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SUMMARY

This High Priority PDUFA Directed Inspection as conducted in response to a BIMO inspection assignment from the Office of Scientific Investigations, Center for Drug Evaluation and Research (CDER). The assignment was conducted under **FACTS #11963013** and **OP ID 136583** and in accordance with 7348.810-Sponsors, Contract Research Organizations and Monitors.

The previous inspection covering BIMO operations was conducted on 1/9-17/20 and was classified as NAI. No FDA 483 Inspectional Observations List was issued.

The current inspection did not find any reportable issues. No FDA 483 was issued. There was one discussion item regarding one site where sampling did not meet the (b) (4)% source data verification review sampling as per the monitoring plan, where an additional subject should have been sampled.

The current inspection covered application number BLA 761109, LY900014 (Ultra Rapid Lispro), Protocols I8B-MC-ITRM and I8B-MC-ITRN:

- A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro with an Open-Label Postprandial LY900014 Treatment Group, in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes (PRONTO-TID)

- A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes (PRONTO-T2D)

Current inspection covered seven (7) clinical investigator sites involving studies ITRM and ITRN. The following operations were reviewed during the inspection (but not limited to): site selection and qualification; site staff training in GCP and the protocol; vendor selection and oversight; blinding process; safety and adverse event reporting; Serious Adverse Events (SAEs); protocol deviations; monitoring; site escalations; financial disclosures; test article accountability; and data management.

ADMINISTRATIVE DATA

Inspected firm:	Eli Lilly and Company
Location:	839 S Delaware St Indianapolis, IN 46225-1782
Phone:	1-317-361-3997
FAX:	1-317-276-6331
Mailing address:	839 S Delaware St Indianapolis, IN 46225-1782
Email address:	donnelly_patty@lilly.com
Dates of inspection:	3/16/2020-3/20/2020
Days in the facility:	5
Participants:	**Myra K Casey, Investigator**

Non-FDA Participants: NA

Initially, I had planned to preannounce the inspection on 3/9/20; however, on the same day, Ms. Elizabeth Van Sant Hoffman, Senior Director, Medicines Quality Organization, Eli Lilly and Company (aka Lilly) sent me a courtesy email stating that Lilly implemented work from home status for their US-based employees due to COVID-19 Pandemic; however, in the event of an inspection, employees would come into the office. I telephoned Ms. Van Sant Hoffman and preannounced an inspection to begin on 3/12/20, involving protocols I8B-MC-ITRM and I8B-MC-ITRN (also referred to as ITRM and ITRN).

On 3/10/20, I telephoned Ms. Van Sant Hoffman and discussed with her a news report that some one at the firm contracted COVID-19. Ms. Van Sant Hoffman indicated that precautionary measures had been taken in light of this situation. We also discussed the possibility of remote site review of records electronically; however, I later found that this was not permitted by the agency and therefore was not discussed any further. Ms. Van Sant inquired about which days I plan to cover certain areas so that the appropriate personnel would be available at the firm to assist. She further stated that she would propose a list of areas to be covered (each day) based on the previous inspection flow.

Ms. Van Sant Hoffman sent me an email dated 3/10/20, proposing specific coverage during the inspection based on the previous inspection. Furthermore, attached to this email was an official response dated 3/10/20, which indicates that Lilly implemented measures in their US facilities to reduce the risk of transmission of the Novel Coronavirus (SARS-CoV-2). Also, the email describes what to expect as a visitor to the corporate campus.

On 3/11/20, I telephoned Ms. Van Sant Hoffman requesting if the inspection could be held off site. Ms. Van Sant sent an email indicating that she was following up with her management regarding potential location options.

On 3/12/20, I telephoned Ms. Van Sant Hoffman and informed her that I would initiate the inspection on 3/16/20. With regard to the inspection being held off site, Ms. Van Sant Hoffman, stated that they determined that the corporate location would be the best due to the precautionary measures that had been taken. Ms. Van Sant Hoffman attached to the email an official response which indicated that the Lilly Corporate Center would be the most suitable facility to support the inspection. This email also elaborated on the cleaning of the facility and other measures to ensure my safety during the inspection. The letter also indicates that the Lilly Corporate Center would be the best location for the inspection. Ms. Van Sant Hoffman sent a follow-up email requesting whether I had any questions about the letter.

