TABLE OF CONTENTS

SUMMARY

(Section written by (b) (6), (b) (7)(C)

This comprehensive FY 2020 high priority PDUFA Premarket Original surveillance inspection of a clinical investigator was performed in response to an assignment eNSpect OP ID 179759 issued by the Center for Biologics Evaluation and Research (CBER) Office of Compliance and Biologics Quality Division of Inspection and Surveillance. (Attachment (b) (6), (b) (7)(C) 1) This inspection was conducted in accordance with the assignment memorandum and Compliance Program 7348.811, Clinical

Investigators and Sponsor-Investigators. The assignment requested an inspection of this clinical investigator regarding the conduct of the following protocol:

- Protocol C4591001, titled "A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals"

The sponsor is BioNTech RNA Pharmaceuticals GmbH/Pfizer, Inc., Collegeville, PA. The application submitted for this study is IND #19736 for a COVID-19 vaccine (investigational drug/vaccine BNT162, PF-07302048).

The previous inspection of Charles H. Harper, MD, Clinical Investigator, was conducted on 10/7/2019 - 10/11/2019 and was classified as NAI, no action indicated. A Form FDA 483, Inspectional Observations, was not issued as a result of the previous inspection.

Currently for Dr. Harper's site, 238 subjects have been screened; 21 subjects were screen failures; 216 subjects have been enrolled; and 4 subjects have been lost to follow-up/withdrew. This study is ongoing, and no subjects have completed the study.

Study records audited for the protocol included but were not limited to: IRB approval letters and correspondence; monitoring reports; consent forms, subject medical records, financial disclosure reports, case report forms, drug accountability records, site signature and responsibility logs; subject electronic diary entries; and site training documentation. 55 subject records (approximately 25% of all enrolled subjects) were audited for protocol adherence, adverse event reporting, test article accountability and diary adherence. All reviewed subject records were audited to verify informed consent was obtained according to regulations. Primary endpoint data was not verified for the study because this inspection was not a data audit inspection. Primary endpoint data was however reviewed to ensure the site was properly documenting safety and tolerability data obtained during subject visits and through the eDiaries used by subjects to report adverse events (AE's). Data line listings were not provided with the background materials for this assignment; therefore, this inspection was not conducted as a data audit inspection.

No Form FDA 483 was issued. The following issues were discussed with Dr. Harper at the conclusion of the inspection: 1) Investigational product preparation documentation needs to be contemporaneous; 2) AE's for Subject (b) (6) (increased headaches) was not documented in the subject's study folder or eCRF; 3) case report forms were not complete to include vasectomy surgery for Subject (b) (6) 4) Potential COVID Visit Toxicity Grades were not rated by Dr. Harper for two (2) subjects; 5) Follicle Stimulating Hormone (FSH) levels (eligibility requirement) were not obtained for two (2) subjects who were enrolled as postmenopausal; and 6) Copies of informed consent forms are not certified copies as stated they were per study staff.

Dr. Harper and study staff who were present during the close out visit promised corrections in future studies and provided documentation of processes that have been started to correct the verbal discussion items. Dr. Harper had no further questions or comments.

No refusals were encountered. No photographs were taken. No samples were collected.

ADMINISTRATIVE DATA
(Section written by (b) (6), (b) (7)(C)

Inspected firm:	Charles H. Harper, M.D.
Location:	1410 N 13th St Ste 5 Norfolk, NE 68701-2669
Phone:	402-371-0797
FAX:	888-588-8068
Mailing address:	1410 N 13th St Ste 5 Norfolk, NE 68701-2669
Email address:	charper@mcrmed.com
Dates of inspection:	11/9/2020-11/13/2020
Days in the facility:	5
Participants:	(b) (6), (b) (7)(C)

Non-FDA Participants: None

This inspection was preannounced on 11/2/2020 to Ms. Alicia M. Keipke, Site Manager who confirmed start dates with Dr. Charles H. Harper, Clinical Investigator. On 11/9/2020 we presented our credentials to and issued a Form FDA 482, Notice of Inspection to Charles H. Harper, MD, Clinical Investigator. (**Attachment 2**) Dr. Harper stated he was the most responsible person on site for study C4591001.

The FMD-145 copy of this report and all post inspectional correspondence should be addressed to:

Charles H. Harper, MD, Clinical Investigator
1410 N. 13th, Suite 5
Norfolk, NE 68701
Email: charper@mcrmed.com

HISTORY

(Section written by (b) (6), (b) (7)(C)

The previous inspection of Dr. Harper was conducted on 10/7-11/2019 and was classified as NAI, no action indicated. A Form FDA 483 was not issued during the previous inspection. Dr. Harper is the most responsible person at the site regarding the conduct of study C4591001. Dr. Harper practices internal medicine and maintains a private practice through Yankton Medical Clinic located at Fountain Point Medical Community, 3901 W Norfolk Ave, Norfolk, NE 68701. He acts as one of 2 Principal Investigators for Meridian Clinical Research, LLC located at 1410 North 13th Street, Suite 5, Norfolk, NE 68701. Dr. Harper has a current contract with Meridian as an Independent Contractor that has been in effect since 2016. The contract explains his responsibilities to conduct research as a Clinical Investigator. As an Independent Contractor, Dr. Harper reports to Dr. Brandon J. Essink, Medical Director (Meridian Clinical Research, Omaha, NE).

Dr. Harper divides his time daily between his private practice and clinical research at Meridian. The normal clinic hours are: Monday through Friday 8am to 5pm and as needed on Saturdays.

INTERSTATE (I.S.) COMMERCE/JURISDICTION

(Section written by (b) (6), (b) (7)(C)

The clinical investigator participated in Study Protocol C4591001- "A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals" which is being conducted under IND #19736. Data has not been submitted to date to support an application. The investigational product was shipped to the clinical site from:

(b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

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

Dr. Charles H. Harper, Clinical Investigator, stated he was the most responsible person for study C4591001 conducted at Meridian Clinical Research, Norfolk, NE. Dr. Harper stated he has been conducting clinical trials for approximately 5 years. Dr. Harper's curriculum vitae (CV) is attached as **Exhibit** (b) (6), (b) (7)(C) 1. He is one of two Principal Investigators at this Meridian Clinical Research site. Dr. Harper stated the other Principal Investigator, Dr. Keith W. Vrbicky, owns the facility in which the study was conducted. Dr. Harper stated he often acts as a Sub-Investigator on studies for Dr. Vrbicky and that Dr. Vrbicky acts as a Sub-Investigator for his studies when possible.

Dr. Harper stated his responsibilities as a clinical investigator for all studies he conducts include: communicating with the business development team of Meridian to determine what studies to conduct, recruit subjects from his private practice, conduct subject physical exams, conduct the informed consent process, review adverse events, review subject source and electronic records, monitor subject safety and oversee study staff operations. Dr. Harper's notes, signature and initials were observed in all subject source records reviewed. When asked about subject involvement, he was knowledgeable about study visits, adverse events, protocol deviations and documentation. Dr. Harper was present daily throughout the inspection and provided information relating to specific subjects enrolled in study C4591001 and provided information about the processes and procedures conducted at the clinical site during this ongoing study.

(b) (6) **, CCRC, Site Manager and Coordinator**, was present daily throughout the inspection. (b) (6) stated (b) (6) has held (b) (6) current position for approximately 9 months and previously acted as a clinical research coordinator for 6 years. (b) (6) stated (b) (6) roles and responsibilities for this study include overseeing study staff and subject safety, entering data into the eCRF, addressing queries in the eCRF, processing laboratory samples, conducting informed consents, obtaining medical histories, preforming vitals, training subjects on using electronic diaries, coordinating staff delegation and communicating with the monitor, (b) (4) (eDiary software) staff and the IRB. (b) (6) was our main point of contact for the inspection. (b) (6) provided us with copies of requested records, navigated us through the eCRF, answered subject specific questions, provided information relating to documenting subject visits and the record keeping processes. (b) (6) also navigated us through the eDiaries program (b) (4) to show us how the system worked and how subjects used the diary to report their dispositions. (b) (6) stated (b) (6) is responsible for running (b) (4) reports to ensure subjects are reporting in their diaries per the protocol. When reviewing source records, it was observed that when subjects miss diary entries, (b) (6) reaches out to subjects via telephone to educate the subjects on the need to fill out their diaries. (b) (6) also educates subjects during study visits that occur at the site.

(b) (6) stated (b) (6) reports to (b) (6), BA, CCRC, Site Director, who maintains is office at this clinical facility. (b) (6) did not participate in the inspection.

