt.

Study personnel were delegated the responsibility for receiving, securing, and dispensing the IP, specifically (b) (6).

We reviewed the source documents for 127 of the enrolled subjects audited and found that there was adequate documentation to ensure that subjects were given the required dose of IP.

The IP had to be (b) (4) added prior to injection. The site kept appropriate documentation outlining the preparation of the IP.

Our review of the IP dispensing procedure found that the subjects and blinded study staff remained blinded throughout the study.

Dr. Cardona stated the study medications for the protocol were kept in a temperature controlled and monitored freezer. The clinical site uses a (b) (4) temperature monitoring system called (b) (4) (b) (6) stated that the site regularly sent temperature logs to the monitor for review. Our review of the temperature logs (**Exhibit #14**) found minor temperature excursions down to (b) (4) Celsius (the IP label indicates the minimum storage temperature should be (b) (4) Celsius). Mr. Pineda provided an email from the monitor stating that the temperatures should be rounded to the nearest whole number, so these excursions should not be reported as such (**Exhibit #14, page 1**).

A copy of the IP Accountability Log was collected as **Exhibit #15**.

Our review of the subject accountability logs as well as left over packaging, which contained the study kit number, and vaccine administration logs found that the IP was properly labeled. We found no discrepancies.

### RECORDS CUSTODY AND RETENTION (b) (6), (b) (7)(C)

The study records were stored on site at:  
3700 W 12<sup>th</sup> Avenue, Suite 300  
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Due to the large number of subjects enrolled in the protocol, we did not verify that all records were present and available at the site; however, all subject records requested by the investigational team were available.

Our review of the audited records uncovered no observations related to their custody and retention.

**REPORTS TO SPONSOR** (b) (6), (b) (7)(C)

Dr. Cardona stated that required reports, to include enrollment information and data queries were submitted to the sponsor/monitor as necessary.

The sponsors for the protocol are:

Pfizer Inc.  
500 Arcola Road, Mail Stop D6507  
Collegeville, PA 19426  
USA

BioNTech RNA Pharmaceuticals GmbH  
An der Goldgrube 12  
55131 Mainz  
Germany

**MONITORING** (b) (6), (b) (7)(C)

The protocol was monitored by the CRO:

(b) (4)

Our review of the blinded and unblinded monitor site visit logs and appointment confirmation emails (**Exhibit #4 & 16 respectively**) found that the study site was monitored every (b) (4) from the SIV on 8/3/20. Monitoring was conducted in person and virtually. (b) (6) stated that the monitor instructed the site to scan and upload all of the source documents into a program called (b) (4) where documents were then reviewed by the monitor.

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A protocol deviation log was maintained by the monitor. (b) (6) stated that the site does not maintain its own central log but does document deviations in each subject's individual source document file.

(b) (6) provided a copy of the sponsor's monitoring plan for the protocol (**Exhibit #17**).

The clinical trials have been monitored throughout the study by the monitors to ensure the study's scientific integrity, quality of the data, compliance with ethical principles, local and FDA regulatory requirements, and sponsor regulations, guidelines, and policies were followed. Specifically, the monitor was to ensure that the study staff adhered to the protocol, the trial data recorded was complete and accurate, the accountability records were complete and accurate, regulatory requirements for conducting the clinical trial were followed by the facility, staffing remained adequate to conduct the clinical trial, and the IRB approvals and laboratory certifications were current.

Our review of the monitoring reports uncovered no major deviations other than those mentioned in the **Protocol** section. Sample monitoring reports are included as **Exhibit #18**.

### COMPLAINTS (b) (6), (b) (7)(C)

Dr. Cardona stated that, to his knowledge, there were no complaints for the protocol.

### REFUSALS (b) (6), (b) (7)(C)

No refusals were encountered during the inspection.

