Application Type	BLA
STN	125739/0
CBER Received Date	November 30, 2021
Goal Date	November 30, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Qun Wang, Ph.D.
Clinical Reviewer(s)	Omolara Adewuni, MD
Project Manager	Girish Ramachandran, PhD Margaret Dayhoff-Brannigan, PhD
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician Therapeutics Evaluation Branch 2, DB/OBPV
Supervisory Concurrence	Lihan Yan, Ph.D. Acting Chief, Therapeutics Evaluation Branch 2, DB/OBPV
	John Scott, Ph.D. Director, Division of Biostatistics, OBPV
Applicant	Ferring Pharmaceuticals Inc.
Established Name	Fecal Microbiota, Live – jslm
(Proposed) Trade Name	REBYOTA
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Microbiota suspension of a broad consortium of live microbes, derived from human feces provided by screened and monitored donors
Dosage Form(s) and Route(s) of Administration	Microbiota suspension by rectal administration
Dosing Regimen	150 mL single dose
Indication(s) and Intended Population(s)	Prevention of recurrence of *Clostridioides difficile* infection (CDI) following antibiotic treatment for recurrent CDI in individuals 18 years of age and older

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L<small>IST OF</small> T<small>ABLES</small>

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LIST OF ABBREVIATION AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse events of special interest
BLA	Biologics License Application
C. difficile	Clostridioides difficile
CDAD	C. difficile-associated diarrhea
CDI	Clostridioides difficile infection
CI	Confidence interval
Crl	Credible Interval
DSMB	Data and Safety Monitoring Board
EAC	Endpoint adjudication committee
FDA	Food and Drug Administration
FMT	Fecal microbiota transplantation
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IND	Investigational New Drug
ISS	Integrated summary of safety
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
PP	Per Protocol
rCDI	Recurrent Clostridioides difficile infection
SAE	Serious adverse event
SD	Standard deviation
SOC	Standard of care
SP	Safety Population

1. Executive Summary

The applicant (Ferring Pharmaceuticals Inc., previously Rebiotix, Inc.) submitted an original Biologics License Application (BLA, STN 125739/0) for RBX2660, a fecal microbiota-based live biotherapeutic product. The proposed indication is prevention of recurrence of *Clostridioides difficile* infection (CDI) in adults 18 years of age and older following antibiotic treatment for recurrent CDI. To support the efficacy and safety of the product, the applicant included six clinical studies in this submission: 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).

Efficacy:
The primary efficacy endpoint analysis was based on the randomized, double-blind, placebo-controlled Phase 3 study 2017-01, conducted with a Bayesian hierarchical model borrowing information from Phase 2 study 2014-01. In the modified intent-to-treat (mITT) population, the model-estimated difference in treatment success rates was 0.13 (95% credible interval: 0.02 to 0.24) and the corresponding posterior probability that RBX2660 was superior to placebo was 0.991. This efficacy result met the pre-specified statistical success threshold (posterior probability of superiority of 0.9750) for a single adequate and well-controlled trial. However, this result did not meet the pre-specified success threshold (0.9993) that would have been considered as positive statistical evidence in a single trial that could potentially substitute for two independent adequate and well-controlled trials. The analysis of the intent-to-treat (ITT) population led to the same conclusion.

Safety:
The safety evaluation was conducted based on individual studies and integrated safety analysis. These safety analyses showed generally similar findings. The overall rate of AEs was generally higher in the RBX2660 group compared to the placebo group. Numerical imbalances were observed in gastrointestinal adverse events and serious adverse events (SAEs), including fatal events, between the RBX2660 groups and the placebo group. Across five studies, 18 (1.8%) subjects with adverse events occurring within 6 months since last dose died in the All RBX2660 (1-4 doses) group (N=978) and none in the placebo only group (N=83). These deaths were considered to be not related to the product by study investigators and FDA clinical reviewers.

Overall, the primary efficacy analysis result of the Phase 3 study 2017-01 met the pre-specified statistical success threshold for a single adequate and well-controlled trial. While the rates of adverse events were generally higher among the subjects receiving RBX2660 than those receiving placebo, no major safety concern was identified from the studies. In my view, considering the severity and rarity of the disease and unmet medical need, the data submitted with this BLA can support the conclusion that there is substantial evidence of effectiveness of RBX2660 for preventing recurrence of CDI.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Recurrent *Clostridioides difficile* infection (rCDI)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

ZINPLAVA, a human monoclonal antibody that binds to *Clostridioides difficile* toxin B, is currently approved in U.S. and indicated to reduce CDI recurrence of in individuals 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The investigational product was granted Orphan Designation in March 2014 and Breakthrough Therapy Designation in October 2015.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

The submission presented no data integrity issues.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

N/A

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on two randomized, double-blind, placebo-controlled studies: Phase 2 study 2014-01 and Phase 3 study 2017-01.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- STN 125739/0.4 Module 2.5. Clinical Overview
- STN 125739/0.4 Module 2.7.3. Summary of Clinical Efficacy
- STN 125739/0.4 Module 2.7.4. Summary of Clinical Safety
- STN 125739/0.4 Module 5.3.5.1. Study 2017-01
- STN 125739/0.4 Module 5.3.5.1. Study 2014-01
- STN 125739/0.4 Module 5.3.5.1. Study 2015-01
- STN 125739/0.4 Module 5.3.5.2. Study 2013-01
- STN 125739/0.4 Module 5.3.5.2. Study 2019-01
- STN 125739/0.4 Module 5.3.5.3. Integrated Summary of Safety
- STN 125739/0.8 Clinical Information Amendment (Response to Information Request IR #4: Request for statistical programs and other items)
- STN 125739/0.13 Clinical Information Amendment (Response to IR #7: Request for additional statistical information)
- STN 125739/0.21 Clinical Information Amendment (Response to IR #12: Request for clarification regarding Study 2017-01 and 2014-01 data analysis)
- STN 125739/0.25 Clinical Information Amendment (Response to IR #15: Request for additional analyses on Study 2014-01, 2017-01, and the integrated Bayesian analyses on the primary efficacy endpoint, etc.)
- STN 125739/0.32 Clinical Information Amendment (Response to IR #21: Request updated secondary efficacy analysis in Study 2017-01)
- STN 125739/0.45 Clinical Information Amendment (Response to IR #28: Request in additional safety analyses using censoring strategies)
- Vaccines and Related Biological Products Advisory Committee September 22, 2022 Meeting Briefing Document- Sponsor- Rebiotix - RBX2660
- Vaccines and Related Biological Products Advisory Committee September 22, 2022 Meeting Presentation- BLA for Fecal Microbiota, Live (REBYOTA) - Rebiotix

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the studies in the clinical development program.