(b) (6) **, APRN, COO of Meridian Clinical Research**, stated (b) (6) oversees all clinical research conducted at all Meridian Clinical Research facilities (26 sites) around the country. (b) (6) stated (b) (6) responsibilities include overseeing all managing branches which include operations, strategic development, business development, finance, human resources and recruitment. (b) (6) stated (b) (6) has held (b) (6) current position for approximately 5 years and has worked for Meridian since 2009. (b) (6) stated (b) (6) started with the company as a Sub-Investigator at the only Meridian Clinical Research site in Omaha, NE. (b) (6) stated (b) (6) still acts as a Sub-Investigator on studies depending on the work load and subject enrollment needs. (b) (6) was present daily during the inspection. (b) (6) provided study records and copies of records, communicated with the sponsor to answer our questions, explained processes and procedures and assisted in explaining how the Meridian Clinical Research business works between all locations. (b) (6) reports to Nicole Osborn, CEO, who maintains her office at the Meridian Clinical Research Headquarters in Omaha, NE.

(b) (6) **, CCRC, Medical Assistant, Midwest Clinical Operations Regional Director for Meridian Clinical Research**, stated (b) (6) has held (b) (6) current position for approximately 3 years and has worked for Meridian for 10 years. (b) (6) stated (b) (6) oversees daily operations and is responsible for scheduling staff and subjects, hiring/firing, setting up training objectives and schedules and assisting in site inspections. (b) (6) was present daily for the inspection. (b) (6) provided copies of requested records and explained Meridian processes for conducting clinical research. (b) (6) Katherine Stoddard, VP Operations, who maintains her office in Wichita, KS.

(b) (6) **, Medical Assistant, Unblinded CRC**, is the most responsible person for keeping the blind for study C4591001. (b) (6) stated (b) (6) has held (b) (6) current position for 1.5 years. (b) (6) stated (b) (6) responsibilities for the study include keeping the blinded staff and subjects blind to the study vaccines, randomizing subjects in (b) (4) (IWRS used for the study), assigning drugs to subjects in (b) (4) verifying study drug processing and maintaining drug processing records. We observed (b) (6) preparing 2 doses to randomized subjects (b) (6) provided us with information on the procedures for temperature monitoring for the study drugs and the processes for assigning and processing the vaccines. (b) (6) stated (b) (6) reports to Russell Herstein, CCRC and Site Director.

(b) (6) **, VP of Recruitment for Meridian Clinical Research**, was interviewed via telephone for information regarding the recruitment process for study C4591001. (b) (6) stated (b) (6) has been involved with clinical research for approximately 20 years and has held (b) (6) current position for approximately 1.5 years. (b) (6) stated (b) (6) roles include overseeing how studies are implemented at research site, providing recruitment strategies for all Meridian sites, maintaining a recruitment budget and overseeing the three Meridian call centers located in Omaha, NE; Statesboro, Georgia; and Sioux City, IA that are used for recruitment and contacting subjects for study visit date reminders. (b) (6) reports to (b) (6), COO.

(b) (6) **Regulatory Specialist**, was present for the entirety of the inspection. She gave us access to (b) (4), the eRegulatory system used for maintaining regulatory records. (b) (6) also provided copies of requested records. (b) (6) stated the site has used (b) (4) for approximately 2 years. (b) (6) stated (b) (6) is responsible for uploading regulatory records into (b) (4) and keeping the filings up to date. (b) (6) stated (b) (6) reports to (b) (6) y, Director of Regulatory Affairs.

The organizational chart for Meridian Clinical Research across all sites in the United states is attached as **Exhibit** (b) (6), (b) (7)(C) **2**.

FIRM'S TRAINING PROGRAM
(Section written by (b) (6), (b) (7)(C)

See the Authority and Administration Section for information on the site's training.

AUTHORITY AND ADMINISTRATION FOR STUDIES INVOLVING HUMAN DRUG, BIOLOGICS AND DEVICES

(Section written by (b) (6), (b) (7)(C)

Charles H. Harper, MD, was the Clinical Investigator.

Sub-investigators were identified as: (b) (6), APRN-NP, (b) (6), APRN, (b) (6) -C, (b) (6), APRN-NP, (b) (6) and (b) (6), MD.

The Statement of Investigator Form FDA 1572 is included as Exhibit (b) (6), (b) (7)(C) 3.

A list of Dr. Harper's clinical research in which he was identified as the Principal Investigator is included as Exhibit (b) (6), (b) (7)(C). In addition, a list of studies in which Dr. Harper is identified as the Sub-Investigator is included as Exhibit (b) (6), (b) (7)(C) 5.

All study procedures for the protocol were performed at Meridian Clinical Research, Norfolk, NE. The Standard Operating Procedure Handbook for Meridian Clinical Research was reviewed and is included as Exhibit (b) (6), (b) (7)(C) 1. Dr. Harper recruited patients from his private practice as well as through Meridian Clinical Research's recruitment team. Advertisements used to recruit subjects include yard signs, posters, brochures, post cards, emails and radio advertisements (see Exhibit (b) (6), (b) (7)(C) 3). These materials were approved by the IRB prior to use.

Authority for the conduct of the various aspects of this study was delegated properly so that Dr. Harper retained control and knowledge of the study. When reviewing source records it appeared delegated staff were preforming their delegated tasks. The Site Signature and Delegation of Duties Log for this study is included as Exhibit (b) (6), (b) (7)(C) 6.

Protocol training was provided to staff during site initiation visits held on 6/18/2020. Dr. Harper also attended the virtual Investigator's meeting held on 6/26/2020. After the site initiation visit, Dr. Harper and site staff had meetings to discuss implementing the protocol at the site. In addition to protocol training, all delegated staff had Collaborative Institutional Training Initiative (CITI Program) certificates of training for research, ethics and compliance which included training for GCPs, reporting adverse and serious adverse events, informed consents, investigator obligations, subject safety, monitoring, FDA regulations and ICH regulations. Along with the trainings for the delegated staff were current licensures relating to their positions.

Relevant study dates are as follows:

FDA Form 1572 Electronically Signed: 5/19/2020
IRB Approvals:
Initial site approval: 6/4/2020

Amendment 5 IRB approval: 7/24/2020
Amendment 6 IRB approval: 9/11/2020
Amendment 7 IRB approval: 10/6/2020 (not used at site)
Amendment 8 IRB approval: 10/16/2020
Amendment 9 IRB approval: 11/5/2020
First Subject Screened: 8/11/2020
First Subject Signed the Informed Consent Document: 8/11/2020
Date of First Test Article Administration: 8/11/2020
Last administration of test article (ongoing study): 11/12/2020
Last subject visit to date (ongoing study): 11/12/2020

The facility performing laboratory testing required by the protocol is: (b) (4) (b) (4). The laboratory is CLIA certified. The CLIA certifications were maintained at the site. Laboratory reports were not provided to the site to maintain the blind. The site was informed by the laboratory through email when subjects tested positive for COVID-19. The clinical site did not preform any laboratory testing.

The site enrollment log is included as Exhibit (b) (6), (b) (7)(C) 7. Ms. Kiepke stated the site has not rescreened any subjects who were determined as screen failures.

CLINICALTRIALS.GOV REQUIREMENTS
(Section written by (b) (6), (b) (7)(C)

Dr. Harper's clinical site, Meridian Clinical Research, is listed on clinicaltrials.gov for study C4591001 as recruiting. Data results from this study have not been uploaded to clinicaltrials.gov since the study is actively recruiting subjects. All other study data relating to study details, outcome measures, eligibility criteria, contacts and location are listed on clinicaltrials.gov.

PROTOCOL
(Section written by (b) (6), (b) (7)(C)

The primary objectives of this study are to assess:

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

Key primary endpoints are listed as:

- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
- COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Key secondary endpoints are listed as:

- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
- Confirmed severe COVID-19 incidence per 1000 person-years of follow-up

The most current version of the protocol included with this assignment was not the same as the version at the site. The most current version of the protocol is attached as Exhibit (b) (6), (b) (7)(C) 8, Protocol Amendment 9 dated 29 October 2020. This was IRB approved prior to its implementation at the site.

Data line listings were not provided with the background materials for this assignment because the study is ongoing and not data analysis has occurred. This inspection did not involve a data audit. The inspection focused on Dr. Harper's adherence to protocol requirements and procedures.

To date, Dr. Harper has followed the protocol with respect to subject selection, number of subjects enrolled, randomization scheme, blinding, required procedures and evaluations, storage and maintenance of investigation product, administration of investigational product, data collection, and follow-up of subjects except for the instances explained below.

The protocol defined postmenopausal women as no menses for 12 months without an alternative medical cause. In addition, a

- high FSH (follicle stimulating hormone) level in the postmenopausal range must be used to confirm postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT (hormonal replacement therapy).
- Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

When Dr. Harper and his staff were asked about this, they were unaware of the need to have a laboratory value for FSH for women under 60. We found two (2) instances where women under the age of 60 did not have documentation of a high FSH level or documentation the woman was on HRT. The site asked the sponsor about this requirement and the sponsor responded by stated the site would be responsible for obtaining an FSH value for subjects that fall into this requirement and that the site would be reimbursed for the testing. We collected the Visit 1 case report forms for the 2 subjects we found which did not have FSH values documented or documentation they were on an HRT. These case report forms are attached as: Subject (b) (6) (Exhibit (b) (6), (b) (7)(C) 9) and Subject (b) (6) (Exhibit (b) (6), (b) (7)(C) 10). Page 6 and 8 in Exhibits (b) (6), (b) (7)(C) 9 and (b) (6), (b) (7)(C) 10 provide the information relating to reproductive status/contraception and medical histories. On 11/13/2020, the site provided medical laboratory records for these two subjects which show both subjects have high FSH levels that would confirm a postmenopausal state. These laboratory reports are included in Exhibit (b) (6), (b) (7)(C) 9 page 17-18 for subject (b) (6) and Exhibit (b) (6), (b) (7)(C) 10 page 17-30 for subject (b) (6).

