Summary Basis for Regulatory Action

Date:	November 30, 2022
From:	Qun Wang, PhD Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125739/0
Applicant:	Ferring Pharmaceuticals Inc.
Submission Receipt Dates:	Rolling Submission: May 3, 2021; July 1, 2021; and November 30, 2021
Action Due Date:	November 30, 2022
Proper Name:	fecal microbiota, live-jslm
Proprietary Name:	REBYOTA
Indication:	REBYOTA is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Recommended Action: The Review Committee recommends approval of this product.

Director, Office of Vaccines Research and Review

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product • Facilities review • Establishment Inspection Report • QC, Test Methods, Product Quality	 Paul Carlson, PhD, OVRR/DBPAP Miriam Ngundi, PhD, OCBQ/DMPQ Kathleen Jones, PhD, OCBQ/DMPQ Gregory Price, OCBQ/DMPQ Marie Anderson, MS, PhD, OCBQ/DBSQC Varsha Garnepudi, MS, OCBQ/DBSQC
Clinical • Clinical • Postmarketing safety epidemiological review • BIMO	 Omolara Adewuni, MD, OVRR/DVRPA Jane Woo, MD, OBPV/DPV Kanaeko Ravenell, MS, OCBQ/DIS
Statistical • Clinical data • Non-clinical data	 Zhong Gao, PhD, OBPV/DB Ho-Hsiang Wu, PhD, OBPV/DB
Labeling • Promotional • PNR • Container/Carton	 Michael Brony, PharmD, OCBQ/APLB Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA
Other Reviews not captured above categories, for example: • Consults Clinical data standardization PLLR Real world data Device • CMC reg coordinators	 Brenda Baldwin, PhD, OVRR/DVRPA Cara Fiore, PhD, OVRR/DVRPA Artur Belov, MD, OBPV/ABRA Andrea Gray, ORO/DROP Jennifer Bridgewater, MPH, OVRR/DBPAP Sheila Dreher-Lesnick, PhD, OVRR/DBPAP
Regulatory Project Managers	Girish Ramachandran, PhD, OVRR/DVRPA Margaret Dayhoff-Brannigan, PhD, OVRR/DVRPA
Advisory Committee	September 22, 2022

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1. Introduction

Ferring Pharmaceuticals Inc. (the Applicant) submitted a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) for licensure of REBYOTA. The non-proprietary name of the product is fecal microbiota, live-jslm. The requested indication for REBYOTA is the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

REBYOTA is a combination product for rectal administration. It is supplied as a pre-packaged single-dose 150 mL fecal microbiota suspension in a 250 mL ethylene vinyl acetate bag. An administration tube set is provided separately. REBYOTA is prepared from human fecal material collected from pre-screened and qualified donors and tested for prespecified pathogens. Each 150 mL dose of REBYOTA contains between $1x10^8$ and $5x10^{10}$ colony forming units per mL of fecal microbes, including $>1x10^5$ CFU/mL of *Bacteroides,* in a solution containing no greater than 5.97 grams of polyethylene glycol 3350 in saline. The shelf life for the final drug product is 36 months from the date of manufacture when stored at -80°C. The date of manufacture is defined as the date of initiation of drug substance manufacturing when the donor human stool is combined with the polyethylene glycol 3350/saline solution.

The clinical development program included three Phase 2 studies (2013-001, 2014-01 and 2015-01), two Phase 3 studies (2017-01 and 2019-01), and one retrospective study (2019-02) conducted in the United States and Canada. A total of 978 participants were exposed to at least one dose of REBYOTA across the five prospective studies. Data from two randomized, double-blind, placebo-controlled studies, 2014-01 and 2017-01 contributed to the evaluation of product effectiveness based on a Bayesian analysis. Safety data from 2014-01 and 2017-01 and three open-label, uncontrolled studies, 2013-001, 2015-01, and 2019-01 were pooled in an integrated summary of safety that included 6 months of follow-up after the last dose of REBYOTA across all studies.

2. Background

Clostridioides difficile is a spore-forming, rod-shaped, Gram-positive anaerobic bacterium that colonizes through the fecal-oral route. It is a common cause of antibiotic – associated diarrhea and colitis. CDI is an urgent public health concern, associated with significant morbidity and mortality. A half million *C. difficile* infections are reported in the United States each year. According to the Centers for Disease Control and Prevention (CDC) 2019 report, 223,900 estimated cases occurred in hospitalized patients, and 12,800 deaths were associated with CDI.[1,2] Although the estimated burden of healthcare-associated CDI has decreased in recent years, the rate of community-associated CDI remains unchanged.[3]

Recurrent CDI is an episode of CDI occurring within eight weeks after resolution of symptoms of a previous episode of CDI. Approximately one in six CDI patients will experience a recurrence, and each recurrence increases the risk of subsequent recurrences, with a reported recurrence rate of 65% after three episodes of CDI.[1,4,5,6] Recurrent CDI complications include dehydration, hypotension, kidney failure, severe

diarrhea and rarely toxic megacolon, colonic rupture, septicemia and death. The cost associated with recurrent CDI was estimated to be $2.8 billion in the United States due to considerable morbidity and prolonged hospital stays.[7]