Table 1 Overview of individual studies

Study design features	2014-01	2017-01	2013-001	2015-01	2019-01
Phase	2B	3	2	2	3
Total enrolled	150	320	40	162	293
Study design	Double-blind, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled	Open label, non-controlled	Open label, historical controls	Open label, non-controlled
Population	Adults with documented rCDI	Adults with documented rCDI	Adults with documented rCDI	Adults with documented rCDI	Adults with documented rCDI
Number of previous CDIs	≥ 2 recurrences and ≥ 2 rounds of SOC oral antibiotic therapy	≥ 1 recurrence and ≥ 1 round of SOC oral antibiotic therapy	≥ 2 recurrences and ≥ 2 rounds of SOC oral antibiotic therapy	≥ 2 recurrences and ≥ 2 rounds of SOC oral antibiotic therapy	Investigator discretion
Common comorbidities allowed	None	None	None	None	Yes
Antibiotic washout	24 to 48 hours	24 to 72 hours	24 to 48 hours	24 to 48 hours	24 to 72 hours
Efficacy Endpoint Adjudication	DSMB	EAC	None	None	EAC
Treatment received	Placebo or RBX2660	Placebo or RBX2660	RBX2660	RBX2660	RBX2660
Randomization: treatment groups (treatment dose) treatment regimen	1:1:1 ratio: Group A: RBX2660 (2 doses); Group B: Placebo (2 doses); Group C: RBX2660 (1 dose)/ placebo (1 dose) administered 7±2 days apart.	2:1 ratio: RBX2660 (1 dose) Placebo (1 dose)	RBX2660 (1 dose)	RBX2660 (2 doses) administered 7 ± 2 days apart	RBX2660 (1 dose)
Optional second treatment course?	Yes	Yes	Yes	No	Yes
Follow-up duration (months)	24	6	6	24	6

Source: adapted from Table 1 in Summary of Clinical Efficacy

5.4 Consultations

5.4.1 Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held on September 22, 2022, to discuss the findings from this BLA. VRBPAC members voted 13 to 4 that the data were adequate to support the effectiveness of RBX2660 to reduce the recurrence of CDI in adults 18 years of age and older following antibiotic treatment for recurrent CDI. The Committee also voted 12 to 4 with 1 abstention that the data were adequate to support the safety of RBX2660.

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 2014-01

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

6.1.1 Objectives

6.1.1.1 Primary Objectives
To assess the efficacy of two enemas of RBX2660 vs. two enemas of placebo for the prevention of recurrent *Clostridium difficile* infection.

6.1.1.2 Secondary Objectives
- To evaluate the efficacy of [1 enema of RBX2660 and 1 enema of placebo] vs. 2 enemas of placebo.
- To evaluate the efficacy of 2 enemas of RBX2660 vs. [1 enema of RBX2660 and 1 enema of placebo].
- To assess the safety of RBX2660.
- To assess quality of life as measured by the SF-36 Form.
- To assess the efficacy of *C. difficile* infection therapies administered to patients with confirmed Treatment Failures.

6.1.2 Design Overview

Study 2014-01 was a prospective, multicenter, randomized, double-blinded, placebo-controlled, three-arm Phase 2B study to evaluate efficacy and safety of RBX2660 for the prevention of recurrent Clostridium difficile infection (rCDI). Subjects were taking or started a course of antibiotics to control rCDI symptoms at the time of enrollment followed by a 24 - 48 hours washout period prior to receiving the first assigned study treatment. Subjects' symptoms must have been controlled while taking this course of antibiotics to be randomized to treatment. Randomization was at a 1:1:1 ratio to one of the following groups: Group A (2 enemas of RBX2660), Group B (2 enemas of placebo), and Group C (1 enema of RBX2660 followed by 1 enema of placebo). One complete assigned study treatment consisted of two enemas administered 7 ± 2 days apart; the second enema could be administered sooner if CDI diarrhea (passage of ≥ 3 unformed stools in ≤ 24 consecutive hours for at least two consecutive days) recurred in less than 7 days.

6.1.3 Population

The study population included adults (≥ 18 years old) with rCDI who had either (a) at least two recurrences after a primary episode (i.e., at least three episodes) and had

completed at least two rounds of standard-of-care oral antibiotic therapy or (b) had at least two episodes of severe CDI resulting in hospitalization.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The active treatment was RBX2660 (microbiota suspension) (b) (4)/150 mL in an enema bag. Each bag of RBX2660 consisted of a suspension of a minimum of (b) (4) live organisms/mL in polyethylene glycol 3350/0.9% Sodium Chloride for Irrigation, (b) (4), solution. The placebo was an enema of normal saline and cryoprotectant in the same proportions as found in RBX2660.

6.1.6 Sites and Centers

A total of 21 centers in the US and Canada.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints

- Primary efficacy endpoint: Treatment Success, defined as the absence of *C. difficile*-associated diarrhea (CDAD) without the need for retreatment with C. difficile anti-infective therapy or Fecal Transplant at 56 days after administration of the last assigned study enema, of Group A (two enemas of RBX2660) vs. Group B (two enemas of placebo) during the blinded period.
- Key secondary efficacy endpoints:
  o Treatment Success between Group C (1 enema of RBX2660 and 1 enema of placebo) vs. Group B (two enemas of placebo) during the blinded period.
  o Treatment Success between Group A (two enemas of RBX2660) vs. Group C (1 enema of RBX2660 and 1 enema of placebo) during the blinded period.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

Subjects, site personnel, the Medical Monitor, and Clinical personnel from the study team were blinded to the randomization assignment through completion of the study.

- Randomization

Randomization was at a 1:1:1 ratio to one of three study groups: Group A (2 enemas of RBX2660), Group B (2 enemas of placebo), and Group C (1 enema of RBX2660 and 1 enema of placebo). The randomization was stratified by the antibiotic regimen used by the subject at screening.