Ms., Van Sant Hoffman sent an email at the end of the day on 3/12/20, confirming my arrival on 3/16/20. The email also confirmed our previous discussion regarding the protection of myself and their staff (i.e. social distancing, no more than 5 people in the room) and that staff will also be available remotely to process requests. Ms. Van Sant Hoffman indicated that based on the previous inspection and using the BIMO compliance guide as a reference, a tentative schedule was proposed for the inspection for the inspection during 3/16-20/20.

On 3/16/20, I issued an FDA 482-Notice of Inspection to Ms. Patty J. Donnelly Vice President, Global Quality Research and Development (R&D). Ms. Donnelly acknowledged that she was the most responsible person in charge of studies ITRM and ITRN. Also present at the opening meeting and throughout the inspection was the following (core) individuals: Mr. Brian Mitchell, Director, Global Quality R&D, Mr. (b) (6), Advisor, Clinical Development-Diabetes, Ms. Kim Holton, Director, Global Quality R&S. Ms. (b) (6), Advisor, Global Quality R&D. Ms.

(b) (6) was not present at the opening meeting, but later came into the room; she was present each day during the inspection and served as a scribe.

During the beginning of the inspection, Mr. Hemiup provided a slide presentation where the following individuals were present via telecom: Ms. Patty Donnelly, VP Global Quality; Mr. Chad Grothen, Senior Director, Clinical Development-Diabetes; Mr. Thomas Hardy, Senior Director, Medical Diabetes/Endo; Mr. Jonathan Denne, Vice President, Clinical Development and Ms. Elizabeth Van Sant Hoffman, Senior Director, Medicines Quality Organization.

On 3/20/20, Ms. Patty J. Donnelly, Vice President, Global Quality R&D and Ms. Elizabeth Van Sant Hoffman, Senior Director joined the core group of individuals at the close of the inspection. Also, present via telecom was Mr. Chad Grothen, Senior Director, Clinical Development-Diabetes; Mr. Thomas Hardy, Senior Director, Medical Diabetes/Endo; Mr. Jonathan Denne, Vice President, Clinical Development

Exhibit 1- Emails and official letters

HISTORY

The history of business remains the same as reported in the previous inspection report dated 1/20. At the onset of the inspection, the firm provided a slide presentation consisting an overview of the firm, clinical development and oversight (including organizational structure) and overview of the Ultra Rapid Insulin trial. **(Exhibit 2**)

Lilly has overall accountability for quality management, conduct and oversight of the LY900014 program studies with the utilization of various 3rd party organizations such as:

(b) (4) -Site Monitoring
(b) (4) -Central Monitoring
(b) (4) -Data Management and validation
(b) (4) .-eData Capture (b) (4))
(b) (4) -Packaging and Labeling

The hours of operation are (b) (4)

Any agency correspondence should be directed to the following individual:

Patty J. Donnelly, Vice President Research and Development Quality
Eli Lilly and Company
839 South Delaware Street
Indianapolis, IN 4628

INTERSTATE (I.S.) COMMERCE/JURISDICTION

Application number BLA 761109, LY900014 (Ultra Rapid Lispro), Protocols I8B-MC-ITRM and I8B-MC-ITRN were conducted in support of IND #(b) (4). (**Exhibits 3, 4** -Protocols)

The Investigational Product (IP) for ITRM and ITRN was manufactured by (b) (4) (b) (4) The IP was packaged by (b) (4), (b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Ms. Patty J. Donnelley, Vice President Research and Development Quality duties and responsibilities remain the same as reported in the previous inspection report of 1/20, which includes the following: Leads Quality oversight for R& D activities, including the Medicines Quality Organization (Medical, Regulatory and Safety, Pharmacovigilance, Quality oversight), and the Product Research and Development Quality organizations, including Global Clinical Trial supply and distribution Quality oversight. Her responsibilities also include oversight for contracted quality activities for R&D performed for and on behalf of Eli Lilly and Company. Dr. Donnelly reports directly to Ms. Johna Norton, Senior Vice President Global Quality. Ms. Norton reports directly to David Ricks, Chairman, President and Chief Executive Officer. (Exhibit 2)

During the inspection, Mr. Brian Mitchell, Director, Global Quality Research and Development facilitated the inspection by serving as the host; he provided me with information and records and accompanied me during the inspection. Mr. Mitchell acknowledged that he does not have any specific duties and responsibilities as it relates to the inspected studies.

On a daily basis, information was also provided by Mr (b) (6), Advisor, Clinical Development-Diabetes and Kim Holton, Director, Global Quality R & D.

