



Our STN: BL125739/0

**LATE-CYCLE
MEETING MEMORANDUM**

Rebiotix, Inc
Attention: Karen Kuphal, Ph.D.
2660 Patton Road
Roseville, MN 55113

Dear Dr. Kuphal:

Attached is a copy of the memorandum summarizing your August 30, 2022, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Managers, Drs. Margaret Dayhoff-Brannigan (Margaret.dayhoff-brannigan@fda.hhs.gov), and Girish Ramachandran (girish.ramachandran@fda.hhs.gov) at (301)796-2640.

Sincerely,

Rebecca Reindel, MD
Acting Deputy Director – Clinical
Division of Vaccines and Related Products
Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: August 30, 2022, 1.30 PM EDT
Meeting Location: Teleconference

Application Number: BLA STN 125739/0
Product Name: Fecal Microbiota, Live
Proposed Indications: Reduce the recurrence of *Clostridioides difficile* infection in adults following antibiotic treatment for recurrent *Clostridioides difficile* infection.

Applicant Name: Rebiotix, Inc
Meeting Chair: Qun Wang, PhD

FDA ATTENDEES

Omolara Adewuni, MD	CBER/OVRR/DVRPA
Marie Anderson, PhD	CBER/OCBQ/DBSQC
Prabhakara Atreya, PhD	CBER/OM/DASC
Brenda Baldwin, PhD	CBER/OVRR/DVRPA
Artur Belov, PhD	CBER/OBPV/ABRA
Michael Brony	CBER/OCBQ/DCM
Paul Carlson, PhD	CBER/OVRR/DBPAP
Dennis Cato	CBER/OCBQ/DIS
Margaret Dayhoff-Brannigan, PhD	CBER/OVRR/DVRPA
Jon Daugherty, PhD	CBER/OVRR/DVRPA
Sheila Dreher-Lesnick, PhD	CBER/OVRR/DBPAP
Oluchi Elekwachi, PhD	CBER/OCBQ/DCM
Donald Ertel, MS	CBER/OCBQ/DMPQ
Meghan Ferris, MD	CBER/OVRR/DVRPA
Doran Fink, MD, PhD	CBER/OVRR
Theresa Finn, PhD	CBER/OVRR
Cara Fiore, PhD	CBER/OVRR/DVRPA
Richard Forshee	CBER/OBPV
Zhong Gao, PhD	CBER/OBPV/DB
Varsha Garnepudi, PhD	CBER/OCBQ/DBSQC
Maureen Hess, MPH, RD	CBER/OVRR
Kathleen Hise, MD	CBER/OVRR/DVRPA
LCDR Kelsy Hoffman, PhD	CBER/OVRR/DVRPA
Andrea Hulse, MD	CBER/OVRR/DVRPA
Kathleen Jones, PhD	CBER/OCBQ/DMPQ
Jennifer Kirk, PhD	CBER/OBPV/DB
Gumei Lu, PhD	OOPD
Peter Marks, MD	CBER/IOD
Adamma Mba-Jonas, MD	CBER/OBPV/DPV
Loris McVittie, PhD	CBER/OVRR/DVRPA

Miriam Ngundi, PhD	CBER/OCBQ/DMPQ
Sussan Paydar, PhD	CBER/OM/DASC
Lori Peters	CBER/OCBQ/DMPQ
Douglas Pratt, MD	CBER/OVRR/DVRPA
Gregory Price, PhD	CBER/OCBQ/DMPQ
Kirk Prutzman, PhD	CBER/OVRR/DVRPA
Girish Ramachandran, PhD	CBER/OVRR/DVRPA
Kanaeko Ravenell, MS	CBER/OCBQ/DIS
Rebecca Reindel, MD	CBER/OVRR/DVRPA
Carolyn Renshaw	CBER/OCBQ/DMPQ
John Scott, PhD, MA	CBER/OBPV/DB
Earl Scott Stibitz, PhD	CBER/OVRR/DBPAP
Daphne Stewart	CBER/OVRR/DVRPA
Lisa Stockbridge	CBER/OCBQ/DCM
Debra Vause	CBER/OCBQ/DMPQ
Qun Wang, PhD	CBER/OVRR/DVRPA
Jane Woo, MD	CBER/OBPV/DPV
Ho-Hsiang Wu, PhD	CBER/OBPV/DB
Lihan Yan, PhD	CBER/OBPV/DB

APPLICANT ATTENDEES

Lindy Bancke	Head of Clinical Development, Rebiotix
Jonas Pettersson	Senior Medical Director, Ferring
Scott Berry	Berry Consultants
Bjarke Klein	VP Global Biometrics, Ferring
Hari Nagaradona	VP US Regulatory Affairs, Ferring US
Greg Fluet	Chief Operating Officer and Site Head, Rebiotix
Debbora Markus	Senior Director, Quality, Rebiotix
Mirjam Mol-Arts	Chief Science and Medical Officer, Ferring
Lene Melchiorson	VP Global Regulatory Affairs, Ferring
Karen Kuphal	Senior Director, Regulatory Affairs, Rebiotix

BACKGROUND

BLA STN 125739/0 was submitted on November 30, 2022, for Fecal Microbiota, Live.