Treatment options for recurrent CDI are limited and depend on the initial course of therapy. Recent clinical practice guidelines recommend tapering/pulsed-dose vancomycin or a ten-day course of fidaxomicin for patients experiencing a first recurrence after an initial course of antibiotics for CDI treatment.[6,8] Bezlotoxumab (Zinplava™), a human monoclonal antibody that binds to *C. difficile* toxin, is indicated to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence. Treatment options are similar for patients with more than one recurrence, although they also include treatment with rifaximin if a standard course of vancomycin is used.[9] While no safe and effective fecal microbiota for transplantation (FMT) product is FDA-approved for prevention of recurrent CDI, FMT has been recommended in various infectious diseases and gastroenterology practice guidelines and has been widely administered for this purpose under FDA's investigational new drug application (IND) enforcement discretion policy for use of FMT to treat CDI not responding to standard therapies.[8,9,10]

Quality-of-life scores in patients with recurrent CDI are lower compared to patients with a first episode of CDI and consistently decrease with increasing number of CDI episodes.[11] In considering the benefits and harms of treatment for recurrent CDI, the expert panel contributing to the development of the Clinical Practice Guidelines by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America judged, based on clinical experience, that patients experiencing recurrent CDI will invariably put a high value on avoidance of a subsequent CDI episode.[9] Prevention of recurrent CDI represents an unmet medical need. Bezlotoxumab, indicated to reduce recurrence of CDI, is for use only in conjunction with antibacterial drug treatment for CDI.

The Applicant initiated REBYOTA product development under IND in 2013. Over the course of REBYOTA development, CBER held several consultations with the Applicant. Table 1 provides a list of key regulatory activities associated with this BLA submission.

Table 1. Regulatory History

Regulatory Events / Milestones	**Dates**
1. Pre-IND meeting	December 20, 2012
2. IND submission	March 21, 2013
3. Fast Track designation granted	May 21, 2013
4. Orphan Drug designation granted	March 10, 2014, amended on November 9, 2017
5. Breakthrough Therapy designation granted	October 8, 2015
6. End of Phase 2 meetings	December 22, 2016, Clinical July 26, 2017, CMC
7. Pre-BLA meetings	October 6, 2020, CMC March 23, 2021, Clinical
8. BLA 125739/0 submissions (rolling submission)	May 3, 2021; July 1, 2021; November 30, 2021
9. BLA filed	January 28, 2022
10. Mid-Cycle communication	May 31, 2022
11. Late-Cycle meeting	August 30, 2022

Regulatory Events / Milestones	Dates
12. VRBPAC* meeting	September 22, 2022
13. Action Due Date	November 30, 2022

*VRPBAC: Vaccines and Related Biological Products Advisory Committee

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

REBYOTA is a fecal microbiota suspension derived from qualified donor human stool (DHS). A single dose of REBYOTA contains 150 mL DHS containing $1x10^8$ to $5x10^{10}$ CFU/mL of fecal microbes (including $>1x10^5$ CFU/mL of *Bacteroides*), (b) (4) polyethylene glycol (PEG) 3350 and 0.9% sodium chloride filled in a 250 mL ethylene vinyl acetate (EVA) bag. REBYOTA is supplied with an administration tube set consisting of a rectal tube, spike port adaptor, and clamp.

Manufacturing Overview

The REBYOTA manufacturing process was developed at the Rebiotix, Inc. facility in Roseville, MN. The source material is DHS from donors qualified through health screening by questionnaire and physical examination for health concerns and potential risk factors. Donor screening also includes blood and stool testing for potentially transmissible pathogens of concern.

The manufacturing process is initiated after collection of a stool donation from a single donor by combining the donor stool with a cryoprotectant excipient solution of PEG3350 and 0.9% saline (b) (4) . A 150 mL volume of DS is (b) (4) filled into the final container (EVA bag) to produce the drug product (DP). Each EVA bag is affixed with a temporary label and stored at -80°C under quarantine while awaiting final stool and blood pathogen test results. Donor stool and blood pathogen testing is performed by (b) (4) . The final drug product is released from quarantine only after receipt of acceptable donor testing results. After removing the DP from the quarantine freezer, the temporary label is replaced with the final label. The DP is packaged in the final carton and stored in a different -80°C freezer until it is shipped to distributors or end users.

Drug Substance

Manufacturing Process

The DS is a suspension of DHS with PEG 3350 and 0.9% sodium chloride prior to filling into the final container. The DS manufacturing process involves the following steps:

(b) (4)

Manufacturing steps (b) (4) are conducted in a manufacturing suite which is maintained at an operating temperature of (b) (4) .The resulting DS proceeds (b) (4) to filling into the final container closure system (DP manufacturing) (b) (4) .

Process Validation

The Applicant uses a (b) (4) manufacturing process for this product. DHS is processed by mixing with excipient solution, (b) (4), and moved directly into DP manufacturing. There are no storage steps or specification/release tests performed on the DS prior to moving into DP manufacturing. The Applicant identified the (b) (4) as the (b) (4) with a critical process parameter for DS manufacturing. The parameters for this step include (b) (4) . The process validation sections for both the DS and the DP were combined as the manufacturing process is continuous.