### GENERAL DISCUSSION WITH MANAGEMENT (b) (6), (b) (7)(C)

Present at the closing meeting on 11/17/2020 were:

- Dr. Jose F. Cardona, Clinical Investigator
- (b) (6), Clinical Research Supervisor
- (b) (6)
- Ms. Maria Vicky Perez, Site Director/Owner
- (b) (6)

No Form FDA 483, Inspectional Observations, was issued to Dr. Cardona, but the following discussion items were addressed during the inspection and at the closing meeting:

1. Failure to complete the investigation in accordance with the investigational plan.

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Three of 127 subjects reviewed who were randomized and enrolled into the study as of 10/30/2020 did not complete the Unplanned Potential COVID-19 Illness Visit (COVID Visit) as required by the protocol. Section 8.13 of protocol amendments 6, 7, 8, and 9 entitled “COVID-19 Surveillance (All Participants)” states in part:

“If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution).”

Section 8.13.1 of protocol amendments 6,7, 8, and 9 entitled “Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)” states in part, “If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff).”

- a. Subject (b) (6) (Exhibit #19, page 5) had Visit 1 on 9/29/20. The subject reported COVID-19 symptoms on 10/7/20 and 10/8/20 (Exhibit #10, page 2) and was contacted by site on 10/8/20. According to the telephone contact form (Exhibit #19, page 3), the subject complained of rhinitis and was not available to come in for an unplanned visit due to work. According to Dr. Cardona, he preferred that all unscheduled visits to include nasal swabs be done at the study site. The site contacted the subject again on 10/12/20 (Exhibit #19, page 2) and according to the telephone contact form, the subject was not asked to come in for an unplanned visit or schedule a telehealth visit. A deviation report was signed on 10/14/20 (Exhibit #19, page 1) stating that the subject told the site that she was unable to come in for an unplanned visit due to her job.
- b. Subject (b) (6) (Exhibit #20, page 50) had Visit 2 on 10/13/20. The subject reported COVID-19 symptoms on 10/15-19/20; and 10/22/20 (Exhibit #10, page 2). The subject came in for the COVID Visit on 10/22/20 (Exhibit #20, page 44) during which no nasal swab was taken. After the monitor discovered the deviation, the subject came in for an additional unplanned visit on 11/2/20 in order to have the swab completed (Exhibit #20, page 41). A deviation report was also signed on 11/2/20 (Exhibit #20, page 39).

Dr. Cardona understood and agreed with the observations contained in (a) and (b). He stated that he and the staff were retrained via a PowerPoint presentation created by Pfizer which outlined the requirements for when subjects should come in for a COVID Visit and what procedures need to take place. He committed to ensuring that future subjects will complete COVID Visits for confirmed positive COVID-19 symptoms reported after 7 days from the time of the vaccination visits.

- c. Subject (b) (6) completed Visit 1 on 09/22/2020 and arrived on-site for an Unplanned Visit on 10/02/2020 following a report of potential COVID-19 symptoms within their e-Diary on 10/01/2020 (Exhibit #10, page 1). Subject (b) (6) reported nasal congestion from

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09/30/2020 to 10/03/2020. During the unplanned visit, no nasal swab was taken (**Exhibit #21, page 1**).

Two EDC queries occurred on 10/08/2020 requesting the following: details regarding what concomitant non-drug treatment is considered to be the cause for the adverse event, as well as site consideration whether this symptom could have been due to COVID-19 since nasal congestion is a CDC-defined COVID-19 symptom. The site replied to the queries on 10/16/2020 stating the adverse event was not related to COVID-19 nor to any concomitant medication which subsequently closed the query on 10/25/2020. Dr. Cardona added a note on the Unplanned Visit source (**Exhibit #21, page 2 of 7**) on 10/16/2020 stating that no concomitant medication was related to the nasal congestion, as well as the nasal congestion was not related to COVID-19. Another note underneath this statement on 11/10/2020 states that nasal congestion was due to allergic rhinitis. The adverse event term was changed from nasal congestion to allergic rhinitis on 11/10/2020 on the Adverse Event Log by Dr. Jose F. Cardona (**Exhibit #21, page 5 of 7**). The adverse event was closed on 10/06/2020 after the site telephoned the subject for follow-up (**Exhibit #21, page 6 of 7**).