As stated in Protocol Section 6.5.1, Prohibited During Study, prophylactic antipyretics and other pain medications to prevent symptoms associated with study intervention administration were not permitted. These medications were only allowed if a participant was taking a medication for another condition. Source records for Visit 1 do not clearly indicate that study staff verified if participants had taken prophylactic pain medications to relieve symptoms in anticipation of receiving the study drug. Instead the source record was formatted to require clinical staff to provide instructions regarding prohibited concomitant therapy prior during the study, see Exhibit (b) (6), (b) (7)(C) 17, pg 1. Dr. Harper was asked to consider changing the source for this visit, and to ensure potential subjects are made aware of this requirement when scheduling the screening visit. In addition, Dr. Harper was reminded the protocol allowed for Visit 1 to be conducted across two (2) consecutive days.

Subject instructed on prohibited medications and vaccines throughout the study, including prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention.
☒ Done

Staff Initials: (b) (6) Date: 12 Aug 2020

Deviations from the protocol did not receive prior approval from the sponsor and IRB. Deviations were listed on a protocol deviation log and within subject folders. The log, generated by Meridian Clinical Research is attached as Exhibit (b) (6), (b) (7)(C) 11. (b) (6) stated an Excel spreadsheet will be generated at the completion of a study to record protocol deviations. During the inspection, site staff reported 2 protocol deviations to the IRB. They are attached as Exhibit (b) (6), (b) (7)(C) 12. The reportable events are listed below:

1. Subject (b) (6) Patient had post dose vitals performed inadvertently 1 minute early (Exhibit (b) (6), (b) (7)(C) 12 pages 8 1-4).
2. Subject (b) (6) Patient had post dose vitals performed 15 minutes early due to an emergency and having to leave the site (Exhibit (b) (6), (b) (7)(C) 12 pages 5-8).

We did not observe any other unreported deviations from the approved protocol.

To date, six (6) subjects have had a positive COVID-19 nasal swab result. Correspondence regarding positive COVID-19 PCR results are only provided to Dr. Harper, Principal Investigator (see Exhibit (b) (6), (b) (7)(C) 4). Below is a table summarizing testing dates, result dates and place of testing:

Subject #	Location of Testing	Date of Nasal Swab	Date Shipped to Pfizer Lab	Date Sponsor Reported Result
(b) (6)	At home	10/12/2020	10/14/2020	11/5/2020
(b) (6)	At home	10/1/2020	10/1/2020	10/8/2020
(b) (6)	At home	10/28/2020	10/29/2020	11/5/2020
	Site- Baseline Visit	9/8/2020	9/9/2020	9/16/2020
(b) (6)	Site- V4 Prior to Vaccine #2	10/1/2020	10/1/2020	10/7/2020
(b) (6)	At home	10/28/2020	10/30/2020	11/5/2020

Subject #	Location of Testing	Date of Nasal Swab	Date Shipped to Pfizer Lab	Date Sponsor Reported Result
(b) (6)	At home	11/3/2020	11/5/2020	11/10/2020

Two examples to document the documentation process and the shipping records are attached as: Exhibit (b) (6), (b) (7)(C) 13- subject (b) (6) (at home sample) and Exhibit (b) (6), (b) (7)(C) 14- subject 1125-1189 (on site sample). All nasal swabs were shipped to (b) (4) (b) (4). A copy of the instruction guide provided to study participants for the at home swab and photo of the swab itself is included as Exhibit (b) (6), (b) (7)(C) 5. (b) (6) informed us the sponsor recently provided a video which can be used to train study participants on the proper technique. (b) (6) reported the site has only used the video once (Subject (b) (6)). (b) (6) reported (b) (6) has only had two (2) issues involving the same day pick up of these sample by (b) (4).

Negative test results are not provided to the site. Per the sponsor Pfizer, their research laboratory - generated positive results from the nasal swabs are performed as part of the study procedures, not as a diagnostic for clinical care. If subjects are exhibiting potential COVID-19 symptoms, the sponsor suggests subjects seek counseling from their primary care physician and receive additional testing that will be analyzed at a licensed clinical laboratory. We observed documentation of study coordinators reaching out to subjects with positive test results, to tell them to reach out to their primary care physician for additional testing and counseling/care.

In April 2020, Meridian Clinical Research implemented clinical operating guidelines to address the conduct of clinical trials during the COVID-19 pandemic. This document was reviewed and is included as Exhibit (b) (6), (b) (7)(C) 2.

INSTITUTIONAL REVIEW BOARD (IRB)

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

The Ins

(b) (4)

The IR (b) (6)

(b) (6)

The protocol, informed consent documents, protocol amendments and recruitment materials have received IRB approval before initiation of study-specific procedures on subjects. IRB approvals were

reviewed for all amendments, ICF versions, advertisements and reportable events, along with general correspondence. Annual Progress Reports have yet to be submitted to the IRB since the study has not been active at this site for a years' time. There have been no reportable SAE's at the site. Two reportable incidents as described in the *Protocol* section of this report have been reported to the IRB.

HUMAN SUBJECTS RECORDS

Informed Consent

(Section written by (b) (6), (b) (7)(C)

Delegated staff including Dr. Harper, Sub-Investigators and clinical research coordinators (CRCs), explained the investigational study and consent document to prospective study subjects. Dr. Harper stated he participated in some of the consent process but it was mostly dedicated to the CRCs. He also stated he was available to answer questions for subjects during the consent process while he was on site.

eInformed Consent was not utilized at this site. It was approved for use by the IRB, but the site did not utilize the eInformed Consent process. Dr. Harper and (b) (6) explained that subjects were consented in person in a private exam room with enough time to review the consent form independently and with delegated staff. This step of the consent process was documented in each subjects' study folder for each version a subject was consented or reconsented with. The subject and/or the legally authorized representative would sign the ICF along with the delegated staff after all questions or concerns were addressed. A copy of the consent was given to the subject and/or the legally authorized representative after all signatures were completed. No short form ICF was utilized. The IRB did not stipulate specific requirements for the consent process.

100% of the audited subjects' informed consent documents were reviewed. Consent was obtained from all subjects prior to enrollment and all informed consent forms were appropriately signed and dated by the subject and the individual obtaining consent. The most current IRB approved versions of the informed consent document were used for all subjects and subjects were re-consented with the updated new versions as the ICFs were approved by the IRB. Three main versions of the ICF were used at the site for adult subjects as listed below:

- Version 3.0, IRB approved on 7/31/2020, Exhibit (b) (6), (b) (7)(C) 15
- Version 4.0, IRB approved on 9/11/2020, Exhibit 16
- Version 5.0, IRB approved on 10/10/2020, Exhibit (b) (6), (b) (7)(C) 17

Two other consents were used for the one child subject, to date, who has enrolled in the study:

- Phase 1/2/3/ Clinical Study Assent for Older Children Version 2.0, IRB approved 10/10/2020, Exhibit (b) (6), (b) (7)(C) 18
- Parent/Legal Guardian Permissions and ICF and HIPPA Authorization Version 3.0, IRB approved 10/15/2020, Exhibit (b) (6), (b) (7)(C) 19

The two above listed consents are the only versions used at the site to date.

The consent forms contained all the basic elements outlined in 21 CFR 50.25. The consent documents include the statement required by 21 CFR 50.25(c), "A description of this clinical trial will be available on https://ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

All original ICFs are maintained in separate version delegated binders. Subject folders contain a copy of the original ICFs and have a "Copy" or "Certified Copy" red stamp on page 1 of every consent form. These stamped copies cannot be verified as exact certified copies. There are no signatures of who made the copies or who verified them. There are initials and a date located on the bottom right of the last page of every consent which signifies the forms have been reviewed by the quality assurance department. There is no indication from these signatures that the copied ICFs in subjects' folders are exact copies of the original documents. Three examples of the stamped copied 1st page and the quality assurance initials/date on the last page are included as Exhibit (b) (6), (b) (7)(C) 20 (pages 1-2: Subject (b) (6) (b) (6) pages 3-4: Subject (b) (6) and pages 5-6: Subject (b) (6) . The site has no written procedures for this process. This was discussed with Dr. Harper as a verbal discussion item during the close out visit.