Drug Product

Manufacturing Process

The DP manufacturing consists of the following steps:

1. Sampling and Filling: (b) (4) , samples are taken for final release testing. (b) (4) DS is (b) (4) transferred into the primary container closure, an EVA bag, through the fill port and replace the fill tube cap.

2. Container closure sealing and inspection: The fill tube is (b) (4) sealed to form a (b) (4) seal. All filled EVA bags are inspected for appearance and integrity.
3. Storage: The DP bag is affixed with a temporary label and stored under refrigerated conditions for no more than (b) (4) followed by transfer to long-term storage at -60°C to -90°C.
4. Labeling and 2nd packaging: the DP is not released from quarantine until all acceptance criteria are met for the DP, DHS, and the donor of the DHS. After negative donor testing results are received, the DP bag is affixed with the final container label and placed into an outer bag whose opening is (b) (4) sealed. The sealed outer bag is inserted into an inner carton, which goes into the final carton, and then stored in a separate -80°C freezer until it is shipped.
5. Shipping: After inspection, the DP container is packed in a box on dry ice, and the administration tubing set is packed at ambient temperature; then both are shipped together in a dual temperature shipper.

Process Validation

The Applicant conducted the process performance qualification (PPQ) studies for DS/DP manufacturing, packaging, and labeling, and shipping. The PPQ protocol was designed to confirm that drug product manufacturing processes perform as expected to consistently produce acceptable quality product. The study included a total of (b) (4) batches manufactured using DHS from (b) (4) unique donors. The PPQ actions for the DP manufacturing process met the specified acceptance criteria. The diversity measurements fell slightly below the expected lower confidence limit for process width. The Applicant plans to perform continued process verification to confirm long-term process performance regarding the diversity measurement. DP labeling and secondary packaging PPQ were examined with (b) (4) batches across (b) (4) days, within (b) (4) packaging campaigns. All test results met the acceptance criteria. The PPQ for DP shipment from the manufacturer to the distributor were also performed. CBER considers the DP manufacturing and shipping processes to be consistent and validated.

DP Specifications

REBYOTA DP specifications for release and stability are included in Table 2.

Table 2. REBYOTA DP Specification

Test	Method Description	Acceptance Criteria
Appearance	Visual	Opaque suspension
***Bacteroides* Species Growth**	(b) (4) *Bacteroides* (b) (4)	Growth Observed (b) (4)
Viable Bacterial Count	(b) (4)	$1.0x10^8$ CFU/mL to $5.0x10^{10}$ CFU/mL (R^1) (b) (4)
Diversity	(b) (4)	(b) (4)

1. R=used for release, S=used for stability

Stability

The Applicant conducted the stability studies to support long-term frozen storage and in-use thaw of the DP.

Long-term Stability – Frozen Conditions (-60°C to -90°C)
(b) (4) frozen batches of DP and (b) (4) DP PPQ batches were manufactured and placed into the long-term stability program at -60ºC to -90ºC (freezer set point of (b) (4) ºC). The DP for the (b) (4) stability batches were stored in EVA bags (b) (4) . The Applicant stored stability samples for the PPQ batches in (b) (4) as the routine batch size of final DP lots in EVA bags is limited to a few doses. The small amount of final DP filled in the (b) (4) allowed them to perform full stability testing of each batch at all timepoints. These samples were tested at 0, 3, 6, 9, 12, 18, 24, and 36 months. The Applicant provided data demonstrating stability of the frozen DP lots through the 36-month time-point. Similarly, PPQ lots on stability remained within specifications for the full 24-month time course assessed.

Short-term Stability – Refrigerated Conditions (2°C to 8°C)
The Applicant assessed the DP stability at refrigerated conditions (2ºC to 8ºC) following storage at frozen conditions (-60ºC to -90ºC). (b) (4) batches manufactured from a single stool donor were assessed at 0, 24, and (b) (4) hours of storage in refrigerated conditions (2°C to 8°C) and the results met all release specifications at each time point tested. A second stability study under refrigerated conditions measured product stability at 0, 72, and (b) (4) hours in refrigerated storage. The (b) (4) lots tested in this study were derived from (b) (4) independent donors. One of these lots exhibited significant loss in viability at 72 and (b) (4) hours, although the final numbers were still within the current specifications for product release. Based on the results from the refrigerated stability studies, the DP is stable for 96 hours (4 days) when stored at refrigerated conditions (2ºC to 8ºC) after a 24-hour thaw.

The Applicant agreed to perform post-licensure annual stability studies on DP packaged in the final container closure system (EVA bags). (b) (4) of DP will be placed on stability studies per (b) (4). These lots will be (b) (4) chosen from lots with sufficient material for all stability timepoints planned. The DP stability lots will be stored at -80°C. The lots will be removed from -80°C storage then thawed at 2-8 C for 24 hours prior to performing stability testing. The lots will be tested after 0, 3, 6, 9, 12, 18, 24, and 36 months for potency, the presence of *Bacterioides* species, and diversity. The Applicant's commitment to continue DP stability studies post licensure is appropriate.

Comparability Protocols

There are no comparability protocols.

b. CBER Lot Release

The product is not subject to CBER Lot Release testing. Accordingly, there is no requirement for submission of product samples to CBER. The basis for this decision is

that lot release of the product has not been deemed necessary for its safety, purity, or potency.

c. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the REBYOTA DS and DP is listed in Table 3 below. The activities performed and inspectional history are noted in the table and in the paragraph that follows.