- Definitions of analysis populations
  o Safety Population (SP): randomized subjects who received any study treatment. Subjects were analyzed according to the treatment they actually received.
  o Intent-to-Treat (ITT): all randomized subjects, regardless of whether they complete their assigned study treatment. Subjects were analyzed according to the

  randomized treatment rather than the actual treatment received should any
  treatment misallocations or discontinuations occur.

  o Modified Intent-to-Treat (mITT): the mITT population included subjects who
   completed at least one dose of study treatment, regardless of treatment received,
   but excluding subjects who discontinued from the study during the blinded period
   for any reason prior to evaluation of Treatment Failure or Success, and subjects
   who had deviations from any inclusion or exclusion criteria. Subjects who were
   declared Treatment Failures without meeting all four criteria for Failure, as
   assessed by the DSMB adjudication, were included under the category
   Indeterminate and counted as Treatment Failures for purposes of efficacy
   analysis.

  o Per Protocol (PP): the PP population consisted of all ITT subjects who received
   the treatment (both blinded enemas) to which they were randomized and were
   evaluable for Treatment Success/Failure at 56 days after the last assigned
   treatment. Subjects who withdrew consent or were lost to follow-up during the
   blinded period (discontinued the study), prior to evaluation of Treatment Failure
   or Success, those who expelled a moderate or large amount of either of the
   blinded enemas, those with inclusion/exclusion criteria deviations, or those who
   did not receive both blinded enemas were excluded. Finally, the PP population
   also excluded subjects deemed upon clinical review to have major protocol
   deviations that might affect outcome such as use of non-dietary probiotics,
   vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide, IVIG, or
   systemic steroids, and female subjects of child-bearing potential who had a
   positive pregnancy test upon enrollment.

- Sample size planning

To demonstrate 80% success in the 2-enema treatment group (Group A) vs. 40% success
in the 2-enema control group (Group B), 105 subjects were planned (power 90%; Type I
error: two-sided 0.05). An additional 12 subjects were to be enrolled to allow for a 10%
loss-to-follow up rate, for a total of approximately 117 subjects.

- Statistical Analysis for Primary Efficacy Endpoint

The primary efficacy variable was Treatment Success defined as the absence of
CDAD without the need for retreatment with C. difficile anti-infective therapy or Fecal
Transplant through 56 days after completing the assigned study treatment. The evaluation
of treatment success was conducted by the DSMB adjudications for Treatment Success
and Failure.

The primary comparison was between Group A and Group B. The primary efficacy
endpoint was summarized by frequencies and percentages and analyzed based on
Pearson's chi-square test, using the ITT population. A Fisher's exact test would be used if
the total sample size and expected values were too small (< 5 in any cell). Two-sided
95% confidence intervals for the differences in proportions between treatment arms were
calculated based on the normal distribution approximation. The primary analysis was
repeated using the mITT and PP populations to assess the sensitivity of the primary
endpoint.

- Statistical Analysis for Key Secondary Efficacy Endpoints

The comparisons of Group C vs. B and Group A vs. C were conducted using the same approach as the primary endpoint analysis.

- Multiplicity adjustment

The primary comparison was between Group A and Group B with other comparisons possible using a closed hierarchical testing method. The two-sided alpha level for this comparison was 0.05. If the null hypothesis that the success rates for these two groups are equal was rejected, Group C would be compared with Group B using a two-sided alpha level of 0.05. If this null hypothesis was rejected, Group A will be compared to Group C using a two-sided alpha level of 0.05.

- Statistical Methods for Safety Analyses

The safety population would be used to summarize all adverse event data, unless otherwise specified. Statistical methods for safety analysis are mainly descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographic and baseline characteristics (Table 2) were generally comparable among three groups, based on the data from the safety population (SP).

Table 2. Study 2014-01: Summary of Baseline Demographics and Disease History

	Group A 2× RBX2660 N=42	Group B 2× Placebo N=44	Group C 1× RBX2660, 1× Placebo N=42
Age			
Mean years [range]	62.8 [24 – 89]	58.8 [19 – 92]	61.4 [18 – 88]
< 65 (%)	19 (45.2)	25 (56.8)	24 (57.1)
≥ 65 (%)	23 (54.8)	19 (43.2)	18 (42.9)
Sex			
Male n (%)	17 (40.5)	14 (31.8)	18 (42.9)
Female n (%)	25 (59.5)	30 (68.2)	24 (57.1)
Ethnicity			
Hispanic or Latino	1 (2.4)	2 (4.5)	1 (2.4)
Not Hispanic or Latino n (%)	40 (95.2)	42 (95.5)	40 (95.2)
Not Reported n (%)	1 (2.4)	0 (0)	1 (2.4)
Race			
Black/African American n (%)	0 (0)	1 (2.3)	2 (4.8)
White n (%)	42 (100)	43 (97.7)	40 (95.2)
Antibiotic Used at Screening			
Vancomycin n (%)	39 (92.9)	40 (90.9)	36 (85.7)
Fidaxomicin n (%)	1 (2.4)	3 (6.8)	2 (4.8)

	Group A 2× RBX2660 N=42	Group B 2× Placebo N=44	Group C 1× RBX2660, 1× Placebo N=42
Other n (%)	2 (4.8)	1 (2.3)	4 (9.5)
CDI Episodes			
Total Episodes (n)	178	166	174
Mean Episodes/subject [min-max]	4.2 [3-9]	3.8 [2-10]	4.1 [3-14]
Mean Episode Duration (days)	19.2	19.8	17.2
Subjects with CDI Hospitalizations			
Total Subjects Hospitalized n (%)	24 (57.1)	25 (56.8)	18 (42.9)
ICU n (%)	0 (0)	1 (2.3)	0 (0)
Unknown n (%)	0 (0)	0 (0)	1 (2.4)

Source: Adapted from Tables 8 and 9 in Study 2014-01 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition
A total of 150 subjects were enrolled into the study. Seventeen enrolled subjects did not proceed to randomization due to screen failure and were exited from the study. Of the 133 randomized subjects, five (5) subjects were withdrawn prior to treatment. In total 128 randomized subjects were exposed to blinded enema. After receiving one blinded enema, 14 withdrew for various reasons. Figure 1 summarizes availability / disposition of subjects in the analysis populations.

