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SUMMARY

This High-Priority Premarket BLA Supplement sponsor inspection was conducted in response to a BIMO Inspection assignment from the Office of Scientific Investigations, CDER under **FACTS 11969603 and OP ID 141341**. The inspection was also conducted in accordance with 7348.810 – Sponsors, Contract Research Organizations and Monitors.

The previous inspection covering BIMO operations was conducted on 1/21-25/19 and was classified as NAI. No FDA 483 Inspectional Observations List was issued.

The current inspection did not result in the issuance of an FDA 483. The inspection covered application number BLA 125521/S-019, TALTZ® (Ixekizumab), Protocol I1F-MC-RHBX- A 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naïve Patients with Non-Radiographic Axial Spondylarthritis

Current inspection included the review of six (6) clinical investigator sites covering the following operations (but not limited to): site selection; investigator selection and qualifications; criteria for monitors and qualifications; monitoring procedures and activities (i.e. monitoring plans, monitoring visit reports); FDA 1572 forms; financial disclosure forms; clintrials.gov process; IRB approvals; escalations involving 2 sites; blinding and unblinding procedures; protocol deviations; data management; test article accountability; adjudication procedure; safety and adverse event reporting; and quality assurance.

ADMINISTRATIVE DATA

Inspected firm:	Eli Lilly and Company
Location:	839 South Delaware Street Indianapolis, IN 46285
Phone:	1-317-361-3997
FAX:	1-317-276-6331
Mailing address:	839 South Delaware Street Indianapolis, IN 46285
Email address:	donnelly_patty@lilly.com
Dates of inspection:	1/9/2020-1/10/2020, 1/13/2020-1/17/2020
Days in the facility:	7
Participants:	**Myra K Casey, Investigator**

Non-FDA Participants: N/A

On 1/6/20, I contacted the firm to pre-announce the inspection and spoke to Ms. Thecla Wong, Consultant, Global Regulatory Affairs – North America. I later spoke to Mr. Brian Mitchell, Director – Global Quality Research and Development (R&D). We agreed that the inspection would begin on 1/9/20.

On 1/9/20, I displayed my credentials and issued an FDA 482-Notice of Inspection to Patty J. Donnelly, PhD, Vice President Research and Development Quality. Dr. Donnelly acknowledged that she was most responsible for the operations being inspected.

During the course of the inspection, I was provided with information and records by Mr. Brian Mitchell and Ms. (b) (6) , Advisor, Clinical Development – BioMedicines. Also present were individuals functioning as scribes/request takers. Each day during the inspection various individuals were present, which are listed on a Daily Interview Plan/Summary List. **(Exhibit#1)**

At the close of the inspection, I met with Patty J. Donnelly, PhD, Vice President Research and Development Quality in addition to various individuals, which is listed in Exhibit 1.

No FDA 483 Inspectional Observations List was issued.

HISTORY

The history of business remains the same as reported in the previous inspection report dated 1/21-25/19. At the opening of the inspection, the firm provided a presentation describing the following information: overview of the company; clinical development and oversight; and overview of Ixekizumab Nonradiographic Axial Spondyloarthritis. (**Exhibit #2**-Presentation, 3rd party addresses)

The inspection took place at the Global Headquarters of Eli Lilly and Company located at Lilly Corporate Center, 839 South Delaware Street, Indianapolis, IN. The firm employs approximately (b) (4) employees worldwide. The main therapeutic areas in Research and Development are: Biomedicines (immunology, neuroscience and pain); Oncology; and Diabetes. Approximately, (b) (4) employees are engaged in Research and Development and clinical research is conducted in more than 55 countries.

Eli Lilly and Company utilized various third-party organizations for the conduct of protocol I1F-MC-RHBX; for example:

(b) (4)

(Exhibit 2 page 13, **Exhibit #3-#5**-3rd party contracts)

* (b) (4) (b) (4) ended 3/31/17 and (b) (4)

The core 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
Lilly Corporate Center
839 South Delaware Street
Indianapolis, IN 46285

INTERSTATE (I.S.) COMMERCE/JURISDICTION

Application Number BLA 125521/S-019, TALTZ® (Ixekizumab), Protocol I1F-MC-RHBX was conducted in support of IND (b) (4) . The study is a 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naïve Patients with Non-Radiographic Axial Spondylarthritis.