Table 3. Manufacturing Facility for REBYOTA (fecal microbiota, live-jslm)

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
Rebiotix Inc . 2660 Patton Road Roseville, MN 55113 *DS and DP manufacturing, DP labeling, packaging, storage, and QC and release testing*	3012047188	47695166	Pre-license inspection	CBER/DMPQ May 2 to 6, 2022 No action indicated

CBER/DMPQ conducted a pre-license inspection (PLI) of Rebiotix Inc. from May 2 to May 6, 2022. At the end of the inspection, no FDA Form 483 was issued, and the inspection was classified as No Action Indicated.

d. Container/Closure System

The DP is filled in a sterile, single-use 250 mL EVA bag configured with a fill port and a spike port to dispense the DP. The bag is made up of a (b)(4)-layer (b) (4) film consisting of EVA (fluid contact surface), (b) (4) (exterior surface). The bag is manufactured by (b) (4), a subsidiary of (b) (4). The Applicant assessed the integrity of the EVA bag by visual inspection following the (b) (4) test; all acceptance criteria were met.

e. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical and toxicology studies are not required for this product.

5. Clinical Pharmacology

The mechanism of action of REBYOTA has not been established.

6. Clinical/Statistical

a. Clinical Program

The REBYOTA clinical development program includes five prospective studies (2013-001, 2014-01, 2015-01, 2017-01 and 2019-01) and one retrospective study (2019-02), which were conducted in the United States and Canada under US IND using the investigational product name of RBX2660. Table 4 provides the overview of all clinical studies submitted to the BLA. A total of 978 participants 18 years of age and older with documented recurrent CDI were exposed to at least one dose of RBX2660 across the five prospective studies. Among these, 67.2% (657/978) were female, 93.8% were white, and 78.5% had experienced at least three previous episodes of CDI.

Table 4. Overview of REBYOTA Clinical Studies

Clinical Studies	Study Design Features	RBX2660 Recipients	Placebo Recipients
2013-001	Phase 2, open-label, safety and effectiveness	34	N/A
2014-01	Phase 2, DB*, RCT#, safety and effectiveness	108	20
2015-01	Phase 2, open-label, safety and effectiveness	149	Historical control
2017-01	Phase 3, DB*, RCT#, safety and effectiveness	204	63
2019-01[a]	Phase 3, open-label, safety and tolerability	204	N/A
2019-02	Retrospective, safety, and tolerability	94	N/A

a. Additional safety update on 229 participants exposed to ≥1 dose RBX2660 from study 2019-01 was provided after initial BLA submission.
*DB: double-blind; #RCT: randomized, placebo-controlled trial.

This SBRA will focus on the two double-blind, placebo-controlled studies, 2014-01 and 2017-01 that contributed to the main evaluation of safety and product effectiveness. Additional safety and supportive effectiveness data generated from three open label studies (2013-001, 2015-01, and 2019-01) are briefly discussed.

Studies 2014-01 and 2017-01

Due to enrollment challenges that precluded the conduct of two placebo-controlled Phase 3 trials, the Applicant conducted a single placebo-controlled Phase 3 trial (study 2017-01) with a primary efficacy analysis that employed a Bayesian hierarchical model formally integrating treatment success rates from a placebo-controlled Phase 2 study (2014-01) into study 2017-01. Study 2014-01 was a Phase 2, double-blind, randomized, placebo-controlled trial in adults ≥18 years old with documented recurrent CDI. A total of 133 participants were randomized 1:1:1 to receive two doses of RBX2660, two doses of placebo, or one dose of RBX2660 and one dose of placebo, administered 7±2 days apart. Study 2017-01 was a Phase 3, double-blind, randomized, placebo-controlled study in adults ≥18 years old with documented recurrent CDI; a total of 289 participants were randomized 2:1 to receive one dose of RBX2660 or one dose of placebo. In both studies, treatment with open-label RBX2660 was an option in the event of treatment failure.

Table 5 lists the key design features and the primary endpoint results for both studies. FDA agreed that the two studies are generally exchangeable. However, because the two studies are not identical, an approach based on Bayesian hierarchical modeling with dynamic borrowing was considered acceptable. Consequently, the specified statistical

success criteria for the Bayesian analysis were established to reflect the levels of statistical persuasiveness for demonstrating substantial evidence of clinical effectiveness. The success thresholds were selected as analogues to frequentist one-sided type I error rates of 0.00125 and 0.025 without borrowing but utilizing the Bayesian posterior probabilities of superiority. Two interim analyses were also considered in the design to allow early stopping due to futility or evidence of outstanding efficacy. An analogue to the Pocock error spending function was planned to address the increased chance of an erroneous conclusion due to the interim analyses. Accordingly, the success criteria for the interim and final analyses (first threshold) were set at a posterior probability of superiority of 0.9993, and the second threshold at a posterior probability of superiority of 0.9750.

