TABLE OF CONTENTS

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

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.