The Investigational Product (IP) was manufactured by Eli Lilly and Company Indianapolis, IN. Clinical supply management (packaging and labeling) was from (b) (4) . and (b) (4) .

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the onset of the inspection, I issued an FDA 482 Notice of inspection to Patty J. Donnelly, Vice President Research and Development Quality. Dr. Donnelly's duties and responsibilities consists of the following: Leads Quality oversight for R&D activities including the Medicines Quality Organization (including Medical, Regulatory and Safety/Pharmacovigilance Quality oversight), and the Product Research and Development Quality organization (including global Clinical Trial supply and distribution Quality oversight). Responsibilities further include oversight for contracted quality activities for R&D performed for and on behalf of Eli Lilly and Company. Dr. Donnelly reports directly to Johna Norton, Senior Vice President Global Quality. Ms. Norton reports directly to David Ricks, Chairman, President and Chief Executive Officer. (Exhibit #2-organizational chart)

During the inspection, Mr. Brian Mitchell, Director – Global Quality Research and Development. served as host by accompanying me during the inspection and providing most of the information and records. Ms. (b) (6) also assisted me during the inspection by providing information. Mr. Mitchell did not have any specific duties and responsibilities involving the conduct of protocol I1F-MC-RHBX. Ms. Hale serves in a key role in the capacity of Advisor, Clinical Development.

According to the firm, protocol approval is the responsibility of the medical organization. The selection of investigators and monitoring is overseen by the Site Engagement Group. Statistical analysis is conducted by (b) (4) (data management statistics). Adverse event and safety information has duel responsibilities of the Global Safety and Medical Organizations. (Exhibit#2)

Exhibit #6 -copy of key individuals responsible for the conduct of protocol I1F-MC-RHBX.

REGISTRATION OF STUDIES ON CLINICALTRIALS.GOV

The firm provided verification that protocol study I1F-MC-RHBX was posted on Clinicaltrials.gov. I observed procedures for clinicaltrials.gov entitled ,Clinical Trial Registries and Results Databases version 5 and Register Trial and Populate Lilly Trial Guide. The initial posting date for study protocol

I1F-MC-RHBX is listed as May 2, 2016, which is prior to the first patient visit (FPV) date of August 2, 2016. I verified that the primary and secondary outcomes measures were listed for the study, which was consistent with the protocol. In addition, I verified that the required clinicaltrials.gov statement appeared on the informed consent forms (all versions) that were used at each site.

SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

The criteria for the selection of clinical investigators involved in the conduct of protocol I1F-MC-RHBX is based on experience and qualifications; for example: licensed physician with a specialty in rheumatology; experience in the diagnosis and treatment of *AxSPA; and at least 1-year previous clinical trial experience (preferable with experience in Rheumatology studies). I conducted a review of curriculum vitae's (CVs) for Principal Investigators at each site. Additionally, the site staff is required to maintain certain qualifications in order to conduct the study. **(Exhibit #7)** (* AxSPA-axial spondyloarthritis)

The firm maintains standard operating procedures (SOPs) that address vendor selection/oversight (i.e. third-party Management procedure Versions1-7). Prior to the conduct of studies, site selection was conducted based on various criteria in written SOPs.

I covered six (6) investigational sites during the inspection. I reviewed various monitoring operations such as: site selection checklists; site initiation reports and monitoring visit reports.

Listed are the six sites that I covered during the inspection:

Site Number	Principal Investigator	PI Address	# of Subjects
105	Kathleen P. Flint, MD	Articularis Healthcare Group, INC dba Columbia Arthritis Center 1711 St. Julian Place Columbia, SC	*4
129	Craig D. Scoville, MD, PhD	Institute of Arthritis Research 2220 E. 25th St Idaho Falls, Idaho	*7
475	Eva Dokoupilova, MD	MEDICAL PLUS, s.r.s Obchodni 1507 Uherske Hradiste 686 01 Czech Republic	36

380	Cesar Ricardo Ramos Remus, MD	Unidad de Investigacion en Enfermedades Cronico Degenerativas Colomos 2292, Providencia Guadalajara, Jalisco 44620 Mexico	30
102	Melvin A. Churchill, MD	Physician Research Collaboration, LLC 3901 Pine Lake Rd Suite 120 Lincoln, Nebraska	11
146	Christine Thai, MD	Care Access Research-Huntington Beach 19582 Beach Blvd Suite 320 Huntington Beach, California	8