Figure 1 Subject Availability by Analysis Population
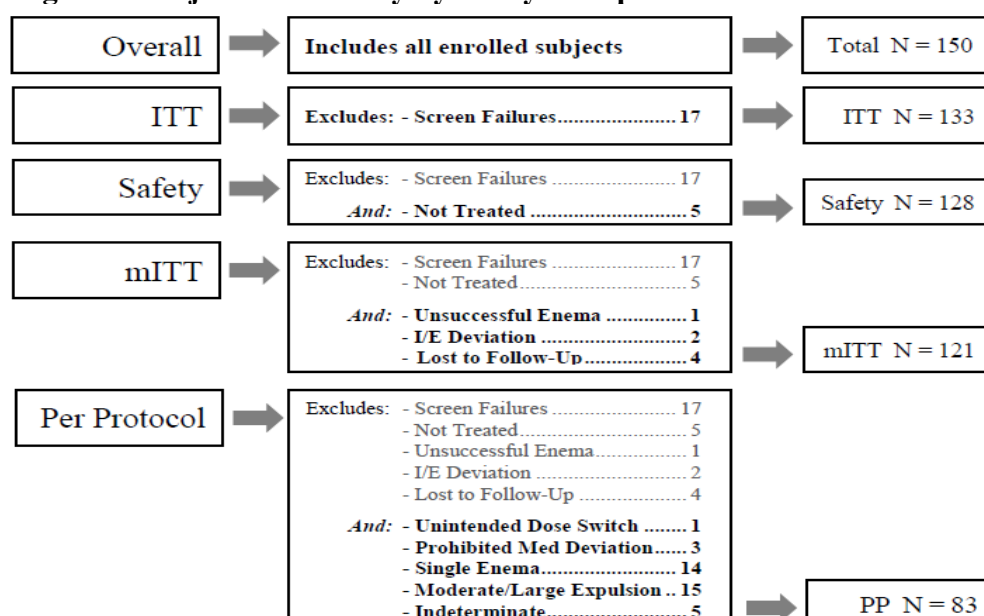
Source: Figure 6 in Study 2014-01 CSR.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Efficacy Endpoint
A comparison of Treatment Success between Group A (2 enemas RBX2660) and Group B (2 enemas placebo), using ITT population, is shown in Table 3. The analysis was repeated using the mITT and PP populations (Table 3) for sensitivity analyses. The differences in Treatment Success rates were not statistically significant.

Table 3 Treatment Success Group A vs. Group B (ITT, mITT, PP)

	ITT Group A N=45	ITT Group B N=44	mITT Group A N=40	mITT Group B N=43	PP Group A N=28	PP Group B N=31
Success n (%)	25 (55.6)	19 (43.2)	25 (62.5)	19 (44.2)	21 (75.0)	18 (58.1)
Failure n (%)	20 (44.4)	25 (56.8)	15 (37.5)	24 (55.8)	7 (25.0)	13 (41.9)
Failure Indeterminate Untreated	13 (28.9) 3 (6.7) 4 (8.9)	18 (40.9) 7 (15.9) -	12 (30.0) 3 (7.5) -	18 (41.9) 6 (14.0) -	7 (25) - -	13 (41.9) - -
Difference (95% CI)	12.4 (-8.2, 33.0)		18.3 (-2.8, 39.4)		16.9 (-6.7, 40.6)	
p-value	0.243		0.095		0.170	

Source: Table 12 in Study 2014-01 CSR.

Reviewer Comments: My analysis showed similar results.

6.1.11.2 Analyses of Secondary Endpoints
• Group C Compared to Group B
A secondary efficacy analysis was conducted to compare Treatment Success rate between Group C (1 enema RBX2660 followed by 1 placebo enema) and Group B (Table 4). In the ITT and mITT populations, the differences in success rate between two groups were not statistically significant. The difference in success rate between two groups (29.4%) was nominally statistically significant in the PP population.

Table 4 Treatment Success Group C vs. Group B (ITT, mITT, PP)

	ITT Group C N=44	ITT Group B N=44	mITT Group C N=38	mITT Group B N=43	PP Group C N=24	PP Group B N=31
Success n (%)	25 (56.8)	19 (43.2)	25 (65.8)	19 (44.2)	21 (87.5)	18 (58.1)
Failure n (%)	19 (43.2)	25 (56.8)	13 (34.2)	24 (55.8)	3 (12.5)	13 (41.9)
Failure Indeterminate Untreated	9 (20.5) 8 (18.2) 2 (4.5)	18 (40.9) 7 (15.9) -	9 (23.7) 4 (10.5) -	18 (41.9) 6 (14.0) -	3 (12.5) - -	13 (41.9) - -
Difference 95% CI	13.6 (-7.1, 34.3)		21.6 (0.4, 42.8)		29.4 (7.6, 51.3)	
p-value	0.201		0.051		0.017	

Source: Table 13 in Study 2014-01 CSR

- RBX2660 Group A Compared to RBX2660 Group C

The difference in Treatment Success rate between Groups A and C was not statistically significant.

Reviewer's Comment: The primary efficacy endpoint analysis (comparison between Group A and B) did not show statistical significance. Hence, the comparisons of Group B vs. Group C and Group A vs. Group C were performed with uncontrolled Type I error rate because the closed testing procedure was not followed.

6.1.11.3 Subpopulation Analyses

The applicant compared Group A and Group B using the ITT population for the following subgroups: antibiotic used at screening, race, ethnicity, and sex. The results were inconclusive due to limited subgroup size.

6.1.11.4 Dropouts and/or Discontinuations

Please refer to section 6.1.10.1.3.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

During the 8-week double-blind period, the percentage of subjects with any AEs was higher in the blinded RBX2660 groups compared to the blinded placebo-only group. The percentages of subjects with moderate and severe AEs were higher in the RBX2660 treatment groups compared to the placebo-only treatment group (Table 5). The rate for SAEs was higher in the RBX2660 treatment groups compared to the placebo-only treatment group.

Table 5 Study 2014-01 8-Week Double-Blind Period – Overview of Adverse Events

	Blinded RBX2660 x 2 n (%) N = 42	Blinded RBX2660 + Placebo, n (%) N = 42	Blinded Placebo x 2 n (%) N = 44
All AEs	26 (61.9%)	29 (69.0%)	25 (56.8%)
Number of AEs	149	80	70
AEs by maximum severity**			
Mild	8 (19.0%)	13 (31.0%)	17 (38.6%)
Moderate	9 (21.4%)	12 (28.6%)	7 (15.9%)
Severe	7 (16.7%)	4 (9.5%)	1 (2.3%)
Potentially life-threatening	2 (4.8%)	0	0
Patient discontinued from study due to AE	0	0	0
All SAEs	8 (19.0%)	5 (11.9%)	1 (2.3%)
Deaths	2 (4.8%)	0	0

Note: Treatment Failures censored at CDI recurrence.
Source: Table 10 in applicant's Briefing Document for the VRBPAC meeting (September 22, 2022)

6.1.12.1 Methods

Please refer to the clinical review and see Statistical Methods for Safety Analyses in section 6.1.9.

6.1.12.3 Deaths

Two subjects in the 2-enema RBX2660 group died during 8-week double blind period. The applicant reported total of 16 deaths (14 in one of the RBX2660 groups and two in the placebo group) during study period of Study 2014-01 and indicated that none of the deaths being identified as related to the IP or the enema procedure by the investigators.