As indicated in the previous report of 1/20, the firm acknowledged that protocol approval is the responsibility of the medical organizations. The selection of investigators and monitoring is overseen by the Site Engagement Group. Statistical analysis is conduced by (b) (4) (data management statistics). Adverse event and safety information is the responsibility of the Global Safety and Medical organizations.

Exhibit #5-ITRM and ITRN Roles and Responsibilities of key individuals.

FIRM'S TRAINING PROGRAM

Training for studies ITRM and ITRN was conducted on-line and/or during an Investigator Meetings/Conferences. Training included topics such as ICH GCP Investigator Training, Protocol, Informed Consent, IWRS, Product Complaints, Privacy, SAE Reporting, Safety Mailings and Source Documentation. Training also included the compound overview, eDiaries, Central Lab Overview, Trial Manager Overview, Critical Data Overview, and Clinical Trial Material Training. Training records indicate that Investigator Meetings were held at various locations such as; Nashville, TN on 6/30/17 and San Francisco, CA on 6/2/17.

I reviewed training certificates of completion for each clinical investigator, study coordinator or sub-investigator. No deficiencies were noted.

MANUFACTURING/DESIGN OPERATIONS

SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

The firm’s selection of clinical investigators remains the same as reported in the previous inspection report, in that, clinical investigator selection is based on experience and qualifications.

The monitoring of clinical investigators is performed in accordance with an Integrated Monitoring Procedure for each study. The plan describes tasks to be performed by the Contract Research Associate (CRA) and Central Monitor including the approximately frequency of monitoring. The plan defines the minimum criteria for on-site, off-site and central monitoring. **(Exhibit 6)**

I reviewed site initiation visit reports, routine monitoring visit reports, site close-out visit reports and monitors follow-up letters for seven (7) clinical investigator (CI) sites involving studies ITRM and ITRN (both studies for site 139). **(Exhibit 7**) The firm also provided initial IRB approvals dates for each site.

Additionally, reviewed the following documents for each site: Global Site Selection Kick Off Meeting slide presentation (same for each site); site selection; safety mailing reports; serious adverse events; protocol deviations; screen shot for one patient at each site the shows the CI sign off of the eCRF prior to database lock. I reviewed Investigator Site Evaluation Checklists, site delegation log, GCP and protocol site training, financial disclosures (for PI and sub-investigators) and clinical investigators CV’s.

Listed are the sites that were reviewed during the inspection:

Site #	CI	# of Subjects
118	Garg, Satish- ITRM Barbara David Center for Childhood 1775 Aurora Court A140 Aurora, CO 80045	14
139	Palal, Betsy -ITRM Palm Research Center 280 W. Sunset Rd Suite 306 Las Vegas, NV 89148	10
139	Palal, Betsy-ITRN (Same as above)	15
156	Warren, Mark -ITRM Physicians East 1006 Wh Smith Blvd Greenville, NC 27843	2
122	Horowitz, Barry -ITRM Metabolic Research Institute Inc. 1515 North Flager Drive Suite 440 West Palm Beach, FL 33401	14
100	Bhargava, Anju -ITRN IDERC, PLC 1031 Office Park Road Suite 2 West Des Moines, IA 50265	18
116	Frias, Juan -ITRN National Research Institute 2010 Wilshire Blvd Suite 302 Los Angeles, CA 90057	11
131	Miers, Wendell-ITRM Kentucky Diabetes Endocrinology Center 1760 Nicholasville Road, Suite 520 Lexington, FY 40503	16

Site 118 (Dr. Satish Garg) had a site escalation due to non-compliances identified during a routine Quality Compliance Visit (QCV) conducted by (b) (4) on 6/7/18. Non-compliances consisted the following issues (but not limited to): for all subjects, the total daily dose (TDD) of insulin was not captured at the screening visit; the sites temperature alarm is set to 1.5-8.4 degrees Celsius which is outside the limits required which is between (b) (4) degrees Celsius; for 2 subjects, the CI signed the informed consent after the date the subjects signed the consent; incomplete investigator trial master files; subject screening ECGs did not contain information identifying the specific subject; concomitant medication log information was inaccurate as all of the concomitant medications were not added to the log; (**Exhibit 8**)

Corrective actions consisted of a joint issue management meeting consisting of Lilly and (b) (4) All issues were reviewed during the meeting on 7/31/18. On 8/13/18, a joint issue management follow-up meeting was held which confirmed that all issues had been closed. An enrollment hold was not enacted, and no non-compliance letter was sent to the site. The site was not terminated.