Table 5. Key Design Features and Primary Endpoints of 2014-01 and 2017-01

Study Design	**2014-01 (NCT 02299570)**	**2017-01 (NCT 03244644)**
Treatment groups	Randomized 1:1:1 Group A: 2 doses of RBX2660 Group B: 2 doses of placebo Group C: 1 dose of RBX2660/1 dose of placebo	Randomized 2:1 (RBX2660: placebo) 1 dose of RBX2660 1 dose of placebo
Number of RBX2660 doses	1-2 enemas (blinded study) Up to 2 additional open-label doses	1 enema (blinded study) Up to 1 additional open-label dose
Dosage regimen	2 enemas, given 7±2 days apart	1 enema
Number of previous CDIs, including qualifying events	≥2 recurrences and ≥2 rounds of SOC* oral antibiotic therapy or ≥2 severe CDI resulting in hospitalization	≥1 recurrence and ≥1 round of SOC oral antibiotic therapy or ≥2 severe CDI resulting in hospitalization
Safety follow-up	24 months	6 months
Primary endpoint	Treatment success – absence of CDI recurrence within 8 weeks of completing the last dose of the treatment	Treatment success – absence of CDI recurrence within 8 weeks of completing treatment
Treatment Success rates (mITT population)	Group A: 62.5% (25/40) Group B: 44.2% (25/38) Group C: 65.8% (19/43)	Placebo: 62.4% (53/85) RBX2660: 71.2% (126/177)

*SOC: standard of care; mITT: modified intention-to-treat

In the Bayesian analysis, treatment success was defined as absence of CDI diarrhea (passage of 3 or more unformed stools in 24 or fewer consecutive hours for at least 2 consecutive days) for 56 days (8 weeks) after completing the assigned treatment. The modified intention-to-treat (mITT) population was pre-specified as the primary analysis population. The study 2017-01 data were analyzed with integration of data from study 2014-01, and the extent of borrowing was dependent on the similarity of effect for both RBX2660 and placebo group per the planned design. An initial Bayesian analysis conducted by the Applicant resulted in a posterior probability of 0.986 that RBX2660 was superior to placebo for the mITT population. However, FDA recommended that, in order to lead to a stronger claim of exchangeability between the two studies, the Bayesian analysis be conducted with the analysis population definition of study 2017-01 applied to study 2014-01. Although this change was made after the initial analysis was conducted, it did not impact the conclusions of the analysis with respect to the specified success criteria.

The primary efficacy results (mITT population) for posterior estimates from the Bayesian hierarchical model are summarized in Table 6. The Bayesian analysis borrowing information from study 2014-01 placebo and one dose RBX2660 groups into study 2017-01 resulted in an estimated difference in treatment success rates of 0.13 (95% credible interval: 0.02 to 0.24). The posterior probability that RBX2660 was superior to placebo was 0.991.

Table 6. Posterior Probability for Superiority and Posterior Estimates from the Bayesian Hierarchical Model with Study 2017-01 Analysis Population Definitions Applied to Study 2014-01 (mITT population)

Parameter	Placebo Treatment Success Rate	RBX2660 (blinded) Treatment Success Rate	Treatment Effect
Mean	0.57	0.71	0.13
95% credible interval	0.48, 0.67	0.64, 0.77	0.02, 0.24
Posterior Probability	-	-	0.991*

* Pre-defined threshold for superiority was 0.975

Overall, the efficacy results met the second success threshold (posterior probability of superiority 0.9750). However, the efficacy results did not meet the more stringent first success threshold (posterior probability of superiority 0.9993). The analysis of the intention-to-treat (ITT) population led to the same conclusion.

Supportive Clinical Studies

In addition to placebo-controlled studies 2014-01 and 2017-01, the Applicant submitted data from three open-label studies and one retrospective study to support the BLA (Table 4). The effectiveness results of the three open-label clinical studies are summarized below. In these supportive clinical studies, the Applicant collected the 8-week CDI recurrence data and analyzed them in a descriptive manner. However, the interpretation of these open-label data is limited due to lack of concurrent placebo control, inclusion of a different dosing regimen (2 doses) from what is intended for licensure (1 dose), and differences between study populations in the open-label and placebo-controlled studies. Although the interpretation is limited, a similar trend in RBX2660 treatment success rates was observed in the open-label and placebo-controlled studies, and these studies were therefore determined to be supportive.

Study 2013-001 (NCT01925417) was a Phase 2, multicenter, open-label, prospective, non-controlled study. Forty participants 18 years of age and older who had at least two recurrences after a primary episode or had at least two episodes of severe *Clostridioides difficile*-associated diarrhea resulting in hospitalization were enrolled in the study. Of the 40 enrolled participants, 34 received at least one treatment with RBX2660. The primary efficacy endpoint was treatment success, defined as the absence of *C. difficile*-associated diarrhea (passage of three or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days) at 56 days after the last dose of RBX2660 treatment. Sixteen out of 32 participants who completed follow-up (50.0%) were considered a treatment success after the first treatment course with RBX2660.