Source Records

(Section written by (b) (6), (b) (7)(C)

During the inspection 55 subjects' source records were reviewed. Source records included subject medical histories, physical exams, vitals, informed consents, case report forms, demographic data, procedure notes, printed subject diary entries, dosing records, correspondence of COVID-19 positive nasal swabs, correspondence of reported COVID-19 symptoms, safety monitoring and other required study visit data. Source data was organized, accurate, and legible with exception of the verbal observations discussed in EIR Section – Discussion with Management. There is adequate documentation that all subjects are alive and are available for their participation in the study. Source records contained information on the conditions of subjects at entry and during the study. Documentation of subject's exposure to the test article is maintained in each subjects' study folder as well as in the unblinded staff records, and pharmacy records. Source records clearly identity who is dosing subjects and documenting study procedures.

Following the completion of a study visit, and input of study data into (b) (4) (CRF), source records are uploaded into the (b) (4) which allows remote site monitoring and ongoing review by the CRO and/or sponsor.

Source records relating to the storage and processing of the investigational product were also reviewed. Observations are discussed within the EIR Sections – Control of Investigational Products and Discussion with Management.

Case Report Forms
(Section written by (b) (6), (b) (7)(C)

Paper case report forms were used for documenting subject histories/medical records, study visit procedures, dosing, AEs, concomitant medications, vitals and protocol deviations. Delegated site staff would record the data and Dr. Harper or a Sub-Investigator would review the data and sign off on it. The data would then be entered the eCRF data base by the CRCs and a designated Meridian Clinical Research EDC Specialist, listed as (b) (6) on the delegation log.

Approximately 25% of study subjects records were reviewed. Source data was compared with information recorded within the CRF (b) (4) Multiple discrepancies were noted which are discussed within the EIR Section – Discussion with Management. Dr. Harper and management at Meridian Clinical Research were encouraged to review their quality processes to ensure adequate reporting of study data.

(b) (6) informed us the site was preparing for a data lock which was scheduled to occur within the following weeks after this audit.

No Serious Adverse Events have been reported at this site. Adverse events and reactogenicity events (solicited and unsolicited) were reviewed within subject folder and through (b) (4) Observations are discussed within EIR Section – Discussion with Management.

Line listings were not provided with the background materials for this inspection; therefore, source documents and case report forms were not compared to a line listing.

OTHER STUDY RECORDS
(Section written by (b) (6), (b) (7)(C)

Per the CBER inspection assignment, a contract between Meridian Clinical Research and Dr. Harper was requested to be collected. We reviewed the contract and it was requested that we did not take a copy from the site per Meridian's legal team. We were able to collect the pertinent pages of the contract explaining Dr. Harper's role as an Independent Contractor acting as a Principal Investigator. These pages include the contractor's expected contributions to the business, duties and responsibilities and the signature page, Exhibit (b) (6), (b) (7)(C) 21. This contract went into effect on 5/25/2016.

The site uses a Clinical Trial Management System (CTMS) called (b) (4) for a patient database. In (b) (4) subject demographics, contact information and study participation information is managed across the Meridian Clinical Research sites in the United States. The site uses this management system to determine if subjects are eligible to participate in the screening process for studies. If subjects are enrolled in other studies conducted within the Meridian Clinical Research network, they cannot participate in other studies.

We reviewed (b) (4) with (b) (6) to observe what information is contained in the system for 8 enrolled subjects to see if they were participating in any other studies while participating in study C4591001. (b) (6) explained four dedicated staff members manage (b) (4) (b) (4) and that (b) (4) reports are discussed with staff to audit the study enrollment numbers and subject participation. (b) (4) is the only system they use to determine if subjects are enrolled in other studies. Other than that, the site relies on subject reporting.

INTERVIEWS OF SUBJECTS/PERSONNEL

(Section written by (b) (6), (b) (7)(C)

No significant deviations from the applicable regulations required interviewing study subjects. No Form FDA 463a, Affidavit, was collected from study personnel to document significant observations.

FINANCIAL DISCLOSURES

(Section written by (b) (6), (b) (7)(C)

Dr. Harper completed the financial disclosure form on 5/19/2020. Sub-Investigators and other required staff signed financial disclosures on 5/19, 21, 23 & 26/2020.

ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

(Section written by (b) (6), (b) (7)(C)

The (b) (4) Interactive Response Technology (IRT) System is currently used for participant screening, randomization, shipment receipt acknowledgment, inventory management, and breaking the blind by blinded site personnel. The IRT system also manages the expiry of supplies with regards to dispensing. This investigator site did not participate in the pilot mobile application, (b) (4) (b) (4) which could be utilized to verify kits/containers prior to dispensing. During the inspection, we observed the randomization, review of subject information and drug assignment within this system as conducted by unblinded site staff. (b) (4) permissions/user roles for delegated staff were reviewed for appropriateness. No observations were noted.

The first 43 subjects enrolled at this clinical site were included within the reactogenicity subset of study participants. As stated within Protocol Section 8.2.2 - Electronic Diary, these participants were required to complete a reactogenicity e-diary through the (b) (4) application which was either installed on a provisioned device or on the participant's own personal device. These participants documented events of local reactions and systemic events (including fever) and use of antipyretic medication that occurred in the 7 days after administration of the study intervention. The reactogenicity e-diary allowed recording of these assessments only within a fixed time window, from 600pm -1259pm.

All study participants utilized the (b) (4) application to record potential COVID-19 symptoms. Subjects reported symptoms of fever; new loss of taste/smell; new/increased cough; new/increased nasal discharge; new/increased shortness of breath; chills; new/ increased muscle pain; new/increased sputum production; new/increased wheezing; new/increased sore throat; diarrhea; vomiting; headache; and fatigue.

The (b) (4) for the e-diary was reviewed and included as Exhibit (b) (6), (b) (7)(C) 6. (b) (6) reported each study participant was individually trained (at clinical site) by study staff on the use of the software application. Source records were observed to document this training was provided. The sponsor did not provide a video to assist in this training.

Clinical sites were required to review and monitor diary compliance and solicited events through (b) (4). Evidence was observed within study participant folders for telephone contact as required by the protocol. Study participants were contacted after two weeks of non-compliance for the weekly COVID illness reporting. The clinical site also received email notifications for non-compliant participants. *The sponsor has not provided clinical sites access to review participant responses from the COVID illness e-diary in* (b) (4). The clinical site can only determine if there is a positive and/or negative response. Telephone contact is required in order for the site to determine what symptoms the subject has reported.

DCF (Data Clarification Forms) requesting modification to a study participants e-dairy were reviewed. The following DCFs were noted:

- Subject (b) (6) – A DCF was submitted requesting the study participant number be changed from (b) (6) to (b) (6) (Exhibit (b) (6), (b) (7)(C) 27, pg 1). As such, study source records from both subjects (b) (6) and (b) (6)) were reviewed. Neither folder included any description noting they had been previously identified as a duplicate subject within (b) (4) (b) (4).

  Study records revealed that Subject (b) (6) was randomized on 8/22/2020 at 10:32 (Randomization # (b) (6) see Exhibit (b) (6), (b) (7)(C) 27, pgs 4-5. Subject (b) (6) was randomized on 8/22/2020 at 10:17 (Randomization # (b) (6) see Exhibit 26, pgs 2, 4. Both subjects reported data into the (b) (4) application prior to the change of the data on 9/7/2020. Specifically, Subject (b) (6) reported data on 8/30/20 and 9/4/20 (Exhibit (b) (6), (b) (7)(C) 27, pg 2), and Subject (b) (6) reported data on 8/22/2020, 8/29/2020, 8/30/2020, and 9/5/2020 (Exhibit (b) (6), (b) (7)(C) 26, pg 1). (b) (6) was unable to immediately remember the details of how (b) (6) resolved this issue. Eventually, (b) (6) explained that (b) (6) contacted Subject (b) (6) who had kept the activation code initially provided during activation. The code was used to review subject information within (b) (4) prior to requesting the DCF. (b) (6) was instructed (b) (6) should have documented the discovery of the issue, and the actions taken within the subject records at the time. In response, an update was added to the source on 11/13/2020 (Exhibit (b) (6), (b) (7)(C) 27, pg 6).

- Subject (b) (6) – A DCF was submitted requesting to change the response for symptoms reported for the COVID e-diary from "Yes" to "No" (Exhibit (b) (6), (b) (7)(C) 25, pg 1). Source documents reported that on 9/11/2020 the patient inadvertently reported "yes" within the diary prior to recognizing the mistake. The subject confirmed that had no potential COVID-19 systems (Exhibit (b) (6), (b) (7)(C) 25, pg 2). The DCF was submitted on 9/14/2020 requesting this change, but has not been finalized.

  (b) (6) stated (b) (6) has since been informed that changes of this nature are not permitted.

- A number of DCFs have been submitted by the site to remove data which was entered in error for subjects who were not a part of reactogenicity subset, see example included as Exhibit (b) (6), (b) (7)(C) 31. (b) (6) stated there was only one option provided within (b) (4) at the time of enrollment for these subjects. I observed that (b) (4) has been updated to provide either a "yes/no" response to prevent the association of all subjects into this subset.