Site 585 (Dr. Moon-Kyu Lee). It was identified that some Korean sites had deviations mostly related to not switching to study allowed basal insulin at visit 2 or adding new OAM at visit 2 or not discontinuing non-allowed OAMs (except metformin, SGLT2 inhibitor) at visit 2. Screening was paused for Korean sites but were all allowed to resume enrollment after retraining, except for Dr. Lee's site due to additional detected data issues regarding 2 patients. On 10/24/17 a face to face review was conducted. The site was told to hold screening and delay the patient schedules. The site had 2 subject that were discontinued before they were randomized. On 10/24/17, the site was retrained. A hold on the screening was still enacted, but later removed after retraining. No subjects participated in the study. **(Exhibit 9)**

Exhibit 10-Site Escalations SOP

The clinical trials registry was posted on CT.gov dated 7/10/17, and the first ITRM patient was consented on 7/17/17. The clinical trials registry was posted on CT.gov dated 7/10/17, and the first ITRN patient was consented on 7/14/17. In addition, the Statistical Analysis Plan (SAP) for both ITRM and ITRM were both approved on 7/7/17 which is prior to the first patient visits for each study.

MONITORING PROCEDURES AND ACTIVITIES

Monitoring procedures and activities remain the same as reported in the previous inspection report on 1/20, in that, sites are monitored using a risk-based monitoring plan per an integrated monitoring plan. **(**Exhibit 6**)** Monitoring includes 100% of critical data and processes such as; inclusion/exclusion criteria and informed consent forms. Source Data Verification is performed every (b) (4) subject thereafter.

I reviewed routine monitoring visit reports and follow-up letters for sites 118, 139, (both ITRM and ITRM), 156,122,100,116 and 131. The firm provided a listing of subjects reviewed for source data verification at the site and whether the (b) (4) % requirement had been met. From this list, site 139 that did not meet (b) (4) % of source data verification review per the monitoring plan. In addition, in some instances the monitor did not review the correct subject since the monitoring plan required source data review of subjects (b) (4) and (b) (4) thereafter. (**General Discussion with Management**)

The firm stated that approximately (b) (4) % of sites were audited including two sites (139 and 100), which were two sites reviewed during the inspection. (**Exhibit 11)**

SAFETY/ADVERSE EVENT REPORTING

Safety/adverse event reporting remains the same as reported in the previous inspection report of 1/20. The firm utilizes the electronic Safety Report Notification System (b) (4)) whereby safety letters are sent to clinical investigators for their review. The timeliness of these reviews are verified during monitoring visits. I reviewed (b) (4) Safety Mailing Reports for each site. The sponsor indicated that some sites were not always reviewing safety reports in a timely manner which involved a new process for signing on the system. (**Additional Comments**)

The firm stated that there were no 7- or 15-day IND safety reports that required FDA notification for studies ITRM and ITRN. There were no Individual Case Safety Report (ICSR) safety notifications sent that met notification criteria such as serious, unexpected, considered related by the sponsor or considered unanticipated. Only safety line listings and Single Sign On site communicates were sent to all sites.

According to the firm, there were no monitoring boards or adjudication committees involved in the review of ITRM or ITRN.

Exhibit 12 is an SOP entitled, "Safety and Efficacy Quality Standard" SEQ-301, which describes the pharmacovigilance standard that covers the collection, receipt, evaluation, monitoring and communication of safety information.

DATA COLLECTION AND HANDLING

Data collection and handling procedures remains the same as reported in the previous inspection report dated 1/20. End point data was collected throughout the study through a web-based portal. The sites utilized electronic Case Report Forms (eCRFs) to enter source data. The system requires a user name and password for access. The clinical investigator or designated personnel were the only ones authorized making or approving any changes to the electronic source data. Audit trails were maintained to indicate any changes. Exhibit 2 indicates when database locks occurred throughout the study for both ITRM and ITRN.(**Additional Comments**)

The firm stated that data management encompasses the activities for planning, delivering, and archiving clinical data to ensure data integrity for safety and efficacy data. Data management activities include:

- Defining data needs, creating data management plans, and data transfer plans. The procedure PRD-00098 Data and Analysis Planning details activities involved in determining Critical Data and Critical Processes, Data Management Planning, and Data Transfer Planning. **(Exhibit 13**)