Investigator (b) (6), (b) (7)(C) asked Dr. Cardona why a deviation was not created since the subject did not undergo a nasal swab at the unplanned visit. Dr. Cardona stated that it was his belief that the nasal congestion was related to chronic allergic rhinitis caused by the subject mixing cleaning chemicals at their job. Investigator (b) (6), (b) (7)(C) then stated that the COVID Visit with nasal swab should occur regardless of the perceived etiology of the symptom as stated in the protocol. Dr. Cardona agreed with the observation and committed to obtaining a nasal swab during each Unplanned Potential COVID-19 Illness Visit without exception. A protocol deviation was recorded on 11/16/2020 for failure to complete the nasal swab at the visit (**Exhibit #21, page 7 of 7**).

2. Failure to contact subjects with reported COVID-19 symptoms from the e-Diary in a timely manner.

12 of 127 subjects reviewed who were randomized and enrolled into the study as of 10/30/2020 were not contacted for at least four days after subjects reported potential COVID-19 symptoms in the e-Diary. The following subjects were affected:

Subject	Date Subject Entered Pertinent COVID Symptoms into E-diary	Date Site Made Initial Contact with Subject	Exhibit Number
(b) (6)	11/7/20 ( <b>page 5</b> )	11/10/20* ( <b>page 1</b> )	<b>22</b>
(b) (6)	10/29/20 ( <b>page 1</b> )	11/2/20 ( <b>page 3</b> )	<b>23</b>
(b) (6)	10/5/20 ( <b>page 1</b> )	10/9/20 ( <b>page 7</b> )	<b>24</b>
(b) (6)	9/1/20 ( <b>page 1</b> )	11/12/20 ( <b>page 4</b> )	<b>25</b>

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(b) (6)	10/2/20, 11/5/20 (page 1)	10/7/20, 11/6/20* (pages 2 & 4)	26
(b) (4)	9/4/20 (page 1)	9/8/20 (page 5)	27
(b) (6)	10/29/20 (page 1)	11/2/20 (page 3)	28
(b) (6)	10/31/20 (page 1)	11/4/20 (page 5)	29
(b) (6)	10/1/20 (page 1)	10/8/20 (page 4)	30
(b) (6)	10/6/20 (page 1)	10/13/20 (page 12)	31
(b) (6)	10/7/20, 10/26/20 (page 1)	10/13/20, 11/2/20 (pages 54 & 4)	32
(b) (6)	11/4/20 (page 1)	11/11/20 (page 2)	33

\*Denotes Subjects that were contacted after issue identified by FDA Investigators during the inspection.

We asked Dr. Cardona and (b) (6) how quickly they contacted subjects after they received the email notification of the subject entering a positive COVID-19 symptom into the e-diary and they stated they tried to call as soon as possible but did not have a firm timeline of when this should happen. (b) (6) also stated that oftentimes the staff would contact subjects and would not record those attempts in the source documents or in the (b) (4) program for subjects who could not be reached. We explained to Dr. Cardona and the study staff that contacting subjects and scheduling COVID Visits were very important and that they should document all attempts to contact the subjects. Dr. Cardona agreed with the observation and (b) (6) provided a new written procedure (**Exhibit #42**) outlining how the site would contact subjects who report COVID-19 symptoms in the future.

3. Failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Five of 127 subjects randomized and enrolled into the study as of 10/30/2020 did not have adverse events reported into the EDC at the time of our inspection on 11/10/2020.

Subject	Date A/E was Recorded	Exhibit Number
(b) (6)	9/15/20	34
(b) (6)	10/21/20	35
(b) (6)	10/2/20	36
(b) (6)	10/2/20	37
(b) (6)	10/13/20	38

Dr. Cardona agreed with the observation and committed to entering all adverse events into the EDC in a timely fashion. (b) (6) provided a written procedure (**Exhibit #43**) outlining how adverse

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events would be entered into the EDC in the future. Based on our findings, (b) (6) stated the staff went back and reviewed all the subject charts and ensured all AEs/SAEs had been recorded into the EDC. (b) (6) also provided screenshots of the EDC showing that the missing AEs we uncovered during the inspection were now entered (**Exhibit # 44**).

Investigator (b) (6), (b) (7)(C) informed Dr. Cardona that the aforementioned discussion items may be determined, upon further review by the Agency, to be violations of the FD&C Act and that administrative actions, injunction, fines, and prosecution are options available to FDA. Dr. Cardona agreed with the discussion items presented.