*Escalations

There were 2 sites that had escalations. At site 105, the escalation summary indicates that during the monitoring visit on 10/18,19/17, the Clinical Research Associate (CRA) noted repeated non-compliances related to Principal Investigator (PI) oversight, inadvertent subject enrollment, delay in review of eligibility criteria, inadequate source documentation and additional issues related to good documentation practices. The site underwent an enrollment hold that was not lifted due to the end of study screening prior to site issues being resolved. As a result of the findings, the site held various joint escalation meetings between the sponsor and(b) (4) that involved identification of the issues and corrective actions. Corrective actions were identified through more frequent monitoring to ensure compliance with the issues. Retraining was also provided regarding PI oversight responsibilities. All issues were resolved. The site was not terminated. (**Exhibit #8)**

Site 129 was escalated due to concerns regarding GCP noncompliance at the site that was not adequately resolved. The issues involved insufficient evidence of adequate PI oversight (unavailable for monitoring visits), failure to correctly assess clinical significance of laboratory values and sign off in a timely manner. Lack of source documentation for medical history and concomitant medication logs, noncompliance with good documentation practices (raising concerns about consenting process and reliability of source data), numerous source discrepancies over course of study,(b) (4) data entry errors in the(b) (4) tablet, and retrospective completion of source documentation. Also, lack of timely completion of required training and lack of proper storage of investigational products which resulted in a temperature excursion. The site was put on hold to enrollment and a noncompliance letter was issued dated 9/27/17. Various joint issue management meetings were held where the issues were

identified, and corrective actions were put into place (i.e. screening hold). Monitoring visits activities and corrective actions were identified. The site responded to the noncompliance letter. The joint team accepted the PI's proposed actions. The issues were subsequently resolved, and the escalation process was closed. The site was not terminated. **(Exhibit #9**)

SELECTION OF MONITORS

Regulatory compliance is monitored by(b) (4) (formerly (b) (4) ended 3/31/17 and (b) (4) (formally (b) (4)) for protocol I1F-MC-RHBX. The criteria for the selection of site monitors are based(b) (4) job descriptions (i.e. Clinical Research Associate1,2). I reviewed a list of all monitors for each site along with their job descriptions and qualifications. No deficiencies were noted.

MONITORING PROCEDURES AND ACTIVITIES

Prior to the first patient visit (FPV), study and site risk assessments are performed during study development by the cross functions study team. During this risk assessment, mitigations were identified, Source Data Verification (SDV)/Source Data Review (SDR) sampling and intervention levels were determined and incorporated into the integrated monitoring plan. After the FPV site monitoring is performed by Clinical Research Associates (CRAs), site monitoring intervention levels were adjusted based on Site and Central Monitoring outputs. Central monitoring was performed by Central Monitors and Medical Reviewers (per the Operational Risk Monitoring Plan and Medical Data Review Plan.

I reviewed monitoring procedures for sites 105,129, 475, 380,102 and 146. Sites are monitored using a risk-based monitoring plan. I reviewed the following as it relates to monitoring procedures as activities:

- I reviewed all versions of Monitoring Plans, Site Monitoring Plans, the Medical Data Review Plan and Operational Risk Monitoring Plans. **(Exhibit #10, #11)** I compared the plans with the SDVs/SDRs that were conducted at each site. Monitoring plans indicate the percentage of SDV Verification (SDV) and Source Data Review (SDR) which is calculated based on the risks. SDV is required on the (b) (4) subject thereafter.

- I verified according to procedures, the Site Initiation Visit should occur occurred within 10 business days of notification that the site is declared ready to initiate the study. I also verified that the first monitoring visit should also occur within 2 weeks of the 1st subject being enrolled (randomized at visit 2).

- I reviewed the following records: Welcome email provided to clinical investigators to show that the IB and protocol was provided prior to enrollment. I also reviewed the protocol signature page; IRB approvals; informed consents, contracts; Curriculum Vitae (CV) of

clinical investigator; financial disclosures, investigator training, and all versions of the Form 1572.