- Developing data collection tools. Data collection tools are designed in accordance with procedure PRD-00133 Design and Develop Data Collection and Data Aggregation Tools. The site is responsible for entering data into these tools during the clinical trial. (**Exhibit 14**)

- Collecting, verifying, transferring and delivering data for statistical analysis is done in accordance with procedure PRD-00097 Data and Analysis Delivery. **(Exhibit 15)**

Exhibit 16-Data Flow Diagram

TEST ARTICLE ACCOUNTABILITY

Test article accountability remains the same as reported in the previous inspection report of 1/20. Investigational products are shipped to sites which are documented on a Shipment List. Upon review of shipping records for sites 139 and 100, I noted that a Shipment List indicates the item number, lot number, ship date, order number, quantity, expiration date and serial numbers. IP accountability is maintained on an Individual Subject Investigational Drug Accountability Log for each subject. The log provides for the visit number, date dispensed, lot number, IVRS/IWRS Package number of dispensing units, number of pens dispensed, site recorder initials and data, date returned to site by subject, number of pens returned by subject, site recorder initials and data, and comments. Upon tracing IP received, used and returned, I observed whether the products were destroyed (via Certificate of Destruction), returned to the sponsor.

In discussion with the firm, I found that investigational sites may or may not use a Master Accountability Log, which is not required. Standard Operating Procedure (SOP) entitled, Monitoring of CT Material and/or investigational Devices Management at Site from Operations Plan (Version 6.0)-Site Management and Monitoring Chapter effective 11/15/19 indicates that Investigational Medicinal Product and/or Investigational Device Accountability Forms at the subject participant level are required for all trials. Non-IWRS trials use a Master Log as well as a subject participant level log. If the site has its own accountability form using these forms is permissible if they have been reviewed by the CRA and found to be acceptable.

IP was refrigerated for both studies during shipment. Shipments were contained in pre-conditioned shipping containers between (b) (4) degrees Celsius. Each shipment contained a temperature monitor which is used to determine fit-for-use upon receipt at the sites. The firm stated that temperature monitoring data is stored at the site and that temperature monitoring data is provided to the sponsor only in the event of an alarm. Instructions are included in each shipment to provide guidance on how to receive shipments and process the temperature monitor. There were no temperature excursions during transit of IP to sites 139 and 100. (**Exhibit 17)**

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

None

REFUSALS

None

GENERAL DISCUSSION WITH MANAGEMENT

On 3/20/20, at the closing meeting, I discussed with the firm source data verification during monitoring visits and whether the monitoring plan was being followed. I requested a listing of subjects whose visits were source data verified at each site during the inspection for both studies.

The firm provided information indicating that most sites had appropriately source data verified the (b) (4) and (b) (4) subject thereafter and therefore met the (b) (4) % sampling requirement except for site 139 (ITRN). In this instance, the (b) (4) and (b) (4) enrolled subjects were sampled correctly, however the (b) (4) enrolled subject was selected which resulted in the (b) (4) and (b) (4) enrolled subjects to be included. For example:

Site #	Enrollment Order	Subject number	Visit 2 Date (Enrolled)	Visit 8 Date Randomized	SDV Sampling	Last Visit number #	Last Visit Date
139	1	(b) (6)	1-Aug-2017	29-Sep-2017	(b) (4)	801	23-Apr-2018
139	2		16-Aug-2017	16-Oct-2017		801	21-May-2018
139	3		24-Aug-2017	19-Oct-2017		803	1-Nov-2018
139	4		24-Aug-2017	18-Oct-2017		802	1-Aug-2018
139	5		28-Aug-	23-Oct-2017		802	6-Aug-2018

		(b) (6)			(b) (4)		
			2017				
139	6		29-Aug-2017	24-Oct-2017		802	17-Aug-2018
139	7		31-Aug-2017	n/a		5	13-Sep-2017
139	8		31-Aug-2017	26-Oct-2017		802	8-Aug-2018
139	9		6-Sep-2017	2-Nov-2017		802	6-Aug-2018
139	10		7-Sep-2017	1-Nov-2017		803	13-Nov-2018
139	11		11-Sep-2017	8-Nov-2017		802	8-Aug-2018
139	12		12-Sep-2017	n/a		5	22-Sep-2017
139	13		14-Sep-2017	8-Nov-2017		18	4-Jun-2018
139	14		10-Oct-2017	5-Dec-2017		17	19-Apr-2018
139	15		16-Oct-2017	12-Dec-2017		801	10-Jul-2018
139	16		18-Oct-2017	14-Dec-2017		801	12-Jul-2018
139	17		19-Oct-2017	12-Dec-2017		802	11-Sep-2018