Study 2015-01 (NCT02589847) was a Phase 2, multicenter, open-label, prospective study to compare one dose RBX2660 with antibiotic-treated historical controls. Participants 18 years of age and older who had at least two recurrences after a primary

episode or had at least two episodes of severe CDI resulting in hospitalization were enrolled in the study. The primary efficacy endpoint was treatment success, measured by the recurrence-free rate of CDI diarrhea without the need for retreatment with *C. difficile* anti-infective therapy or fecal transplant through 56 days after completion of study treatment with RBX2660. The efficacy analysis was performed on RBX2660 treated participants (n=142) who received at least one dose of RBX2660, compared with a closely matched Historical Control arm (n=75) chosen from a retrospective chart review of participants treated with antibiotics for recurrent CDI who matched key eligibility criteria and had an evaluable treatment outcome. The proportion of participants with treatment success was higher in the RBX2660 arm (78.9%) as compared with the Historical Control arm (30.7%).

Study 2019-01 (NCT03931941) is an ongoing Phase 3, multicenter, open-label, prospective, non-controlled study to evaluate the safety and tolerability of RBX2660 for the prevention of recurrent CDI in participants who have had prior recurrent CDI that was resolved with antibiotic treatment. The primary efficacy endpoint is treatment success, defined as the absence of CDI through 8 weeks after treatment. An ad hoc analysis of study 2019-01 effectiveness data available at the time of the cut-off date (April 20, 2021) showed that, at 8 weeks post RBX2660 treatment, 73.4% (113/154) of participants in the mITT population experienced treatment success.

REBYOTA Effectiveness Summary

The primary efficacy analysis of the Phase 3 study 2017-01 met the second pre-specified statistical success threshold but did not meet the more stringent first specified success threshold. Prior to the Applicant performing the analysis, FDA concluded that a posterior finding equivalent to meeting the first specified success threshold would be sufficient to demonstrate substantial evidence of effectiveness. After the primary efficacy analysis only met the second specified success criteria, FDA considered whether the data from the study, as well as the data from the studies described in the Supportive Clinical Studies section above, would be sufficient to demonstrate substantial evidence of effectiveness. In coming to their conclusion about substantial evidence of effectiveness, the review team took the following information into consideration:

1. the clinical context for recurrent CDI, which is a serious condition that can be associated with high morbidity and mortality;

2. the unmet medical need for recurrent CDI because treatment options are limited and can be complex and prolonged. Bezlotoxumab, indicated to reduce recurrence of CDI, requires intravenous infusion, and its usefulness in individuals with pre-existing congestive heart failure may be limited (see Zinplava, Drug Label Information, Warnings and Precautions, updated 23 May 2022);

3. the challenges of enrolling placebo-controlled trials for FMT given availability of other FMT products under enforcement discretion; and

4. the observed RBX2600 treatment success rate in the placebo-controlled study 2017-01 was similar to the treatment success rates reported from the open-label studies of RBX2660 and from randomized, placebo-controlled studies of other FMT products.[12,13,14,15,16]

After presenting the data at the advisory meeting and receiving a positive recommendation from a substantial majority of committee members that the clinical data were adequate to support effectiveness of the product (see Section 9), the review team concluded that the data submitted to the BLA demonstrate substantial evidence of effectiveness for the prevention of recurrent CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

b. Bioresearch Monitoring (BIMO) - Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed for the Applicant, one foreign and three domestic clinical study sites that participated in the conduct of Study 2014-01 and 2017-01. The inspections did not reveal any issues that impact the integrity of the data submitted in this original BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA granted orphan designation to RBX2660 for “prevention of recurrent *Clostridioides difficile* infection in individuals with prior recurrent *Clostridioides difficile* infection resolved following antibiotic treatment.” Section 505B(k) of the FD&C Act contains a statutory exemption from the requirement to conduct pediatric studies under PREA for certain drugs with orphan designation. Therefore, the BLA is exempt from PREA requirements.

7. Safety and Pharmacovigilance

Across the 5 prospective clinical studies, participants recorded solicited adverse events in a diary for the first 7 days after each dose of REBYOTA or placebo. Participants were monitored for all other adverse events by queries during scheduled visits, with duration of follow-up ranging from 6 to 24 months after the last dose. In the largest placebo-controlled study, 2017-01, the Applicant analyzed safety data from the double-blind period, from the point after study participants received RBX2660 or placebo treatment to the point at which an individual either completed the specified follow-up period, was lost-to-follow-up, or experienced a CDI recurrence. Individuals who experienced a CDI after treatment were censored from analysis at the day of CDI recurrence. During the 8 week follow up period, 47 RBX2660 recipients (26.1%) and 30 placebo recipients (34.5%) were censored from the analysis. The most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to Investigational Product by the investigator) reported by ≥ 3% of RBX2660 recipients, and at a rate

greater than that reported by placebo recipients, were abdominal pain (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%) within 8 weeks after receipt of RBX2660 or placebo. Most adverse reactions occurred during the first 2 weeks after treatment. After this, the proportion of subjects with adverse reactions declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse reactions were mild to moderate in severity. No life-threatening adverse reaction was reported.

Safety data from studies 2013-001, 2014-01, 2015-01, 2017-01 and 2019-01 were pooled in an integrated summary of safety (ISS) that included 6 months of follow-up after the last dose of study treatment across all studies. Safety was assessed by examining the incidence of treatment emergent adverse events (TEAEs), serious TEAEs, discontinuations due to TEAEs, and deaths due to TEAEs that occurred through 6 months after treatment. The ISS population included any subject who received at least one dose of RBX2660 or placebo. The Applicant provided a safety update to the BLA six months after the BLA submission, with safety data from an additional 229 participants enrolled in study 2019-01 and exposed to at least one dose of RBX2660. This update increased the overall RBX2660 exposure from 749 participants to 978 participants. In general, the data included in the safety update did not reveal any trends or events to suggest a new safety concern. Thus, the safety analysis for the BLA was conducted using the initial ISS dataset provided by the Applicant.