6.1.12.4 Nonfatal Serious Adverse Events

The percentage of subjects with SAE was higher in the RBX2660 treatment groups compared to the placebo-only treatment group during 8-week double blind period of the study (Table 6). During the entire study period, percentage of subjects with serious Treatment Emergent Adverse Events (TEAE) was higher in Group A (2×RBX2660) than Group B (2×placebo); percentage of subjects with serious TEAE was similar between Group C (1×RBX2660 followed by 1×placebo) and Group B. It is noted that three serious TEAEs in Group A were reported as related to the IP.

Table 6 Summary of Reported Serious Treatment Emergent Adverse Events by Relatedness (SP)

	Group A 2x RBX2660 N=42 Events/subjects (% of subjects)	Group B 2x Placebo N=44 Events/subjects (% of subjects)	Group C 1x RBX2660 1x Placebo N=42 Events/subjects (% of subjects)	Total N=128 Events/subjects (% of subjects)
SAEs Overall	48/22 (52.4)	49/16 (36.4)	49/15 (35.7)	146/53 (41.4)
SAEs Related to IP	3/3 (7.1)	0	0	3/3 (2.3)
SAEs Related to Procedure	0	0	0	0
SAEs Related to *C diff* Disease	9/5 (11.9)	4/2 (4.5)	8/3 (7.1)	21/10 (7.8)
SAEs Related to Pre-existing Condition	37/18 (42.9)	28/12 (27.3)	32/13 (31.0)	97/43 (33.6)

Source: Table 31 in Study 2014-01 CSR

6.1.12.5 Adverse Events of Special Interest (AESI)

NA

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

There were no discontinuations due to an AE reported in the study groups.

6.2 Phase-3 Study 2017-01

Title: 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

6.2.1 Objectives

6.2.1.1. Primary Objectives
To confirm the efficacy of RBX2660 as compared to a placebo in preventing recurrent episodes of CDI through 8 weeks.

6.2.1.2 Secondary Objectives
To evaluate the Sustained Clinical Response rate of RBX2660 as compared to placebo after blinded treatment.

6.2.2 Design Overview

Study 2017-01 was a Phase 3 randomized, double-blind, and placebo-controlled study to evaluate the safety and efficacy of Rebiotix RBX2660. At the time of enrollment, subjects were already taking or had been prescribed antibiotics to control rCDI symptoms. Subjects were randomized in a 2:1 ratio to receive a single dose of RBX2660 or placebo. The randomization was stratified by antibiotics used at screening (vancomycin alone, vancomycin in combination, fidaxomicin, or other). Eligible subjects received treatment administered as a single, blinded study enema. Study treatment was completed following an antibiotic washout period of 24 to 72 hours and within 14 calendar days of randomization. In-office study follow-up visits occurred at weeks 1, 4, and 8 after completing the blinded study treatment. Telephone assessments for AEs occurred during weeks 2, 3, and 6 after the study enema and at months 3 and 6. Subjects who were deemed failures by the Investigator following the blinded treatment, per the pre-specified Treatment Failure definition, might have elected to receive an open-label RBX2660 enema.

6.2.3 Population for Study 2017-01

The target population of Study 2017-01 was subjects ≥ 18 years old with medical record documentation of recurrent CDI per the study definition, including either: a) at least 1 recurrence after a primary episode and had completed at least 1 round of standard-of-care oral antibiotic therapy or b) had at least 2 episodes of severe CDI resulting in hospitalization within the last year.

6.2.4 Study Treatments in Study 2017-01

- Placebo arm: 1 × blinded placebo enema
- RBX2660 arm: 1 × blinded RBX2660 enema

6.2.6 Sites and Centers

Study 2017-01 was performed in the United States and Canada, a total of 44 sites.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints

- Primary Endpoint

Recurrence of CDI within 8 weeks of blinded treatment. CDI diarrhea was defined as:
The passage of three or more unformed/loose (i.e., Bristol Stool Scale type 6-7) stools in
24 or fewer consecutive hours for at least two consecutive days; *and* a positive stool test
for the presence of *C. difficile* toxin; documented at the time of the diarrhea.

- Secondary Endpoint

Loss of Sustained Clinical Response through 6 months after blinded treatment. Sustained
clinical response was defined as Treatment success of the presenting CDI recurrence and
no new CDI episodes through 6 months after completing a blinded treatment.

6.2.9 Statistical Considerations

Originally, the applicant planned to conduct two independent Phase 3 randomized,
double-blind, and placebo-controlled Phase 3 trials of approximately 300 subjects each to
support licensure. Study 2017-01 was initially designed to evaluate the efficacy of
RBX2660 versus placebo using a frequentist approach. To demonstrate a 69% success
with 1 dose of the RBX2660 treatment group vs. 47% success in the placebo control
group, 240 treated subjects were needed to achieve power 90% at 2-sided alpha 0.05. The
planned target enrollment was 300 subjects to allow for a 20% loss-to-follow up rate.

The study started on July 31, 2017 (first subject visit); the database was locked on
September 30, 2020. During the course of this study, the applicant reported that they
encountered difficulties in enrollment in the study due to both low prevalence of the
disease in this orphan population, as well as the liberal provision of FMT under
enforcement discretion. Under this circumstance, they proposed potentially using a single
placebo-controlled Phase 3 study as the basis for demonstrating substantial evidence for
clinical effectiveness. In March 2019, the applicant amended the statistical analysis plan
(SAP) for the 2017-01 study with two blinded interim analyses and a Bayesian
hierarchical model for the primary efficacy analysis, formally integrating data from the
2014-01 study. The first interim analysis was completed on Aug 26, 2019, when 178
subjects (information fraction 0.679) had been adjudicated for primary efficacy endpoint.
The second interim analysis was completed on Oct 23, 2019, when 214 subjects
(information fraction 0.817) had been adjudicated for primary efficacy endpoint. The
final analysis included 262 subjects.

6.2.9.1 Evaluation of Exchangeability between Studies 2017-01 and 2014-01
At the time of planning the Bayesian analysis, Studies 2017-01 and 2014-01 were
evaluated for study exchangeability. In study 2014-01, only data from Group C (a single
dose of RBX2660 along with a placebo) and Group B (2 doses of placebo) would be
borrowed. Group A (two doses of RBX2660) would be excluded due to the difference in
treatment dosage. The two studies were then considered to be generally exchangeable

based on similarity of the studies, including study design, study population, product formulation and dosing regimen, and treatment success definitions (Table 7).