The firm also provided information that site 116 (ITRN) and site 122(ITRM) sampled the incorrect subjects; however, the (b) (4) % sampling was met per the monitoring plan. For site 116, the CRA based sampling on Visit (b) (4) and not Visit (b) (4) per the monitoring plan, which resulted in the (b) (4) and (b) (4) enrolled subjects to be included. At site 122, the incorrect subject was sampled. CRA inadvertently sampled the (b) (4) subject instead of the (b) (4) subject.

Ms. Van Sant Hoffman stated that this issue would be discussed with the vendor.

ADDITIONAL INFORMATION

During the inspection, I verified issues disclosed in the Clinical Study Report (CSR) Regulatory Response. I discussed with the firm issues and corrective actions; For example:

1). The Regulatory Response for I8B-MC-ITRM section 4.1, describes that for 34 patients, the date of the last treatment dose was recorded to be later than the last treatment visit (Visit 22) date.

Mr. Mitchell stated that as they locked the data for ITRM week 52, it was reported in the CSR that there were 34 patients (was actually 24) at sites with the wrong information in the eCRF regarding the date the patient took their last dose (treatment date). The trial design was that there was still a 4-week safety follow-up, so sites inadvertently put in dates that were after the 52-week time. Therefore, 24 patients had the wrong dates entered (21 sites had at least one patient that the wrong information was listed for). Mr. Mitchell further explained that they input in the 801 visit instead visit 22 date or different date. They recognized the mistake and queried them; each site corrected the

actual treatment date. The corrected information is in the data base. In addition, audit trails reflect that a change was made.

2). Regulatory Response section 4.2. Per the Clinical Study Report for ITRM and ITRN, there were 33 sites in 11 countries and 19 sites in 9 countries that had site-level important protocol deviations for a significant delay in safety mailing review. The firm reported that a change was made to the Safety Report Notification System on 3/14/18 where the CI or designee receives and reviews safety mailing that are posted to his or her accounts. The changed involved the implementation of the (b) (4) "Single Sign On" for the (b) (4) which was a change in the way the CI or designee logs into the system. In preparation for this change, communications were sent out via email to all users of the system on 10/30/17 and 3/5/18. Alerts were also posted on the systems homepage in order to prepare users for the upcoming changes. New users also received a communication related to registration for (b) (4) Single Sign On. However, in May 2018 as part of the standard monitoring review process between (b) (4) and Lilly it was noted that there was in increase in the number of protocol deviations regarding safety mailing review delays.

Mr. Mitchell further stated that the firm made a change to the system that went live in March 2018, which required a different way of logging into the system; as a result, some CI's didn't understand how to access the Safety Reports. The monitoring process saw an influx of safety reports that was not being reviewed. If the CI did not acknowledge the communications that there was a change in the safety communications within a specified time frame, it was deemed late. Retraining was provided by CRA's regarding the late review of safety reports in (b) (4) which were listed as protocol deviations.

3). Regulatory Response Question 3. I verified the firm's corrective actions regarding the use of the electronic Clinical Outcome Assessment (eCOA) diary that wirelessly received all glucose data directly from the blood glucose meters.(Attachment 2) The investigator was to access the diary and classify all events as "severe" or "not severe," based upon data collected and consultation with the patient; however, there was a potential for loss of data or identification for data obtained which required patches in the software.

During the inspection, the firm's response is as follows: "ITRM and ITRN glucometers and eDiaries were connected using Bluetooth technology. At times, devices required re-pairing following the initial connection between the two devices in the system. Example reasons for re-pairing included use of a new device (either eDiary or Glucometer), loss, or lost Bluetooth connection between the Glucometer and eDiary.

The eCOA system cleared the glucometer memory during pairing of devices, deleting blood glucose (BG) readings not previously transferred to the eDiary. This functionality was present in all patient devices until the patch was applied.

This issue was detected August 2017 and it was corrected with software updates released in September 2017.

For context of missing BG data, this issue was present for the first three months of the trial and was remedied with the patch. The sponsor assessed BG data from the impacted time frame and concluded missing BG values of approximately 1% for ITRM and approximately 2% for ITRN of all BG data points across all sites and patients. The majority of patients with gaps in BG readings due to the device paring issue were compliant to collecting a minimum of (b)(4) BG readings per day on all other days with data (i.e. without missing BG values due to the sync issue).