The ISS included an analysis of data from participants enrolled in double-blind, randomized placebo-controlled studies (n=312 RBX2660 recipients and 83 placebo recipients) and an analysis of data from all five studies (n=749 RBX2660 recipients, including participants who received open-label RBX2660, and 83 placebo recipients). The safety review focuses on the participants who received one dose of blinded or open-label RBX2660 (dosing regimen proposed for licensure; n=429), participants who received one dose of blinded RBX2660 (n=193), participants who received any dose of RBX2660, regardless of blinding or regimen (Any RBX2660; n=749), and placebo recipients (n=83).

Solicited adverse events (AEs), specified as gas or flatulence, abdominal distension or bloating, rectal bleeding, irritation or pain, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, nausea, vomiting, and fever, were collected from participants via subject diary from the date of enrollment through the seventh day after receiving the assigned treatment (studies 2013-001, 2017-01 and 2019-01) or through the seventh day after receiving the second assigned study treatment (studies 2014-01 and 2015-01). In Study 2017-01, the most frequently reported solicited AEs from day 1 through day 7 were gas (flatulence), abdominal distension or bloating, and abdominal pain or cramping. Most solicited AEs were mild or moderate in severity.

The proportion of participants reporting TEAEs was 61.8% in the one-dose RBX2660 group, 69.9% in the blinded RBX2660 group, and 68.8% in the Any RBX2660 group compared to 60.2% in the placebo group. In all groups, the most commonly reported events were gastrointestinal. In both the one-dose and blinded RBX2660 groups, numerically higher proportions of participants reported events of abdominal pain, nausea, flatulence, and abdominal distention were observed compared to placebo. The

proportions of participants reporting severe and life-threatening TEAEs were higher in the RBX2660 groups compared to the placebo group.

The proportion of participants reporting serious TEAEs was 8.4% in the one-dose RBX2660 group, 10.4% in the blinded RBX2660 group, and 13.8% in the Any RBX2660 group, compared to 7.2% in the placebo group. Higher rates of serious TEAEs were observed in the multiple dose populations (19%, 28.6%, and 83.3% of participants who received two, three, or four-doses of RBX2660, respectively). The most frequently reported serious TEAEs were in the MedDRA system organ classes (SOCs) of *Infections and infestations*, *Gastrointestinal disorders*, and *Respiratory, thoracic and mediastinal disorders*. Although the overall imbalances in serious TEAEs between RBX2660 and placebo group are notable, a review of the events did not identify apparent trends in serious TEAEs by MedDRA SOC or Preferred Term that would suggest a causal association. Following review of individual case narratives, the FDA did not identify any serious TEAEs that we considered causally related to RBX2660.

The proportion of participants reporting fatal TEAEs was 1.2% in the one-dose RBX2660 group, 2.6% in the blinded RBX2660 group, and 1.8% in the Any RBX2660 group, compared to 0% in the placebo group. The proportion of participants reporting any TEAEs leading to death increased as the number of treatment exposures increased, ranging from 3.4% in participants who received two doses of RBX2660 to 16.7% of participants who received 4 doses of RBX2660. One death due to relapsed CDI on Day 21 (study 2015-01) was considered possibly related to RBX2660 by the investigator. Following review of the narrative and case report form by the FDA, the event was considered not to be causally related to RBX2660, with a clear alternative etiology of CDI. None of the fatal events were considered plausibly related to RBX2660 treatment by the FDA.

Considerations in the interpretation of comparisons between the placebo and RBX2660 groups in the ISS include: 1) the open-label nature of many of the RBX2660 doses in the ISS population; 2) subjects crossed over to receive RBX2660 in an open-label fashion due to recurrence of CDI, which may reflect increased risk for adverse events due to underlying risk factors that predispose to recurrent CDI or morbidities attributable to the CDI; and 3) subjects were followed for 6 months after the last dose of study treatment, resulting in a longer duration of follow up for subjects who received multiple doses. Furthermore, randomization was no longer preserved between the blinded placebo and RBX2660 groups as a result of exclusion of the subjects who experienced a CDI recurrence and received open-label RBX2660. The observed safety profiles may not be representative of those expected in the placebo or RBX2660 groups.

Overall, the safety review demonstrated imbalances in gastrointestinal TEAEs and serious adverse events (SAEs), including fatal events, between the RBX2660 groups and the placebo group. However, no specific pattern or trend was identified in review of TEAEs, serious TEAEs, TEAEs leading to discontinuation or adverse events of special interest that would suggest a causal relationship to RBX2660.

Pharmacovigilance Plan

The Applicant submitted a pharmacovigilance plan for REBYOTA. There are no important identified risks associated with the product. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80, quarterly periodic safety reports for 3 years, and annual periodic safety reports thereafter.