All subjects who have been lost to follow-up have been de-activated within (b) (4). Specifically, Subject (b) (6) (10/9/2020); Subject (b) (6) (10/30/20); Subject (b) (6) (10/9/2020); and Subject (b) (6) (10/9/2020). Subject (b) (6) was provided a provisioned device (b) (4) on 9/2/2020 after reporting the (b) (4) would not function on (b) (6) personal cellular device (Exhibit (b) (6), (b) (7)(C) 19, pgs 3-4). To date, this subject has yet to return the device. A certified letter, marked undeliverable, was sent to the participant requesting the device and that they contact the center (Exhibit (b) (6), (b) (7)(C) 19, pgs 6-8). (b) (6) stated the equipment will be reconciled at study end, and the sponsor notified at that time should the participant not return the device.

Help desk tickets (submitted by study participants) reporting issues with the (b) (4) application were documented for Subjects (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6). No significant findings were noted during our review.

Study data is recorded in the electronic Case Report Form (CRF) referred to as (b) (4). According to the CRF Completion Requirements for (b) (4), all study data must be recorded into the CRF within one (1) calendar day of assessments being completed (Exhibits (b) (6), (b) (7)(C) 33, pg 21 and (b) (6), (b) (7)(C) 32, pg 25). The inspection included a review of queries generated for data requiring clarification, and a comparison of source records with data which has been recorded within the CRF. Audit findings are discussed within the EIR Section - Discussion with Management.

CONTROL OF INVESTIGATIONAL PRODUCTS

(Section written by (b) (6), (b) (7)(C)

Pfizer supplied investigational products to include: BNT162b2 vaccine 250 mcg/0.5 ml (active), and 0.9% Sodium Chlorine Injection, USP (placebo and diluent) which were shipped to Meridian Clinical Research from (b) (4). As referenced in

Protocol Section 6 – Study Intervention, full details regarding the administration, preparation, handling, dispensing, storage and accountability are contained within the Investigational Product Manual (current version included as Exhibit (b) (6), (b) (7)(C) 13). Version 7.0 of this manual was the most recent manual at the time of audit (effective 10/16/2020); however, Version 3.0 was effective at study initiation.

Preparation and administration of the investigational drug products required aseptic technique. Employees were observed gowned, wearing a face shield, and wearing gloves during the preparation of the investigational drug product. The sponsor recommended that all handling and preparation of the drug products be carried out in a laminar air flow hood. Investigational drug was observed prepared in a laminar flow hood; however, the unit is not turned on during the preparation. (b) (6) reported the unit is never turned on during the preparation; only the surface of the equipment is utilized. During our observation on 11/12/2020, (b) (6) failed to contemporaneously record the time at which the syringe needle was inserted in the vaccine vial (see EIR Section – Discussion with Management). The IP Manual states that dose preparation may occur outside of an ISO 5 or better environment, such as on a tabletop or countertop. The in-use period for IP that is prepared within or outside of an ISO 5 environment or better is (b) (4) from the point of first stopper puncture to completion of administration. The unit, an (b) (4) laminar flow workstation manufactured by (b) (4) provides positive-pressure, ISO 5 air throughout the chamber. (b) (6) reported the unit was purchased approximately a year ago. The unit was recently calibrated /certified in April 2020; no issues were noted.

Temperature logs for the storage of all investigational products were reviewed for the period of 8/4/2020 through 10/30/2020 (Exhibit (b) (6), (b) (7)(C) 8). Temperatures are (b) (4) recorded during operational hours, excluding weekends and holidays. However, all refrigerated equipment is linked to an alarm system. For this study, 0.9% Sodium Chlorine Injection, USP requires storage at (b) (4) (b) (4) with (b) (4) allowed. We observed these drug products to be stored in a locked cabinet, yet the temperature probe was not in close proximity to the cabinet location and is also used to monitor the temperature of the entire room. Section 6.1 – Storage and Temperature Monitoring of Investigational Product at a Clinical Site of this manual states the active IP (BNT162b2 vaccine) must be stored in a freezer that has the appropriate temperature settings to maintain the IP at its labeled conditions of (b) (4), see Exhibit (b) (6), (b) (7)(C) 13, pg 53.

Freezer temperature logs documented temperature excursions occurred during the first and second week of study start. Specifically, the following temperatures were noted between 8/13/2020 through 8/20/2020 (see Exhibit (b) (6), (b) (7)(C) 8, pg 1):

Date	Temperature Recording (°C)	
	Minimum Temperature	Maximum Temperature
8/13/2020	-81.09	-73.83

Date	Temperature Recording (°C)	
	Minimum Temperature	Maximum Temperature
8/14/2020	-81.18	-76.39
8/17/2020	-81.10	-76.80
8/18/2020	-81.14	-76.80
8/19/2020	-81.10	-77.76
8/20/2020	-80.87	-80.32

As directed within Section 6.2 – Temperature Excursion During Site Store, the site should have immediately quarantined the supply of investigational product and informed the unblinded CRA, see Exhibit (b) (6), (b) (7)(C) 13, pgs 53-54. All temperatures were to be reported on the (b) (4) Site Temperature Excursion Form.

This observation also noted Meridian Clinical Research staff deviated from their approved procedures. Standard Operational Procedure (SOP) 5 – Handling of Investigational Product states that temperatures should be recorded (b) (4) of the temperature log and log printed (b) (4) The temperature must be checked and recorded (b) (4) (b) (4) (Exhibit (b) (6), (b) (7)(C) 1, pgs 18-20). Furthermore, SOP 6 – Temperature Monitoring states the temperature must be checked and recorded (b) (4) . Should the temperature be observed as outside of the required levels, the employee should immediately notify both the CRC responsible for the investigational product involved, Meridian Clinical Research management, and the appropriate sponsor personnel (see Exhibit (b) (6), (b) (7)(C) 1, pg 22). The temperature should then be carefully monitored until the temperature requirement is satisfied again.

(b) (6) was notified that although the temperature was documented as being outside of the acceptable range (b) (4) of the BNT162b2 vaccine, the employee failed to realize the issue and perform any of the required steps outlined within Meridian SOPS, or the protocol. (b) (6) , RN (unblinded CRC) explained (b) (6) thought there was a wider range for the storage of the BNT162b2 vaccine. There was no evidence of a quality review of the temperature logs. In response (b) (6) stated that (b) (6) does perform a review these logs, but does not document this task as there isn't any requirement to perform such a review within either SOP.

These deviations were first noted during the monitoring visit performed by the unblinded CRA on 8/20/20. As recorded within the follow-up letter, the monitor documented the site had explained the low temperatures (-81°C) was due to the opening and closing of the freezer to pull investigational IP (Exhibit (b) (6), (b) (7)(C) 12, pg 4-5). This explanation differed from those explained by (b) (6) and (b) (6) (b) (6) during the inspection.

The following Site Temperature Excursion Forms were approved on 8/20/2020:

- E12295: Documented temperatures with a minimum of -80.88°C (8/4/2020) and -80.94 °C (8/5/2020) associated with the storage of kits (b) (4) which arrived on 8/4/2020 (Exhibit (b) (6), (b) (7)(C) 7, pgs 1-2). The form documented the reason for the excursion as oversight (Exhibit (b) (6), (b) (7)(C) 7, pg 2)

- E12282: Documented temperatures from 8/13/2020 – 8/19/2020 for kits from shipments (b) (4) which arrived on 8/4/2020 and 8/18/2020, respectively (see Exhibit (b) (6), (b) (7)(C) 7, pgs 3-4). A total of 45 kits were associated with this deviation. The form documented the reason for the excursion as oversight, and due to frequent opening of the freezer door (Exhibit (b) (6), (b) (7)(C) 7, pg 4).

Investigational product materials were approved for use after they had been dispensed to subjects. See email communication included as Exhibit (b) (6), (b) (7)(C) 7, pgs 5-6.

Additional temperature excursions were noted during the transit of shipment (b) (4) containing kits (b) (4) which arrived on 10/27/2020, see Exhibit 7, pgs 8-10. The event included a two (2) hour excursion in which the temperature range was documented with a minimum temperature of 1.5 °C , and a maximum temperature of 40.4 °C, see Exhibit (b) (6), (b) (7)(C) 7, pgs 11-12 . These products should be held between (b) (4) °C. All materials were determined as acceptable for use on 10/27/2020 (Exhibit (b) (6), (b) (7)(C) 7, pg 13).

On 8/13/2020, a Product Complaint Form was submitted to the sponsor in association with kit (b) (4) (Exhibit (b) (6), (b) (7)(C) 30, pgs 1-2). (b) (6) explained that despite the investigational drug being prepared correctly, they were unable to obtain the required amount for the second syringe. The employee was only able to pull approximately 0.25ml instead of the required (b) (4). Ultimately, the subject was assigned a new vial kit (Exhibit (b) (6), (b) (7)(C) 30, pg 3). Pictures were submitted to the sponsor as evidence of the event (Exhibit (b) (6), (b) (7)(C) 30, pgs 4-5).