Enclosed with this response are sponsor communications to sites related to this topic:

- Memorandum CRF Health RE eDiary and Glucometer Pairing 25-Aug-2017
- Memorandum RE eDiary and Glucometer Pairing 08-Sep-2017
- Lilly Communication 14-Sep-2017 RE eCOA Software Update
- MEMORANDUM RE: eDiary and Glucometer Pairing 18-Sep-2017"

Exhibit 18-Sponsor communications

4). Regulatory Response 4. In response to the issues that discrepancies in the reporting database were discovered after the data base lock, the firm responded that data discrepancies were identified by sites and/ or CRAs between source subject data at the site compared to data entered in the Electronic Data Capture (EDC) system. A cross-functional review of these data discrepancies was conducted and was determined that there was no significant potential impact and a relock was not necessary. The report was therefore not updated. Attachment 2 lists some of these discrepancies. Mr. Mitchell stated that after the database was frozen, the sites wanted to add some changes. It was decided that the issues would be logged in as permanent data issues and therefore would not update the system after the data base lock. (Exhibit 2-time lines for database locks)

The firm provided a listing of know database discrepancies and reason for each study, which is similar to the response in table 4.2 such as: "Table 4.2 documents discrepancies between source data and the 26-week database lock for ITRN. Data remained locked to site edits following database lock as patient treatment was complete. These discrepancies were determined to have no impact to primary outcome conclusions reported in the 26-week clinical study report. For ITRM, sites made data changes between 26-week and 52-week locks as patient treatment was ongoing.

Following the 52- week lock, changes to the following critical data were compared for impact against 26-week data:

- Adverse Events
- Hypoglycemia

- Immunogenicity
- HbA1c
- MMTT
- Insulin Dose
-

These comparisons determined there was no meaningful impact to primary and key secondary outcomes. Two summary tables comparing the differences between efficacy and severe hypoglycemia analyses were in the 52-week clinical study report and included with this response." **(Exhibit 19)**

4.5) Regulatory Response 4.5. Mr. Mitchell explained that during staff training (site 576 patient ID (b) (6), the site put in data in the health outcomes questionnaire using dummy/practice data on a real patient by mistake. The regulatory response indicates that the site identified the error and subsequently entered three Data Clarification Forms in the eCOA site web portal on 6/27/18 to remove the test data from the eCOA database. The Data Clarification Forms were initially denied because removal of subject entered data is not permitted for this study. However, the study team was able to verify with the site that they had mistakenly entered test data into the study database and that the data were not obtained from the patient. The CRF Health data management team implemented the note to file and removed the test data from the questionnaires. However, CRF also inadvertently removed all of the subjects' eDiary data immediately prior to the primary outcome database lock on 8/17/18. CRF Health reinstated the subject's eDiary data on 12/11/18. The Subjects eDiary data including blood glucose, hypoglycemia events and insulin dosing data were always available to the site via(b) (4) during the treatment period (through visit 180." Mr. Mitchell indicate that this issue did not impact safety.

I also discussed with the firm regarding extra patient at some Mexico sites. The firm responded as follows: "Explanation of Maximized Extended Enrollment (MEE)- In studies ITRM and ITRN, Lilly implemented maximized extended enrollment (MEE) with the objective to have a single registration trial that would efficiently recruit patients globally and satisfy global regulatory requirements, in addition to regional or local needs. Many non-US/EU regulatory agencies (such as Mexico) have requirements for local patient data for registration of a new drug, indication or line extension. All analyses of any MEE country-specific cohort would be for submission only to that country and will not be incorporated into the analysis of the global cohort. These patients were not part of the primary analyses of the main study as defined in the addendum.

Mexico MEE Sites and Patients:

Mexico Site	ITRM Number of Randomized Subjects	
	Main Study	MEE
600	0	14
601	10	2

603	8	9
604	0	3

Mexico Site	ITRN Number of Randomized Subjects	
	Main Study	MEE
600	12	0
601	15	2
602	3	0
603	13	0

Lilly provided details of this approach to US FDA in the End of Phase 2 briefing document outlining the MEE approach to be implemented. For ITRN, the MEE data was provided in the BLA. For ITRM, the MEE data was provided in the 120-day safety update. Additionally, Lilly responded to an information request regarding MEE on 15 January 2020 (see, "Regulatory Response (BLA 761109 MEE).pdf")."