Proposed indication: Reduce the recurrence of *Clostridioides difficile* infection in adults following antibiotic treatment for recurrent *Clostridioides difficile* infection.

PDUFA goal date: November 30, 2022

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on August 19, 2022.

DISCUSSION

1. Discussion of Substantive Review Issues

CBER indicated that no substantive review issues were identified at this time.

2. Discussion of Minor Review Issues

CBER indicated that no minor review issues were identified at this time.

3. Additional Applicant Data

CBER indicated that there were no additional Applicant data required at this time.

4. Information Requests

Outstanding Information Requests:

- IR#25 dated September 13, 2022: Request for information regarding Monkeypox questionnaire/revised ICF and Clinical Datasets
- IR#26 dated September 23, 2022: Request for missing information under Section 3.2.P.3.4 "Controls of Critical Steps and Intermediates", a risk assessment and justification for the lack of leachable studies for EVA bag, tubing set, etc.
- IR#27 dated September 26, 2022: Request for aggregate numbers of cases of Preferred Terms for (1) all adverse events (AE), (2) all treatment-emergent adverse events (TEAE), (3) all serious adverse events (SAE), and (4) all fatal AE
- IR#28 dated September 27, 2022: Request for information regarding safety analysis

5. Discussion of Upcoming Advisory Committee Meeting

CBER indicated that the Advisory committee meeting is scheduled for September 22, 2022, and important dates for briefing package and presentation were communicated to the Applicant.

6. Risk Management Actions (e.g., REMS)

CBER stated that no issues related to risk management had been identified, therefore, REMS is not needed.

7. Postmarketing Requirements/Postmarketing Commitments

CBER indicated that Postmarketing Requirements/Postmarketing Commitments (if any) will be communicated to the Applicant by October 28, 2022.

8. Major Labeling Issues

CBER indicated that the package insert, carton and container labels are being reviewed. CBER is working toward providing labeling comments to the Applicant before October 28, 2022.

9. Review Plans

CBER intends to take action on this application no later than November 30, 2022.

10. Applicant Questions

- A. Please provide further insight into the potential topics or key discussion points that the FDA is planning to bring forward for the Advisory Committee Meeting (ADCOM)

The Applicant requested the potential topics or key discussion points that will be brought up by CBER during the AC meeting.

CBER stated that following background presentations by FDA and CDC, data submitted to the BLA will be presented first by the Applicant followed by CBER based on our comprehensive review. Each presentation of the data will be followed by questions from the committee members. Following lunch and the open public hearing, the committee will engage in a discussion of the data, and committee members might have additional questions for the Applicant and/or CBER to address. At the end of the discussion, the committee members will vote on two questions: a) whether the available data support the effectiveness of the product for the proposed indication, and b) whether the available data support the safety of the product when used in the proposed patient population.

The Applicant acknowledged CBER's response.

- B. ADCOM data presentation and how FDA will present the following:
- i. Primary Efficacy Result (referencing response to IR#7, IR#15 revised Bayesian Analysis)

CBER response was communicated to Rebiotix on August 12, 2022

The Applicant acknowledged CBER’s feedback regarding the study 2017-01 primary efficacy endpoint analyses and CBER’s intention to present the results that further aligned studies 2014-01 and 2017-01. The Applicant stated that the results of the aligned analysis and the original planned analysis are similar and lead to the same conclusion. The Applicant requested confirmation that the approach and terminology aligned with what CBER will present at the AC meeting to avoid confusion. The Applicant stated that for completeness they will briefly include the original planned primary analyses for study 2017-01 and then pivot to analysis from IR#15 that has a stronger claim to exchangeability between the two studies. The Applicant further stated that they will also refer to the analysis using the matched mITT population. They plan to present the sensitivity analysis that adjusted for prior CDI episodes as the main difference in the patient population enrolled in the two studies.