- I reviewed all monitoring visit reports for each site (105,129,475,380, 102 and 146), including Investigator Site Evaluation Checklists and site initiation visit reports. All sites appeared to be monitored appropriately.

- I reviewed monitoring visit follow-up letters for the sites to ensure that issues were being appropriately followed-up and resolved.

- Although records for the inspected study are mostly electronic and maintained by the sponsor in an electronic trial master file, on 1/17,19, I walked through the Records Center in building 88 where hardcopy study records are stored.

- Sites remained blinded to study treatment randomization throughout study especially between week 16 and 52. There was no unplanned, unintentional unblinding during the conduct of the study at any sites. The firm stated that investigators and study teams are trained on blinding and unblinding and the systems at the site. Study team and investigators are all firewalled from treatment at all times and adhere to written SOPs to ensure the data integrity and blinding of the study. The firm provided a copy of the Blinding and Unblinding plan for study protocol I1F-MC-RHBX. **(Exhibit #12)**

- Protocol I1F-MC-RHBX is a multicenter study conducted at 106 sites in 15 countries. **(Exhibit #13)** I compared the number of total subjects in the Clinical Study Report (CSR) to the BLA submission; both indicated that there were 303 subjects total.

No deficiencies were noted.

QUALITY ASSURANCE/QUALITY AUDITING

The Global Quality Auditing and Compliance (GQAAC) is responsible for conducting quality audits., including sites, affiliates, centralized functions, global and locally developed computer systems, contract manufacturers, contract laboratories, clinical investigator sites and contract research organizations and studies (GCP and GLP). Audits are typically conducted following a systems approach and others may be conducted for cause or directed as a result of circumstances. (**Exhibit #14**-SOP) Approximately, (b) (4)% of sites were audited.

I was provided with a listing of various investigational sites that received GCP Audit Certificates that were involved in the conduct of protocol I1F-MC-RHBX. **(Exhibit #15)**

SAFETY/ADVERSE EVENT REPORTING

Safety reporting is conducted by way of the firms electronic Safety Reporting Notification System (b) (4)). Safety letters are sent to investigational sites and verification of these safety reviews are conducted during monitoring visits. I reviewed (b) (4) Report Listings which indicate the compound, study, site number, PI, country, report name, assignment date, posted date, accessed day and accessed by at the site.

According to the firm, there were no 7 or 15-day IND safety reports sent to the FDA involving study protocol I1F-MC-RHBX. There were no events that met the criteria of being serious, unexpected, considered related by the sponsor or considered unanticipated. However, 7 and 15-day safety notifications were sent to German sites since Germany requires local sites to receive reports that are also considered related by the investigator. I also reviewed Serious Adverse Events (SAE's) associated with protocol I1F-MC-RHBX. **(Exhibit #16)**

The firm maintains an adjudication process that consists of (b) (4) members of the Adjudication Committee independently reviewing each clinical event package. If in agreement, the case will be considered complete. If a disagreement occurs or adjudicated as insufficient information, a senior adjudicator will review and serve as the tie breaker.

I reviewed the Clinical Endpoint Committee (CEC) Charter dated 6/3/13, which describes the roles and responsibilities of the CEC, identifies its members, and outlines the processes and the criteria used to adjudicate suspected clinical events for the adverse event of special interest of inflammatory bowel disease (IBD) in the study of axial spondyloarthritis. **(Exhibit #17)**

In addition, I was also provided (b) (4)) Clinical Events Committee and Eli Lilly and Company Manual of Operations regarding cardiovascular events (CV) and the adjudication process.(**Exhibit #18)**

DATA COLLECTION AND HANDLING PROCEDURES/ELECTRONIC RECORDS

Data management encompasses the activities for planning, delivering, and archiving clinical data. Data management activities include; defining data needs, developing data collection tools, data management plans, and data transfer plans. Data is then collected, verified, transferred and delivered for statistical analysis. After study completion, the data collection tools and systems are decommissioned and archived.

The firm maintains written procedures to assure the integrity of data collected from clinical investigators. Data management was performed by (b) (4) (formerly (b) (4) ended 3/31/17 and (b) (4) (formally (b) (4)). Applicable data systems were provided for review during the inspection; they are: (b) (4) . Validation summaries were also reviewed.