I discussed with the firm additional information to confirm that patients involved in the Maximum Extended Enrollment (MEE) for study ITRM were not part of the 26-week analyses. The firm provided the following information regarding this issue: "The Clinical Study Report (CSR), section 9.7.1 Statistical and Analysis Plans, states that 'data for the MEE cohort of patients were excluded.' The applicable portion of the CSR is provided with this response. In this response, we have provided the following listings to show that ITRN, Site 601, patients (b) (6) and (b) (6) were excluded from the 26-week Primary Outcome analyses.

- CSR listing: Summary of Patient Allocation by Investigator Sites within Country
- OSI listing: HBa1c Measurements (for site 601)
- OSI listing: Patient Listing for Treatment Assignments—All Randomized Patients"
-

I followed up on the firm's blinding procedures and obtained a list of those Lilly study team member who had access to the unblinded treatment assignment for both studies. According to the firm, no sites were unblinded throughout the duration of both studies. The blinding information remains the same as reported in the previous inspection report of 1/20.

The firm also provided a listing of name and titles of those who were unblinded to treatment codes in accordance to the blinded/unblinded plan. This team consisted of Demand Forecasters, and Clinical Supply Coordinators for both studies:

Demand Forecaster:
(b) (6), Consultant-Clinical Trial Supply Mgmt

Clinical Supply Coordinator:
(b) (6), Associate Consultant – Clinical Trial Supply Mgmt
(b) (6), Associate Consultant – Clinical Trial Supply Mgmt

IWRS Support:
(b) (6), Consultant – IWRS Design & Development

The following individuals were responsible for on-going Global Support Helpdesk of the studies. This included IWRS support of site users for data entry questions/issues, dispensing questions/issues and general access and visit processing questions/issues.

(b) (6), IWRS Development and Site Support
(b) (6), IWRS Development and Site Support
(b) (6) IWRS Development and Site Support
(b) (6), IWRS Development and Site Support
(b) (6), IWRS Development and Site Support
(b) (6) IWRS Development and Site Support
(b) (6), IWRS Development and Site Support
(b) (6), IWRS Development and Site Support
(b) (6), IWRS Development and Site Support

The clinical trial supply management organization for Lilly, Product Delivery, is generally unblinded. SOP PRD 3-60-02, Protection of Blinded Information, provides an awareness of the sensitive nature of the information which Product Delivery representatives have access to and guidance for preventing inappropriate disclosure of this information. (**Exhibit 20**)

SAMPLES COLLECTED

N/A

VOLUNTARY CORRECTIONS

N/A

EXHIBITS COLLECTED

1 Lilly Emails , 10 pages
2 Lilly Opening Slide Presentation, 18 pages
3 Clinical Protocol I8B-MC-ITRM dated 5/22/17, 108 pages
4 Clinical Protocol I8B-MC-ITRN dated 5/19/17, 96 pages
5 ITRN and ITRM Roles and Responsibilities, 10 pages
6 Integrated Monitoring Operating System Integrated Monitoring Plans, 100 pages
7 Site Monitoring and Visit Follow-Up Report dates, 8 pages
8 Escalation Summary Site 118, 6 pages
9 Escalation Summary Site 585, 6 pages
10 Identify and Manage Trial Issues and Site Escalations SOP, 8 pages
11 GCP Audit Certificate Template, 4 pages
12 Pharmacovigilance SOP dated 12/1/19, 42 pages
13 Data and Analysis Planning SOP dated 8/1/19, 8 pages
14 Design and Develop Data Collection and Data Aggregation Tools dated 10/7/19, 10 pages
15 Data and Analysis Delivery SOP dated 8/1/19, 8 pages
16 Data Flow Diagrams, 14 pages
17 Instructions for Receipt of IWRS Temperature Monitored Shipment, 1 page
18 Memorandums sent to sites regarding eDiaries, 4 pages
19 Efficacy Comparison Between the 26 week and 52 week Database Locks, 4 pages
20 Protection of Blinded Information SOP dated 5/15/18, 12 pages

ATTACHMENTS

1. FDA 482 Notice of Inspection, 4 pages
2. Assignment Memo dated 11/1/19, 10 pages

Myra K. Casey -S
Digitally signed by Myra K. Casey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Myra K. Casey -S, 0.9.2342.19200300.100.1.1=1300022926
Date: 2020.03.27 14:49:00 -04'00'