- Enhanced pharmacovigilance: For 3 years following product licensure, the Applicant must submit all SAEs (regardless of expectedness) as expedited 15-day alert reports to the FDA Adverse Event Reporting System (FAERS). The Applicant will also provide aggregate analysis and assessment in periodic safety reports for all SAEs, and any AE (regardless of seriousness) in individuals who receive REBYOTA while pregnant or lactating; in individuals who are < 18 years of age; and in immunocompromised individuals.

- Voluntary sponsor study: The Applicant plans to conduct a General Safety Surveillance Study using a claims-based database, to compare patient demographics, clinical characteristics and safety outcomes (relative risks of Adverse Events of Special Interest (AESIs)) between REBYOTA and comparator(s).

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy or safety-related postmarketing requirement study. There is no safety-related postmarketing commitment study for this product.

8. Labeling

The proposed proprietary name, REBYOTA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 18, 2022, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on March 2, 2022. On April 25, 2022, the Applicant was advised that all of their proposed proper name suffixes were found unacceptable. The Applicant requested an FDA-generated suffix on May 25, 2022 and, on June 3, 2022, a suffix was provided for the proper name: fecal microbiota, live-jslm.

The APLB reviewed the proposed prescribing information and package/container labels on November 10, 2022, from a promotional and comprehension perspective. The prescribing information was found acceptable from a promotional and comprehension perspective. Comments were provided on the package and container labeling.

9. Advisory Committee Meeting

A Vaccines and Related Biological Products Committee (VRBPAC) meeting was held on September 22, 2022. The committee discussed the safety and effectiveness data derived from REBYOTA clinical studies conducted in participants 18 years of age and

older. The committee noted that current available therapies are not sufficient to treat patients with recurrent CDI, which represents an unmet medical need, especially in patients who experience three or more recurrences. Committee members noted the modest treatment effect estimated in each of the two placebo-controlled trials that contributed to the demonstration of effectiveness but acknowledged that even a modest treatment effect could be clinically meaningful for patients with recurrent CDI that have not responded to other available treatment options.

The committee acknowledged the challenges experienced by the Applicant in recruitment of study participants. Some committee members expressed concern about the statistical robustness of the Phase 3 Bayesian posterior credible interval resulting from the limited number of patients enrolled in the trial. However, other committee members acknowledged the difficult circumstances involved with trial recruitment in the setting of the FDA IND enforcement discretion policy for FMT to treat CDI not responding to standard therapies, and these committee members opined that given the patient population and seriousness of the condition, the Phase 3 effectiveness results were sufficiently persuasive. Committee members opined that availability of REBYOTA as an FDA approved product would represent an improvement over unlicensed FMT products that are currently available under enforcement discretion.

Some committee members also expressed concern about imbalances in serious adverse events between treatment and placebo groups; however, committee members acknowledged that FDA did not appreciate any clear basis for a causal association in its review of these adverse events, and the imbalances were difficult to interpret due to the diminishing placebo group size resulting from cross-over of the sickest placebo recipients to open-label treatment.

The committee expressed concern regarding the lack of diversity in participant enrollment because very few people of color were included in the trials. The committee encouraged the conduct of additional studies to include individuals with more diverse racial and ethnic backgrounds and to monitor the safety and effectiveness of REBYOTA in those groups.

Several VRBPAC members stated that quantitative assessments of benefit-risk would be helpful; however, quantitative modeling would involve numerous uncertainties and assumptions. There was broad consensus across the committee that if REBYOTA were approved, postmarketing evaluation of both safety and effectiveness would be critical to further define the benefits and risks of the product. CBER addressed the collection of postmarketing safety data with the Applicant and confirmed that the Applicant plans to conduct a General Safety Surveillance Study using a claims-based database to compare patient demographics, clinical characteristics and safety outcomes between REBYOTA and comparator(s). An enhanced pharmacovigilance plan will be in place following product licensure.

The VRPBAC voted on two questions:

1. Are the available data adequate to support the effectiveness of REBYOTA to reduce the recurrence of *Clostridioides difficile* infection (CDI) in adults 18 years of age and older following antibiotic treatment for recurrent CDI?

   The results of the vote were as follows:
   Yes = 13 No = 4 Abstain = 0

2. Are the available data adequate to support the safety of REBYOTA when administered to adults 18 years of age and older following antibiotic treatment for recurrent CDI?

   The results of the vote were as follows:
   Yes = 12 No = 4 Abstain = 1

10. Other Relevant Regulatory Issues

Not applicable

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Review Committee recommends approval of REBYOTA for the labeled indication and usage based on a review of the clinical and product-related data submitted in the original BLA.

b. Benefit/Risk Assessment

The Applicant has submitted data to support the safety and effectiveness of REBYOTA. The Review Committee agrees that the risk/benefit balance for REBYOTA is favorable and supports approval for use in adults 18 years of age and older.

c. Recommendation for Postmarketing Activities

The review committee agrees with the pharmacovigilance activities in the Applicant's proposed pharmacovigilance plan, which includes enhanced pharmacovigilance for all SAEs, and a voluntary postmarketing study for general safety surveillance using a claims-based database to compare patient demographics, clinical characteristics and safety outcomes (relative risks of AESIs) between REBYOTA and comparator(s).

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