Investigational Product Accountability Logs (IPAL) were reviewed in association with subject records reviewed. During the onsite monitoring visit performed on 8/20/20, the unblinded monitor verified all investigational product dispensed to date, and the site destroyed all vials and syringes (Exhibit (b) (6), (b) (7)(C) 12, pgs 4-5). Outer cartons for the IP are being maintained as part of uCRA accountability. We observed the site has since maintained the empty vials and used syringes until they receive permission for final disposition. These materials are stored within the locked cabinet inside the locked unblinded staff office.

STUDY RECORDS CUSTODY AND RETENTION

(Section written by (b) (6), (b) (7)(C)

All study records for study C4591001 were retained and available during this inspection. Unblinded study records were maintained in a locked office with access to only unblinded staff. We observed unblinded staff using keys to enter the room where records were stored.

When studies are closed at the site and after a period of 1 to 2 years after closure of a study, records are sent to a third-party storage facility located at (b) (4) (b) (4).

REPORTS TO THE SPONSOR
(Section written by (b) (6), (b) (7)(C)

There have been no reportable SAE's at the site. Monitoring reports noted continued issues with the upload of source records within (b) (4) and responding to queries within the required time frames. Study data was required to be recorded in the electronic Case Report Form (CRF) within one (1) calendar day of assessments being completed.

MONITORING
(Section written by (b) (6), (b) (7)(C)

The study is currently being monitored by (b) (4). Monitoring by the blinded monitor(s) has been performed through remote and onsite audits. These audits include a review of documents uploaded within (b) (4). The Monitoring Log is included as Exhibit (b) (6), (b) (7)(C) 9, pgs 1-4. Monitoring records demonstrate that not all subject records have been reviewed through either method. (b) (6) reported monitoring was conducted on a (b) (4).

Investigator site records document remote monitoring has occurred during the following periods: 1) 8/14/2020; 2) 8/172020 - 8/21/2020; 3) 8/24/23020-8/28/2020; 4) 8/31/2020 – 9/4/2020; 5) 9/072020 – 9/11/2020; and 6) 9/24/2020 – 9/25/2020. Correspondence emails document Dr. Harper is not always included in the communications regarding upcoming monitoring visits despite no changes in the CROs monitoring personnel (see examples included as Exhibit (b) (6), (b) (7)(C) 10). Onsite monitoring visits have been held on: 1) 9/17/2020 – 9/18/2020; 2) 10/01/2020 – 10/05/2020; and 3) 10/12/2020 – 10/16/2020. Follow-up reports from these visits are included as Exhibit (b) (6), (b) (7)(C) 9, pgs 5-11. Noted observations include:

- Failure to update (b) (4) with Investigator Site File records
- Failure to upload source records within (b) (4) within the requirement time frame
- Failure to address queries within the required time frames

No reports acknowledged protocol deviations for the site despite the site maintaining an ongoing log.

On 11/4/2020, an oversight visit occurred to review the conduct of the protocol at the site; review of CRFs and corresponding source documents, informed consent documents, adverse events; regulatory binder; and pharmacy operations. This visit was conducted by (b) (6), Senior Site Relationship and Excellence Partner (Pfizer).

Onsite monitoring by the unblinded monitor(s) was completed on 8/20/2020. The monitoring log is included as Exhibit (b) (6), (b) (7)(C) 12, pg 1. Since this time, all monitoring has been conducted remotely. Follow-up reports noted observations to include:

- Temperature excursions within the freezer used to store the BNT162b2 vaccine occurring from 8/13/2020 – 8/19/2020 (see Exhibit (b) (6), (b) (7)(C) 12, pgs 4-5)
- Incomplete training of unblinded staff and failure to update the Site Signature and Delegation of Duties Log (Exhibit (b) (6), (b) (7)(C) 12, pgs 6-11)
- IPAL (Investigational Product Accountability Log) fails to include documentation of the destruction of vials used to dose the second subject (see Exhibit (b) (6), (b) (7)(C) 12, pgs 11-12).

COMPLAINTS
(Section written by (b) (6), (b) (7)(C)

There were no complaints on file in FACTS.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
(Section written by (b) (6), (b) (7)(C)

A Form FDA 483, Inspectional Observations, was not issued as a result of this inspection.

GENERAL DISCUSSION WITH MANAGEMENT
(Section written by (b) (6), (b) (7)(C)

Close-out discussion was held with Dr. Charles H. Harper on 11/13/2020. Additional participants included (b) (6), Site Manager and (b) (6), COO. A Form FDA-483, Inspectional Observations, was not issued. Regulatory sanctions were explained to include: Untitled Letter, Warning Letter, Regulatory Meeting; re-inspection to verify corrective actions; and rejection of the clinical sites data. During the close-out meeting, we discussed the following observations listed below not already mentioned within the EIR. During this discussion, we encouraged the clinical site to review their quality processes to assure adequate data capture, Dr. Harper verbally agreed to address all the observations; however, a formal response was not promised.

Inadequate Source Records / Toxicity Grading

Subject (b) (6) On 8/20/2020, a Potential COVID-19 Illness Visit (unplanned) was completed by telephone. During the visit, the subject reported: 1) new/increased sore throat; 2) new loss of taste/smell; and 3) fatigue (Exhibit (b) (6), (b) (7)(C) 24, pg 2). The subject reported the onset of the first symptoms as occurring on 8/18/2020 (Exhibit (b) (6), (b) (7)(C) 24, pg 1). The symptom assessment for this visit was observed to have several late entries. (b) (6) stated that (b) (6) had only recorded the positive responses on the form during the telephone interview and filled in the remainder of the form on 10/15/2020. At the time of audit, the CRF page (Signs and Symptoms of Potential COVID-10) had

not been updated to include "fatigue" (Exhibit (b) (6), (b) (7)(C) 24, pg 3). A toxicity grade as it relates to the illness/symptoms must be determined even if a diagnosis (e.g. respiratory illness) is not made. This information must be reported within the CRF for the unscheduled visit. The toxicity grade documented within the CRF for this visit was "1", and a diagnosis for the potential COVID-19 illness was not determined (Exhibit (b) (6), (b) (7)(C) 24, pg 4). However, there was no documented evidence of this evaluation by either Dr. Harper or a Sub-Investigator delegated to this study. The audit trail for the toxicity grade was entered into the CRF by (b) (6) on 8/25/2020 following an open query for the missing information initiated on 8/22/2020 (Exhibit (b) (6), (b) (7)(C) 24, pg 6).

(b) (6) confirmed the clinical site discovered the source records for Potential COVID-19 Illness visits failed to include any reference to an evaluation for toxicity grade. We observed the source was updated on 10/9/2020 to include this information (see Subject (b) (6) Exhibit (b) (6), (b) (7)(C) 28, pg 4). According to the Site Signature and Delegation of Duties Log, the assessment of an AE/SAE can only be performed by Drrs. Charles Harper and (b) (6) Dr. Harper was advised to review all of the source records associated with subjects who were seen for Potential COVID-19 Illness visit and/or Convalescent Visits to determine the toxicity grade recorded by clinical staff prior to the updated record. Furthermore, he should ensure there is documentation supporting his evaluation and agreement (or change, if applicable).

During this visit, the protocol requires staff collect and update COVID-19–related standard of care clinical and laboratory information. Our review also noted the source record for this visit failed to include any reference to 1) illness severity assessments; 2) health care utilization; 3) hospitalization; and 4) respiratory treatment. However, the CRF was observed to have been updated with information relative to the visit performed on 8/20/20 (Exhibit (b) (6), (b) (7)(C) 24, pgs 17-26). The audit trail documents this information was entered in the CRF by (b) (6) on 8/22/2020. (b) (6) (b) (6), (b) (7)(C) received multiple queries (including auto generated) in regards to this CRF page (Exhibit 24, pg 17). However, no source was ever generated to capture any response from the subject, and no additional follow-up verifying the information initially recorded for this visit was observed. Instead, source records document the subject was first asked to provide this type of information during the Potential COVID-19 Convalescent Visit conducted on 9/17/2020 (Exhibit (b) (6), (b) (7)(C) 24, pgs 9-11).

Subject (b) (6) On 10/28/2020, a Potential COVID-19 Illness Visit (unplanned) was completed by telephone. During the visit, the subject reported a fever, and a positive COVID test (Exhibit (b) (6), (b) (7)(C) 28, pgs 1-2, 7). The subject reported the onset of the first symptoms as occurring on 10/22/2020. Upon evaluation by Dr. Harper, documented a clinical diagnosis of respiratory illness ("Yes") with a toxicity grade of 1" (Mild), (Exhibit (b) (6), (b) (7)(C) 28, pg 4). However, the information has been erroneously recorded within the CRF. Specifically, the toxicity grade was entered as "2", and a "No" response was entered for the diagnosis for the potential COVIDE-19 illness (Exhibit (b) (6), (b) (7)(C) 28, pg 5). CRF entries were completed by (b) (6) on 10/30/2020 (Exhibit (b) (6), (b) (7)(pg 6). Monitoring reports did not acknowledge a review of the source records for this subject.