Table 7. Key design features of Study 2017-01 vs. Study 2014-01

Study Design Feature	Study 2014-01 (Phase 2b)	Study 2017-01 (Phase 3)
Total enrolled	150	320
Study design	Prospective, multi-center, double-blind, randomized, placebo-controlled	Prospective, multi-center, double-blind, randomized, placebo-controlled
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
Number of previous CDIs, including qualifying events	≥2 recurrences and ≥2 rounds of SOC oral antibiotic therapy	≥1 recurrence and ≥1 round of SOC oral antibiotic therapy
Antibiotic washout	24 to 48 hours	24 to 72 hours
Randomization and treatment groups/ treatment dose/treatment regimen	1:1:1 ratio Group A: RBX2660 (2 doses) Group B: Placebo (2 doses) Group C: RBX2660 (1 dose)/ placebo (1 dose) 2 enemas administered 7 ± 2 days apart	2:1 ratio: RBX2660 (1 dose) Placebo (1 dose) 1 enema administered

Source: Adapted from Figure 1 in Clinical Overview.

Table 8 summarizes the analysis population definitions of Study 2017-01 in comparison with Study 2014-01.

Table 8. Definitions of analysis populations: Study 2014-01 vs. Study 2017-01

	Study 2014-01	Study 2017-01
ITT	All randomized subjects, regardless of whether they complete their assigned study treatment.	All randomized subjects. Randomized subjects who exited prior to receiving blinded treatment will not be included in the analysis.
mITT	All subjects who complete at least one dose of study treatment, regardless of treatment received, but excluding: • subjects who discontinue from the study during the double-blind period, prior to evaluation of treatment failure or success, for any reason; • subjects who any deviations from any inclusion or exclusion criteria.	All randomized subjects who successfully received blinded treatment but excluding: • subjects who withdrew prior to treatment; • subjects in whom treatment was attempted but not completed and; • subjects who discontinue from the study prior to evaluation of treatment failure/success for the primary endpoint if the reason for exit is not related to CDI symptoms.
PP	All ITT subjects who received the treatment to which they were randomized and were evaluable for treatment success/failure at 56 days after the last assigned treatment, excluding: • Subjects who withdrew consent or were lost to follow-up during the double-blind period, prior to evaluation of treatment failure or success; • Subjects who expel a moderate or large amount of either of the double-blind enemas; • Subjects who were declared treatment failures without meeting all four criteria for failure, as assessed by the DSMB adjudication; • Subjects who have major protocol deviations as determined by a clinical review of subject data prior to database lock.	All subjects who successfully received blinded treatment analyzed according to the treatment they received, excluding: • Subjects who have documented deviations to inclusion or exclusion criteria. • Subjects who exited prior to the 8-week efficacy evaluation if the reason for exit was not related to CDI symptoms in the same manner as the mITT population.

ITT=intent-to-treat; mITT=modified intent-to-treat; PP=per-protocol

In consideration of the differences above, per CBER information request (IR#28), the applicant performed a refined primary endpoint analysis to improve exchangeability, by aligning the following aspects between the two studies:

- Alignment of the primary endpoint definitions for treatment success: The applicant indicated that the two definitions are identical although the language varies slightly.
- Alignment of the primary efficacy endpoint assessment period: Because there was 1 week between the two enemas in Study 2014-01, there were 9 weeks of assessment period for each subject compared to 8 weeks in Study 2017-01 after the single enema. The applicant indicated that no treatment failures occurred during Week 9 and suggested that the number of treatment successes and failures in Study 2014-01 would not be changed if the primary endpoint assessment period were set to 8 weeks in Study 2014-01, in line with Study 2017-01.
- Alignment of analysis population (ITT, mITT, and PP) definitions between the two studies.

6.2.9.2 Statistical Methods for Primary Efficacy Endpoint

6.2.9.2.1 Hierarchical Model

The integrated analysis of data from study 2017-01 and 2014-01 was performed using a Bayesian hierarchical model. This analysis approach would account for heterogeneity

between study populations and dynamically borrow less information when the data from the new study differs from the Phase 2b study. The model details are as follows:

Let $N_{k,s}$ be the number of subjects assigned to treatment k ($k = T$ for patients who received a single dose of RBX2660 and $k = C$ for patients who received the placebo) in study s ($s = 1$ for the current Phase 3 study 2017-01, $s = 2$ for the previous Phase 2 study 2014-01). The number of responders, $X_{k,s}$, in each arm/study were modeled as

$$X_{k,s} \sim Binomial(N_{k,s}, p_{k,s})$$

where $p_{k,s}$ is the underlying event rate for arm k in study s. The event rates were transformed to the log-odds scale and modeled as:

$$log\left(\frac{p_{C,s}}{1 - p_{C,s}}\right) = \alpha_s$$

for the control arms and

$$log\left(\frac{p_{T,s}}{1 - p_{T,s}}\right) = \alpha_s + \theta_s$$

for the treatment arms. The parameter θ_s represents the effect of RBX2660, relative to placebo, on the log-odds scale for trial s. Hierarchical models were used to borrow information of the treatment and control effects between studies. The following prior was used for the control rates across the two trials:

$$\alpha_s \sim N(\alpha, \tau_\alpha^2) \ for \ s = 1, 2$$

$$\alpha \sim N(0, 10^2)$$

$$\tau_\alpha^2 \sim Inverse\ Gamma(0.001, 0.1)$$

The prior used for the treatment effects across the two trials was:

$$\theta_s \sim N(\theta, \tau_\theta^2) \ for \ s = 1, 2$$

$$\theta \sim N(0, 10^2)$$

$$\tau_\theta^2 = Inverse\ Gamma(0.01, 0.01)$$

The priors on α and θ were chosen based on a prior assumption of a control response rate near 0.5 with a treatment effect centered around 0. The priors on the hierarchical variance terms τ_α^2 and τ_η^2 were parameterized by their location μ and weight ω.

6.2.9.2.2 Success Criteria

The primary efficacy endpoint analysis would evaluate the efficacy of RBX2660 by testing the hypothesis:

$$H_0: TE \leq 0 \quad vs. \quad H_A: TE > 0$$

Where *TE* is the treatment effect between RBX2660 and placebo for the Phase 3 study 2017-01 ($s = 1$), i.e., $TE = p_{T,1} - p_{C,1}$. The hypothesis was tested by calculating the posterior probability of superiority, $\Pr(TE > 0|Data)$.

