



DATE: October 20, 2022

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SUBJECT: Bioresearch Monitoring Final Discipline Review
SPONSOR: Rebiotix, Inc.
PRODUCT: RBX2660 (microbiota suspension) Rebyota
BLA: STN 125739/0

FINAL SUMMARY STATEMENT:

Bioresearch Monitoring (BIMO) inspection assignments were issued for the sponsor, one foreign and three US clinical investigators (CI) who participated in the conduct of protocols 2014-01 and 2017-01. The inspections did not reveal substantive issues that impact the data submitted in this original Biologics License Application (BLA).

BACKGROUND:

The sponsor, one foreign and three US CI sites for protocols 2014-01 and 2017-01 were identified for BIMO inspections. The BLA review committee concurred with the proposed sites. The sites were selected based upon sponsor-reported deaths, adverse events, protocol deviations, number of subjects enrolled, and previous BIMO inspection histories.

The inspections were conducted in accordance with FDA's Compliance Programs (CP) 7348.811, Inspection Program for CI and CP 7348.810, Sponsors, Contract Research Organizations and Monitors. Information submitted in the BLA was compared to source documents at each inspected site. The inspection assignment also included specific questions concerning the clinical studies.

PROTOCOLS:

Protocol 2014-01: *A Phase 2B Prospective, Randomized, Double-blinded, Placebo-controlled Clinical Study Demonstrating the Efficacy and Safety of Rebiotix RBX2660 (microbiota suspension) for the Treatment of Recurrent Clostridium difficile Infection*

The sponsor reported a total of 150 subjects enrolled under study 2014-01 at 21 sites in two countries. Of the 150 subjects enrolled, 130 were randomized and 127 subjects successfully received at least one dose of the investigational product (IP).

Protocol 2017-01: A Phase 3 Prospective, Randomized, Double-blinded, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of Rebiotix RBX2660 (microbiota suspension) for the Prevention of Recurrent Clostridium difficile Infection

The sponsor reported a total of 320 subjects enrolled under study 2014-01 at 44 sites in two countries. Of the 320 enrolled subjects, 289 were randomized and 180 subjects received the IP.

BIMO INSPECTIONS SUMMARY:

A Form FDA 483 was issued to site 024/VIHPH3 with several violations including failure to ensure the investigation was conducted according to the investigational plan and failure to prepare adequate case histories. Significant BIMO inspectional findings from this site are detailed under "Inspectional Findings." No other sites had significant inspectional findings.

The table below summarizes site information and outcomes from the BIMO inspections:

Site ID	Firm Name	Location	FDA Form 483 Issued	Final Classification
*024	Christine Lee, M.D.	Hamilton, ON, CAN	Yes	Voluntary Action Indicated (VAI)
*VIHPH3	Christine Lee, M.D.	Victoria, BC, CAN	Yes	VAI
017, IDAPH3	Clint Behrend, M.D.	Idaho Falls, ID	No	No Action Indicated (NAI)
011, MMNPH3	Sahil Khanna, M.B.B.S.	Rochester, MN	No	NAI
014, MAZPH3	Robert Orenstein, D.O.	Phoenix, AZ	No	NAI
Sponsor	Rebiotix, Inc.	Roseville, MN	No	NAI

* Site 024/VIHPH3 Represents a single inspection for Dr. Christine Lee with a VAI final classification.

INSPECTIONAL FINDINGS:

Site 024/VIHPH3:

At least three subjects in protocol 2014-01 were determined by the CI to be treatment failures without first completing protocol-required stool testing for *C. difficile*. The investigator subsequently dosed these three subjects with open label IP.

One subject in protocol 2014-01 took the prohibited concomitant medication vancomycin and was administered the IP on the same day, without the protocol required 24 to 48-hour washout of antibiotics.

A subject in protocol 2014-01 experienced a severe adverse event within one year of study treatment but the clinical investigator failed to enter the adverse event into the subject's electronic case report form.

The above findings were reported to the review team and an information request was sent to the sponsor. The sponsor responded satisfactorily.

Site 014/MAZPH3:

In protocol 2014-01, the site used nasal swabs for Methicillin-resistant *Staphylococcus aureus* testing on subjects rather than testing stool as required by the protocol. The sponsor initially only approved the use of nasal swabs for one subject. This finding was also reported to the review team.

SPONSOR MONITORING ISSUES:

No significant sponsor or monitoring issues were identified during the above inspections.

FINANCIAL DISCLOSURE:

The CI CP directs the FDA investigator to ask the CI if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s), and dependent children, as well as if and when the information was last updated. The information submitted to the BLA was verified for each of the inspected clinical study sites.

ADMINISTRATIVE FOLLOW-UP

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at (240) 402-8423.

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