Dose Preparation of Investigational Drug Product

Observation 1: We observed the preparation of investigational drug product on 11/10/2020 and 11/12/2020. On 11/20/2020, following the retrieval of the drug product from the freezer at 1330, (b) (6) recorded the time of "1400" on the Preparation Record as the "Dose preparation start time" (see Exhibit (b) (6), (b) (7)(C) 14, pgs 1, 3). We observed (b) (6) document this time (b) (4) in advance of performing the task. In Section 8.6 – Preparation and Administration of IP of the Investigational Product Manual, the "start of dose preparation" is defined as the time at which the vial stopper is first punctured (Exhibit (b) (6), (b) (7)(C) 13, pg 61). The following steps as listed on the Preparation Record must occur prior to needle insertion, see Exhibit (b) (6), (b) (7)(C) 14, pgs 1-2:

(b) (4)

The (b) (4) . This is the (b) (4) insertion of the needle. Based on the time of this insertion, employees should record the expiration of (b) (4) onto to the Preparation Record, syringes, vials, and product containers.

(b) (6) explained (b) (6) records the time as a reminder to start the process at the recorded time. (b) (6) further explained the form did not specifically include a place to record when the needle was inserted. According to (b) (6) , the actual time of needle insertion is only being documented in situations where a second dose would be administered from the BNT162b2 vial (see examples included as Exhibit (b) (6), (b) (7)(C) 29). In response, I explained to (b) (6) that (b) (6) was incorrect and showed (b) (6) the additional wording stated in the same field where (b) (6) had documented "1400". Both (b) (6) Unblinded CRC) and (b) (6) stated that should they walk away from the room, a timer would be utilized to ensure they returned within (b) (4) of the time which was recorded.

Currently, (b) (6) reports to (b) (6) , Site Director who is a blinded staff participant for this study. (b) (6) stated that staff would immediately be re-trained by (b) (6) (Meridian Clinical Research, Sioux City, IA) who serves as the lead for unblinded personnel at the Norfolk research site. Dr. Harper agreed with the observation and stated all unblinded staff would be re-trained immediately. On 11/23/2020, (b) (6) reported unblinded personnel had been retrained specific to this observation. Documentation of this training was not collected.

Observation 2: Preparation Records for investigational drug product for Subject (b) (6) on 9/1/2020 were reviewed (Exhibit (b) (6), (b) (7)(C) 15). The Drug Assignment Confirmation Report documents the drug vial number was assigned at 12:24 (Exhibit (b) (6), (b) (7)(C) 5, pg 3). The unblinded CRC documented the drug vial was pulled from the appropriate storage area at 12:20 (prior to drug assignment), see Exhibit (b) (6), (b) (7)(C) 15, pg 3. This error was not noticed until the review of the records on 11/4/2020, at which time the time was changed to "1225". I asked (b) (6) to explain why (b) (6) changed the record so many months later, and how (b) (6) would be able to recall the exact time recorded for the correction. (b) (6) explained (b) (6) simply recorded a time after the assignment time, confirming (b) (6) did not recollect any specific time (b) (6) and (b) (6) were informed that in such a case, the error should have been acknowledged, but no time recorded if it was not precisely known. This observation was shared

with Dr. Harper, (b) (6) and (b) (6). (b) (6) explained additional training would be provided by (b) (6) in response to this observation,

Adverse Event Reporting

Subject (b) (6) This subject received their first vaccination on 8/13/2020. During Visit 2 (9/1/2020), the subject reported they had experienced underarm swelling ipsilateral to the injection site (left arm) for approximately 24 hours after the vaccination (Exhibit (b) (6) 18, pg 1). The adverse event was reported on the Adverse Events Logs as occurring from *8/14/2020 – 8/15/2020* (Exhibit (b) (6) 18, pg 2). However, the event has been erroneously recorded within the CRF as occurring from *8/18/2020 – 8/19/2020* (Exhibit (b) (6) 28, pg 3). The Follow-up Monitoring Report for remote monitoring activities performed during 8/17/2020 – 8/21/2020 states the AE was reported appropriately (Exhibit (b) (6) 11).

Subject (b) (6) During Visit 2 (9/3/2020), the subject reported potential COVID-19 symptoms to include: 1) new/increased cough, 2) new/increased nasal congestion, and 3) headache (Exhibit (b) (6) 21, pg 1). The associated CRF page has not been updated to include any reports for 'headache', see Exhibit (b) (6) 21, pg 2. The subjects reported medical history includes migraines; however the record was annotated to state the subject had experienced an increase in the frequency and severity of migraines during the prior week (Exhibit (b) (6) 21, pg 1). Dr. Harper and (b) (6) were also asked to review the subject's record to determine if an adverse event should be recorded since this was an exacerbation of their current medical condition.

The CRF for this subject included an entry noting the subject experience a sinus infection occurring from 8/26/2020 – 8/30/2020 (Exhibit (b) (6) 21, pg 3). However, source records for this subject did not include any documentation supporting this subject ever reported this adverse event.

Missed Reporting of events in the E-diary (Reactogenicity Subset)

Subject (b) (6): This subject was a part of the reactogenicity subset. Following the first vaccination administered at Visit 1 (8/12/2020), the subject recorded within the e-diary headaches occurring on 8/13/2020, 8/17/2020, and 8/18/2020 (Exhibit (b) (6) 17, pg 8). The subject also confirmed medication was taken on these days to relieve reported symptoms. Following the second vaccination at Visit 2 (8/31/2020), the subject recorded headaches occurring on 9/4/2020 and 9/5/2020 within the e-diary (Exhibit (b) (6) 17, pg 11). On 9/8/2020, (b) (6) contacted the subject regarding their documentation of medication within the e-diary. During this contact, (b) (6) was informed the subject had taken Tylenol on Day 2, 3, 5 and 6 , but all symptoms had resolved (Exhibit (b) (6) 17, pg 9). (b) (6) updated the Concomitant Medication Log to include Tylenol used for a headache on 9/1/2020 – 9/2/2020 and 9/4/2020 – 9/5/2020 (Exhibit (b) (6) 17, pgs 6-7).

We asked why the site did not capture the adverse event of "headache" on 9/1/2020 – 9/2/2020 within the CRF. (b) (6) was asked to explain how the site was advised to handle reporting missed reporting within the e-diary. However, (b) (6) was unable to provide this information. We asked that (b) (6) contact the sponsor for clarification. The following day, (b) (6) reported that (b) (6) had been advised to submit the missing information as a DCF. In response, we reviewed the CRF Completion Requirements for (b) (4) with Dr. Harper and (b) (6). According to the Section entitled – Adverse Event CRF versus e-diary Data, clinical sites can enter e-dairy events into the AE CRF *if* the investigator determines it is necessary. Reasons provided include 1) awareness of missing data reported outside of the diary (including increases in event severity); events for which additional information is available (e.g. event led to participant withdrawal, or for other reasons at the discretion of the investigator (Exhibits (b) (6), (b) (7)(C) 32, pg 158 and 33, pg 141).

The following table was also provided within the CRF and provided scenarios on how to determine accurate reporting. Based on this information, we explained this would require more involvement of Dr. Harper in determining what AE information should/should not be reported. The initial information obtained in regards to AEs was reported to the CRC, who would enter the information on the AE log which is then evaluated by Dr. Harper. The allowance for investigator discretion, and the scenarios presented in the CRF guideline presented a challenge in determining if the clinical site under-reported adverse events. Adverse events which are captured in the (b) (4) application (regardless of reactogenicity or potential COVID illness) are independent of those recorded within the CRF.

This section of the CRF Completion Requirements was included from the most effective version (Version 8, 14 Oct 2020), see Exhibit (b) (6), (b) (7)(C) 32, pg 159). However, the table remained unchanged from the version used at study start (Version 5, 04 Aug 2020). Version 6 (14 Aug 2020) of the CRF Completion Requirements is included since it was utilized as the reference for reporting a large number of subject data following study start (Exhibit (b) (6), (b) (7)(C) 33, pg 143).

#	Scenario	Data Entered in eCRF
1	There are some symptoms that are ongoing on the last day of the diary.	The end dates of these symptoms that are ongoing on the last day of the diary will be recorded on the appropriate section of the Symptom Resolved Dates CRF at the V4_WEEK3_VAX2_S and V6_WEEK2_POSTVAX2_S visits for Stage 1 (b) (4) / Phase 1 subjects and at V2_VAX2_L and V3_MONTH1_POSTVAX2_L for Stage 3 / Phase 2/3 subjects that are in the reactogenicity subset. No AE page should be completed for these symptoms that are ongoing unless investigator deems it appropriate, e.g. increases in event severity.
2	A day is missing in the e-diary, but the event is reported in the e-diary on the previous or following day.	Generally, unless the investigator deems it appropriate, nothing needs to be entered in the CRF.
3	A day (or more) is missing in the e-diary, and the investigator becomes aware of symptoms occurring on missing days that are not captured on previous or following days, e.g., Participant had a fever within 14 days following vaccination that was not captured in the e-diary.	If deemed appropriate by PI, reactogenicity events that are not reported in the e-diary in error can be captured on the AE CRF.