The statistical evidence for the treatment effect was evaluated based on the posterior probability of superiority for the RBX2660 group vs. the placebo group. Two thresholds for success were established: 1) a first, more stringent, success criterion that would be considered sufficiently persuasive to substitute for positive evidence from two adequate and well-controlled trials and 2) a second, less stringent, success criterion that would be considered sufficiently persuasive to constitute positive evidence from a single adequate and well-controlled trial. The success thresholds were selected as analogues to frequentist one-sided type 1 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. The success criteria for the interim and final analyses (first and more stringent threshold) were initially set at posterior probability of superiority 0.99943; the second threshold for final analysis was set at 0.97706.

At the end of the study, the applicant adjusted the success thresholds based on the actual information fraction. Specifically, as shown in Table 9, the number of subjects in the mITT population with adjudicated outcomes was 262. At the time of interims 1 and 2, there were 178 and 214 subjects, respectively, in the mITT population with adjudicated outcomes, which resulted in information fraction of 0.679 and 0.817. Accordingly, the two interim analyses spent a cumulative alpha of 0.000877, leaving 0.000373 remaining (out of the total 0.00125) for the final analysis. Therefore, the applicant proposed the first posterior probability threshold of 0.9993275 for final analysis to controls the overall type I error rate at 0.00125 (one-sided). Success at this level would provide strong efficacy evidence analogous to two adequate and well-controlled trials. The applicant proposed the second threshold of 0.9750338 to control the overall type I error rate at 0.025 (one-sided). Meeting the second success threshold would provide evidence to declare success of the Phase 3 study 2017-01.

Table 9. Group sequential stopping boundaries for success, based on the observed information fraction

Analysis	Complete Subjects	Information Fraction	First Threshold for Posterior Probability	Alpha Spend (1st Threshold)	Second Threshold for Posterior Probability	Alpha Spent (2nd Threshold)
Interim 1	178	0.679	0.99943	0.000566	0.99943	0.000566
Interim 2	214	0.817	0.99943	0.000311	0.99943	0.000311
Final	262	1.000	0.99933	0.000373	0.97503	0.024123
Total				0.001250		0.025000

Source: Adapted from Table 8 and 9 in Protocol 2017-01 for RBX2660 Final Analysis Report, Version 2, March 24, 2022 (STN 125739.0/13)

6.2.9.3 Statistical Methods for Secondary Efficacy Endpoints
The applicant evaluated the rates of sustained clinical response (i.e., the rate of CDI occurrence with treatment success of the presenting CDI recurrence and no new CDI episodes for greater than 8 weeks after completing a blinded study treatment) between the

RBX2660 group and the placebo group during the 6 months of follow-up. A Pearson's chi-square method was used to test the null hypothesis that the response rate in the treatment group is equal to that of the control group at the two-sided 0.05 significance level. In addition, two-sided 95% confidence intervals for the difference in response rate between arms were calculated using a normal distribution approximation. The secondary endpoint analyses were based on Study 2017-01 data only.

An analysis of time to CDI occurrence was performed and presented by the Kaplan-Meier procedure. Time to CDI occurrence is defined as the number of days from enema administration to first assessment indicating recurrence, for those subjects who were deemed Treatment Failures or Indeterminate. Randomized subjects who do not complete the assigned blinded treatment were censored at Day 0. All subjects who are discontinued for any reason prior to the 6-month timepoint were censored at the last assessment date at/prior to Month 6. All subjects considered as a sustained treatment success will be censored at the date of their 6-month assessment.

6.2.9.4 Multiplicity adjustment
A hierarchical, closed-testing procedure would be utilized for the secondary endpoint: only if the primary efficacy analysis declared success, meeting at least one of the thresholds, the secondary endpoint would be analyzed. The secondary endpoint would be tested at a two-sided 0.05 significance level, using a frequentist approach without borrowing data.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed
6.2.10.1.1 Demographics
Subject demographics and baseline disease characteristics (safety population) are summarized in Table 10. The demographics and baseline characteristics were generally similar between RBX2660 and placebo groups except that subjects in the RBX2660 group tended to be slightly older and had higher number of prior CDIs, compared to the placebo group.

Table 10. Demographics (SP) Baseline Disease Characteristics (SP)

Demographics/Baseline Disease Characteristics /Statistics	Placebo N=87 n (%)	RBX2660 N=180 n (%)	Total N=267 n (%)
Age (years)			
Mean (SD)	57.7 (15.95)	61.3 (16.81)	60.1 (16.59)
Median	60.0	64.0	63.0
Min, max	26, 86	19, 93	19, 93
Age group			
< 65	54 (62.1)	91 (50.6)	145 (54.3)
≥ 65	33 (37.9)	89 (49.4)	122 (45.7)
Sex			
Male	27 (31.0)	57 (31.7)	84 (31.5)
Female	60 (69.0)	123 (68.3)	183 (68.5)
Race			
American Indian or Alaska Native	0 (0.0)	2 (1.1)	2 (0.7)

Demographics/Baseline Disease Characteristics /Statistics	Placebo N=87 n (%)	RBX2660 N=180 n (%)	Total N=267 n (%)
Asian	0 (0.0)	1 (0.6)	1 (0.4)
Black or African American	6 (6.9)	8 (4.4)	14 (5.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	78 (89.7)	168 (93.3)	246 (92.1)
Other	3 (3.4)	0 (0.0)	3 (1.1)
Multiple	0 (0.0)	1 (0.6)	1 (0.4)
Ethnicity			
Hispanic or Latino	4 (4.6)	2 (1.1)	6 (2.2)
Not Hispanic or Latino	80 (92.0)	168 (93.3)	248 (92.9)
Not reported	0 (0.0)	5 (2.8)	5 (1.9)
Unknown	3 (3.4)	5 (2.8)	8 (3.0)
CDI at Screening			
<3	40 (46.0)	69 (38.3)	109 (40.8)
≥3	47 (54.0)	111 (61.7)	158 (59.2)
Randomization strata			
Treatment of qualifying CDI episode			
Vancomycin alone	78 (89.7)	157 (87.2)	235 (88.0)
Vancomycin in combination	2 (2.3)	5 (2.8)	7 (2.6)
Fidaxomicin	5 (5.7)	12 (6.7)	17 (6.4)
Other	2 (2.3)	6 (3.3)	8 (3.0)
Hospitalization due to qualifying CDI episode			
Yes	10 (11.5)	23 (12.8)	33 (12.4)
No	77 (88.5)	157 (87.2)	234 (87.6)

Source: Adapted from Table 7 and 8 in study 2017 CSR

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.2.10.1.3 Subject Disposition
Figure 2 shows subject enrollment and disposition. Of the 267 subjects randomized and treated, 33 subjects (12.4%) discontinued the study: 21 (11.7%) subjects from the RBX2660 group and 12 (13.8%) subjects from the placebo group. Twenty subjects (60.6%; 20/33) withdrew during the blinded period and 13 subjects (39.4%; 13/33) during the open-label period. The majority of subjects who withdrew (33.3%; 11/33) discontinued from the study due to "withdrawal-by-subject." In total, 2 (6%, 2/33) subjects discontinued due to AEs (both subjects from the RBX2660 group).