### SAMPLES COLLECTED (b) (6), (b) (7)(C)

No samples were collected.

### VOLUNTARY CORRECTIONS (b) (6), (b) (7)(C)

During the course of the inspection, (b) (6) provided new procedures meant to correct and prevent the discussion items presented from occurring as the study continues. The procedures are as follows:

1. Site Plan to document review of eDiary COVID-19 Symptom Alerts (**Exhibit #42**)
2. Site Plan to Ensure all Adverse Events (AEs) and Serious Adverse Events (SAEs) are Appropriately Captured in EDC (**Exhibit #43**)
3. Site Plan to Document Review of Subject Non-Compliance with eDiary Completion (**Exhibit #12**)
4. Note to File: Positive COVID-19 Result (**Exhibit #41**)

In addition, (b) (6) provided screen shots from the EDC (**Exhibit #44**), showing that the adverse events we identified as missing are now updated.

### EXHIBITS COLLECTED

- 1 (b) (6), (b) (7)(C) Dr. Cardona CV, 2 pages
- 2 List of Studies, 14 pages
- 3 FDA 1572s, 20 pages
- 4 Site Visit Log and Appointment Confirmations-Blinded, 14 pages
- 5 Delegation of Authority Log, 10 pages
- 6 Screening Log, 31 pages
- 7 Protocol Amendment 9, 155 pages
- 8 IRB Approvals, 25 pages
- 9 (b) (6), (b) (7)(C) Sample ICFs, 68 pages
- 10 (b) (6), (b) (7)(C) List of Subjects With Reported COVID Symptoms, 6 pages
- 1 Email Notifications of Subjects With Reported COVID Symptoms, 142 pages
- 1 Site Plan for Non-Compliance with E-diary, 1 page

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- 13 (b) (6), (b) (7)(C) (b) (4) Directions, 36 pages
- 14 Temperature Logs and Rounding Email, 28 pages
- 15 IP Accountability Logs, 69 pages
- 16 Site Visit Log and Appointment Confirmations-Unblinded, 11 pages
- 17 Sponsor Monitoring Plan, 48 pages
- 18 Sample Monitoring Reports, 11 pages
- 19 Subject (b) (6) Source Documents, 53 pages
- 20 Subject (b) (6) Source Documents, 110 pages
- 21 Subject (b) (6) Source Documents, 7 pages
- 22 Subject (b) (6) Source Documents, 54 pages
- 23 Subject (b) (6) Source Documents, 54 pages
- 24 Subject (b) (6) Source Documents, 58 pages
- 25 Subject (b) (6) Source Documents, 63 pages
- 26 Subject (b) (6) Source Documents, 55 pages
- 27 Subject (b) (6) Source Documents, 54 pages
- 28 Subject (b) (6) Source Documents, 56 pages
- 29 Subject (b) (6) Source Documents, 50 pages
- 30 Subject (b) (6) Source Documents, 55 pages
- 31 Subject (b) (6) Source Documents, 62 pages
- 32 Subject (b) (6) Source Documents, 104 pages
- 33 Subject (b) (6) Source Documents, 53 pages
- 34 Subject (b) (6) Source Documents, 3 pages
- 35 Subject (b) (6) Source Documents, 163 pages
- 36 Subject (b) (6) Source Documents, 4 pages
- 37 Subject (b) (6) Source Documents, 6 pages
- 38 Subject (b) (6) Source Documents, 106 pages
- 39 Organizational Chart, 1 page
- 40 Site Notification of Duplicate Subject, 3 pages
- 41 Site Procedures for Subjects with Positive COVID-19 Results, 1 page
- 42 Site Plan for COVID-19 Alerts, 1 page
- 43 Site Plan for Recording of Adverse Events, 1 page
- 44 Screenshots of Updated AE Logs, 14 pages

**ATTACHMENTS**

- 1 (b) (6), (b) (7)(C) FDA 482 Notice of Inspection issued to Jose Cardona, MD, 3 pages
- 2 Assignment Memo, 5 pages

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(b) (6), (b) (7)(C)

(b) (6), (b) (7)(C)

(b) (6), (b) (7)(C)

(b) (6), (b) (7)(C)