Prior to the close of the inspection, (b) (6) reported the sponsor had instructed (b) (6) to report the headache for this subject as an AE within the CRF.

Adverse events which are captured in the (b) (4) application (regardless of reactogenicity or potential COVID illness) are independent of those recorded within the CRF.

Subject (b) (6): Following the administration of the study intervention at Visit 1 (8/14/2020), the subject was contacted on 8/21/2020 after failing to record any information regarding Day 7 in their e-diary (Exhibit (b) (6), (b) (7)(C) 22, pgs 5, 8). During the telephone call, (b) (6) recorded "all symptoms resolved on 20 Aug 2020 by early morning and did not upset normal daily activity" (Exhibit (b) (6), (b) (7)(C) 22, pg 5). Information regarding this contact was documented on the Subject eDiary Review Log and the Additional Source log (see Exhibit (b) (6), (b) (7)(C) 22, pgs 5, 11). The Concomitant Medication Log documented the use of Ibuprofen for chills and fatigue with a start date of 8/16/2020 – 8/17/2020 (Exhibit (b) (6), (b) (7)(C) 22, pg 4).

During Visit 2 (9/4/2020), study staff must obtain the stop dates from stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates are documented in the source documents and the information entered in the CRF. Although the subject did not enter any information into the e-diary for Day 7, this information had been verbally provided during telephone contact. Following the visit, study staff updated the CRF page – Vaccination Symptoms Diary (Symptom Resolved Dates)

to indicate the subject had reported no symptoms (Exhibit (b) (6), (b) (7)(C) 22, pgs 14-20). However, (b) (6) made corrections to the original entries on 9/12/2020. Based on the annotation of the eDiary Review Log, all adverse events were resolved on 8/20/2020 (Exhibit (b) (6), (b) (7)(C) 22, pg 5). Our review documented the entry for 'chills' erroneously reports the end date as "8/21/2020", see Exhibit (b) (6), (b) (7)(C) 22, pg 12). There was no additional supporting documentation within the subject's folder to indicate they continued having any adverse events on this date.

Inadequate Documentation for Medical History

Subject (b) (6): During Visit 1 (8/14/2020), study staff reported "edema" within the subject's Medical History (Exhibit 23, pg 1). Furosemide (40 mg /qd) was reported as an ongoing medication for the treatment of this condition at the visit (Exhibit (b) (6), (b) (7)(C) 23, pg 5). Subsequently, the original entries were annotated to state "Bilateral lower leg" on 10/27/2020. A review of the CRF documented the site was sent a query requesting clarification on the medical diagnosis. As a result, the additional information was added to the medical history, and the concomitant medication log.

No abnormalities and are additional information pertaining to this condition was documented on the source records for the physical exams conducted at Visit 1 (8/14/2020) and Visit 2 (9/2/2020), see Exhibit (b) (6), (b) (7)(C) 23, pgs 2, 4. There was no evidence of contact with the subject which supports the additional information which was documented on 10/27/2020 (Exhibit (b) (6), (b) (7)(C) 23, pg 6).

Dr. Harper was informed the physical exams should be used to document additional findings which may be reported by the subject when self-reporting concomitant medications and medical history. Dr. Harper stated the condition also may not have been observed during either study visit. We agreed this could have been the case, which would require study staff to telephone the subject to obtain this information. Any additional contact with the subject must be documented within the study records.

Subject (b) (6): During Visit 1 (8/12/2020), the subject reported a vasectomy as the method of contraception (Exhibit (b) (6), (b) (7)(C) 16, pg 1). The source record for Medical History asks "Does subject report any medical/surgical history". In response, the form was documented as "No" (Exhibit (b) (6), (b) (7)(C) 16, pg 2). Additionally, no information regarding Medical History has been updated within the CRF (Exhibit (b) (6), (b) (7)(C) 16, pgs 4-5).

FSH Confirmation Testing for Post-Menopausal Women

FSH requirement for women under the age of 60 was also discussed with Dr. Harper during the close out meeting, see discussion included within the *Protocol* Section of this report.

Certified Copies

The copying of ICFs was also discussed with Dr. Harper during the close out meeting, see discussion described in the *Human Subject Records* section of this report

ADDITIONAL INFORMATION

(Section written by (b) (6), (b) (7)(C)

During the inspection, we provided a digital media thumb-drive to collect electronic data and records. The original thumb-drive was sealed in an FDA-525, (Exhibit (b) (6), (b) (7)(C) 34) and filed with the original hardcopy documents within the Kansas District Office.

REFUSALS / SAMPLES COLLECTED

(Section written by (b) (6), (b) (7)(C)

No refusals were encountered. No samples were collected.

VOLUNTARY CORRECTIONS

N/A

EXHIBITS COLLECTED

Exhibits submitted by (b) (6), (b) (7)(C)

Exhibit (b) (6), (b) (7)(C)	1	Dr. Harper CVs, 9 pages
Exhibit	2	Meridian Clinical Research Organizational Charts, 33 pages
Exhibit	3	Submitted Form FDA 1572, 3 pages
Exhibit	4	Dr. Harper List of Studies as Clinical Investigator, 2 pages
Exhibit	5	Dr. Harper List of Studies as Sub-Investigator, 8 pages
Exhibit	6	Delegation of Authority Log, 8 pages
Exhibit	7	Subject Screening Enrollment Log, 8 pages
Exhibit	9	Subject (b) (6) Visit 1 CRFs and Laboratory Records, 18 pages
Exhibit	10	Subject (b) (6) Visit 1 CRFs and Laboratory Records, 30 pages
Exhibit	11	Protocol Deviation Log, 2 pages
Exhibit	12	IRB Protocol Deviation Reportable Events for Subjects (b) (6) and (b) (6) (b) (6) 8 pages
Exhibit	13	Subject (b) (6) Nasal Swab Records, 8 pages
Exhibit	14	Subjec (b) (6) Nasal Swab Records, 4 pages
Exhibit	15	ICF Version 3.0, 28 pages
Exhibit	16	ICF Version 4.0, 29 pages
Exhibit	17	ICF Version 5.0, 30 pages
Exhibit	18	Assent for Older Children, 8 pages

Exhibit	19	Parent/Legal Guardian Permissions Consent, 32 pages
Exhibit	20	Stamped Copy ICFs for 3 Subjects, 6 pages
Exhibit	21	Meridian and Dr. Harper Independent Contractor Contract Pages, 3 pages

Exhibit mitted by (b) (6), (b) (7)(C)

Exhibi	1	Meridian SOP Manual, 50 pages
Exhibi	2	SOP Conduct of Clinical Trials During COVID 19, 6 pages
Exhibi	3	Recruitment Materials, 2 pages
Exhib	4	Notification of Positive COVID PCR Result, 6 pages
Exhib	5	Nasal Swab Instructions and Photo, 5 pages
Exhib	6	(b) (4) , 52 pages
Exhib	7	Temperature Excursions, 13 pages
Exhib	8	Temperature Monitoring Log, 6 pages
Exhib	9	Blinded Monitoring (Onsite), 11 pages
Exhib	10	Email Correspondence for Remote Monitoring, 6 pages
Exhib	11	Remote Monitoring Aug 17 -Aug 21 2020, 2 pages
Exhib	12	Unblinded Monitoring, 13 pages
Exhib	13	Investigational Product Manual V7.0, 98 pages
Exhib	14	Preparation Record Subject (b) (6), 4 pages
Exhib	15	Preparation Record Subject , 3 pages
Exhib	16	Subject (b) (6) , 5 pages
Exhib	17	Subject (b) (6) 13 pages
Exhib	18	Subject (b) (6) , 9 pages
Exhib	19	Subject (b) (6) 8 pages
Exhib	20	Subjec (b) (6) , 4 pages
Exhib	21	Subject (b) (6) , 3 page
Exhib	22	Subject (b) (6) , 20 pages
Exhib	23	Subject (b) (6) , 6 pages
Exhib	24	Subject (b) (6) , 26 pages
Exhib	25	Subject (b) (6) , 2 pages
Exhib	26	Subject (b) (6) , 6 pages
Exhib	27	Subject (b) (6) 6 pages
Exhib	28	Subject (b) (6) 24 pages
Exhibi	29	Examples of IP Dosing Documentation, 2 pages
Exhibi	30	Product Complaint Form, 5 pages
Exhibi	31	DCF Reactogenicity Subset, 6 pages

Exhibit (b) (6), (b) (7)(C) 32 CRF Completion Requirements V8 Oct 14 2020, 184 pages
Exhibit 33 CRF Completion Requirements V6 Aug 14 2020, 166 pages
Exhibit 34 FDA-525, USB Drive of Electronic Documents (Sealed), 1 page

ATTACHMENTS

FDA-482, Notice of Inspection issued to Dr. Charles H. Harper, MD (dated 11/9/2020), 3 pages
Attachment (b) (6), (b) (7)(C) 1 CBER Assignment Memo, 5 pages

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

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

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

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