CBER stated reservations about calling the analysis a “planned analysis” because the success criteria changed retrospectively, and they were not planned in the original analysis. CBER further stated the intention to present the ITT analysis at the AC meeting, along with the mITT analysis.

[Post meeting comment]: Per direction provided by the Applicant, CBER was able to locate the language regarding pre-planned retrospective adjustment of success criteria in their statistical analysis plan. The applicant proposed to refer to this analysis as the “initial analysis” in their briefing document, and CBER finds the proposal acceptable.

The Applicant acknowledged.

- ii. Safety data based on 8 week and 6 months follow-up as discussed at mid-cycle meeting (referencing response to IR#14)

The Applicant stated that at the mid-cycle meeting they proposed to complement the ISS with a new safety analysis of the Phase 3 study 2017-01, based on existing data. The Applicant stated that the placebo-controlled data from the study 2017-01 provided the best assessment of comparative safety data as this was the largest controlled trial in their program. The Applicant planned to remove confounding factors of treatment failure and retreatment to allow comparison of all subjects assigned to the drug product or placebo. The Applicant stated that they have used this analysis in the briefing document, including data from the 8-week double blind period for the randomized and treated safety populations. They also included the 6 month follow up of patients who remained blinded and 6 months of follow up of patients who received open-label product. The Applicant asked whether this was in alignment

with what CBER will present concerning the safety data from study 2017-01 at the AC meeting.

CBER noted that the Applicant may provide both the 8-week and 6-month follow-up safety data; however, the 6-month data should be inclusive of the 8-week time period.

The Applicant acknowledged.

CBER requested for clarification on how the Applicant handled subjects who experienced CDI recurrence but did not receive open label drug product. CBER inquired if the subjects were censored at the time of CDI recurrence or whether all the data through the 6-month period were used.

The Applicant stated that for the short-term, 8-week period of analysis, the subjects were censored at the time of recurrent CDI, but this was not the case for the long-term 6-month follow-up period of analysis.

CBER acknowledged.

- iii. How FDA will present Safety TEAEs and Deaths at 8 weeks and 6 months follow-up (referencing response to IR#14)

The Applicant inquired about how CBER plans to present the number of deaths observed in the Rebiotix clinical program.

CBER stated that a table will be provided in the briefing document with both the time to death and time to onset of the fatal adverse event relative to the last treatment.

The Applicant acknowledged.

C. Confirm Acceptability of the following (due to Information Requests)

- i. CMC Specifications and Lot Release Plan (referencing response to IR#13)

With regards to CMC specifications the Applicant asked if the agency agrees with the (b) (4) sampling plan included in IR#17.

CBER agreed that this plan was reasonable but would need to discuss internally before making a decision.

In addition to the Lot Release Plans (LRPs) in the final template, the Applicant proposed submitting a list of lots that will include lot number and manufacturing date for lots in the release schedule not included in the (b) (4)

sample for the LRPs. The Applicant enquired if this was sufficient for the Lot Release Schedule or is there additional information that the Agency requires for lots in the release schedule that are not sampled for creation of an LRP.

CBER requested that the Applicant submit their proposal to the BLA for review.

The Applicant requested if CBER could provide guidance for the duration of time from when the Agency receives the LRPs to when the sponsor will be notified that the lots are releasable.

CBER requested that the Applicant submit this question to the BLA for a response.

The Applicant acknowledged.

- ii. Post Market Stability Plan (referencing response to IR#13)

With regards to the Post Market Stability plan, the Applicant stated that the samples will be stored in final container closure system (EVA bags) with annual testing at time points 0, 12, 24 and 36 months. The plan to select (b) (4) per (b) (4) i.e., a total of (b) (4) batches per year to be placed into the stability program. The Applicant asked if the CBER agreed to the proposed sampling plan.

CBER agreed to the proposed sampling plan.

- D. Proactively adding a question to further mitigate risk of donor exposure to Monkeypox (in addition to current health screening controls)

The Applicant had drafted a plan that addressed the FDA's required protections as communicated in the FDA Safety Alert for Monkeypox released on August 22, 2022. This plan was communicated to CBER on August 29, 2022. The Applicant requested for any feedback from CBER regarding the plan.

CBER stated that the Applicant's plan was being actively reviewed and the Applicant might expect feedback with additional recommendations in the near future.

The Applicant acknowledged.

[Post meeting comment]: CBER's request to mitigate the potential risks of monkeypox information associated with FMT was communicated to the Applicant on September 13, 2022 (IR#25),

11. Wrap-up and Action Items

- The Applicant will submit lot release related questions as an amendment to the BLA.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.