Furthermore, SOPs indicate the Data Flow Diagram involving data collection to assure the integrity of safety and efficacy data collected. (**Exhibit #19**) When original data entries and changes are made, they can be tracked through an audit trail. I also reviewed SOPs for data and analysis and delivery.(**Exhibit #20**)

Clinical investigator sites input data into the electronic data capture system (via electronic case reports). The EDC system requires a (b) (4) for access. Additionally, the firm stated that medical data reviewer takes a risk-based exploratory approach to conduct the medical data review. The goal is to identify unusual data points or result patterns with potential medical importance, which can be further explored to determine if appropriate action has been or should be taken. The medical data reviewer analyzes medically relevant data using the (b) (4) (b) (4)) took, a component of the (b) (4) Platform. This review uses electronic data from the electronic data capture system and the laboratory results.

E-consent tablets were offered to sites along with paper forms to document the informed consent process. However, the study team decided to discontinue electronic consenting due to the lack of use in this format.

The firm maintains Disaster Recovery written procedures to protect data against loss.

No deficiencies were noted.

TEST ARTICLE ACCOUNTABILITY

The firm's Distribution Network Diagram Template indicates the packaging distribution strategy used for study protocol I1F-MC-RHBX. **(Exhibit #21)** The diagram indicates the flow of distribution from the packaging site, the hub, local depot and distribution to the various clinical sites worldwide. IP lot release is performed by Lilly Product Research and Development Quality Assurance. I verified the release of lots for sites.

I reviewed written SOPs regarding the reconciliation of IP that is sent and returned (i.e. Manage Close Out Clinical Trial Material, Investigational Devices and Ancillary Supplies). I reviewed and verified that each site had IP accountability Master Dispensing and Inventory Logs, US Return Material forms/documentation and non-return material forms/documentation.

The firm stated that temperature monitoring data is stored at the site. Temperature monitoring data is provided to the sponsor only in the event of an alarm. I was provided with instructions that are included in each shipment that provides guidance on how to receive the shipment and process the temperature monitor (i.e. Instructions for Receipt of IWRS Temperature Monitored Shipment Lilly (b) (4)). Furthermore, I reviewed IP storage and transportation records to investigational sites including shipments that were not fit for use. None of the IP that was not fit for use was used by any subjects. There were no recalls or withdrawals regarding protocol I1F-MC-RHBX.

In addition, I reviewed an example of the IP labeling, which indicates a caution statement that the product was "a new drug limited by federal (or United States) law to investigational use only."

No deficiencies were noted.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

None

REFUSALS

There were no refusals.

GENERAL DISCUSSION WITH MANAGEMENT

None

ADDITIONAL INFORMATION

None

VOLUNTARY CORRECTIONS

N/A

EXHIBITS COLLECTED

1	Daily Interview Plan/Summary, 7 pages
2	Lilly Presentation 1/9/20, addresses of 3rd party contracts, 15 pages
3	Third Party Master Service Agreements, 120 pages
4	Third Party Master Service Agreements, 206 pages
5	Master Services Agreement (b) (4) , 124 pages
6	Key Individuals Summary of Duties and Responsibilities, 6 pages
7	Investigator Profile and Equipment Requirements, 9 pages
8	Site Escalation Summary -Site 105, 9 pages
9	General Site Information (Escalation) Site 129, 15 pages
10	Monitoring Plan dated 3/17/16, 86 pages
11	Monitoring Plan dated 3/1/16, 113 pages

12 Blinding and Unblinding Plan for Protocol I1F-MC-RHBX, 11 pages
13 List of Investigators and Summaries of Experience and Training, 15 pages
14 GQAAC Auditing Program, 24 pages
15 GCP Audit Certificate Template, 2 pages
16 Safety System (LSS) Clinical Trial SAE Listing, 3 pages
17 Clinical Endpoint Committee Charter dated 6/3/13, 20 pages
18 Manual of Operations ((b) (4)), 34 pages
19 Data Flow Diagram dated 6/3/16, 5 pages
20 Data and Analysis Delivery SOP dated 12/3/15, 19 pages
21 Distribution Network Diagram Template, 3 pages

ATTACHMENTS

1 FDA 482-Notice of Inspection dated 1/9/20, 4 pages
2 Assignment Memo dated 11/1/19, 8 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: 2020.01.30 14:35:54 -05'00'