Figure 2 Subject Enrollment and disposition in Study 2017-01
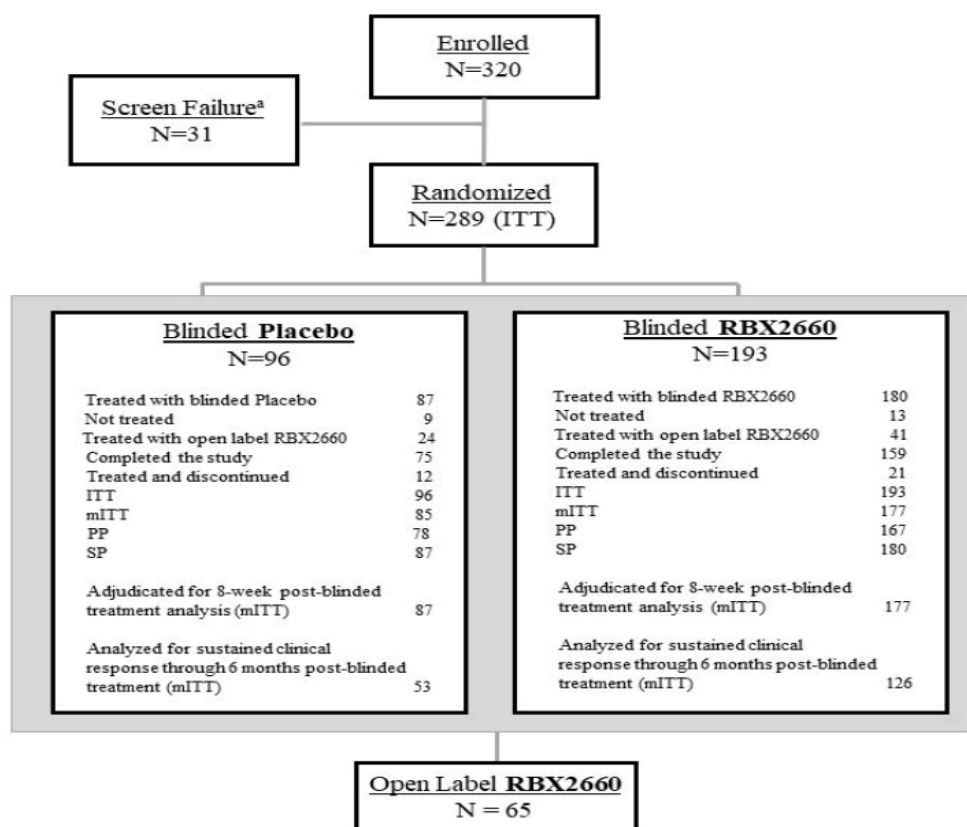
Source: Figure 3 from study 2017-01 CSR

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint
6.2.11.1.1 Interim Analyses
Two interim analyses were performed by a Statistical Analysis Committee (SAC), Data Safety Monitoring Board (DSMB), and Endpoint Adjudication Committee (EAC).

- Interim Analysis 1
Interim analysis 1 was completed when 222 subjects had been treated. Of the 217 subjects in the mITT population, 178 subjects were adjudicated for the primary endpoint analysis. Treatment Success rates in the RBX2660 and placebo arms, based on Bayesian hierarchical model, were 65.4% and 56.4%, respectively. The posterior probability of superiority was 0.91859 and did not exceed 0.99943. The predictive probability of trial success at N=270 (using a final success threshold of 0.97706) was 0.214014 which exceeded the threshold of 0.01. The first interim analysis results warranted continuation of the trial to the next interim analysis.

- Interim Analysis 2
Interim analysis 2 was completed when 239 subjects had been exposed to treatment. Of the 233 subjects in the mITT population, 214 subjects were adjudicated for the primary endpoint analysis. Treatment Success rates in the RBX2660 and placebo arms, based on

Bayesian hierarchical model, were 67.9% and 57.2%, respectively. The posterior probability of superiority was 0.962772 and did not exceed 0.99943. The predictive probability of trial success at N=270 (using a final success threshold of 0.97706) was 0.591304 which exceeded the threshold of 0.01. The second interim analysis results warranted continuation of the trial to the next and final analysis.

6.2.11.1.2 Final Analyses
The primary efficacy analysis was performed with a Bayesian hierarchical model formally integrating treatment success rates from study 2014-01 into study 2017-01.

- Study 2017-01 Data

Table 11 shows the count data on the primary endpoint for each of the mITT, ITT, and PP analysis populations. The mITT population included 262 subjects with adjudicated outcomes for the primary efficacy analysis in study 2017-01. The observed treatment success rates were 0.62 and 0.71 in the placebo and RBX2660 groups, respectively. For the ITT population, the success rates were 0.61 and 0.70 in the placebo and RBX2660 groups, respectively.

Table 11. Primary Endpoint Outcomes by Treatment Arm and Analysis Population, Study 2017-01, mITT, ITT, and PP Populations

Endpoint	mITT Placebo N=85 n (rate)	mITT RBX2660 N=177 n (rate)	ITT[a] Placebo N=96 n (rate)	ITT[a] RBX2660 N=193 n (rate)	PP Placebo N=78 n (rate)	PP RBX2660 N=167 n (rate)
Not treated	0	0	9	13	0	0
Number with adjudicated outcome	85	177	87	180	78	167
Treatment successes	53 (0.62)	126 (0.71)	53 (0.61)	126 (0.70)	48 (0.62)	120 (0.72)
Treatment failures	32 (0.38)	49 (0.28)	32 (0.37)	49 (0.27)	30 (0.38)	46 (0.28)
Indeterminate	0 (0.0)	2 (0.01)	2 (0.02)	5 (0.03)	0 (0.0)	1 (0.01)
Imputed as failure[b]	0 (0.0)	2 (0.01)	0 (0.0)	2 (0.01)	0 (0.0)	1 (0.01)

Source: Adapted from STN 125739/0, Clinical Study Report 2017-01
mITT= Modified intent to treat, ITT= intent to treat, PP= Per protocol
a. For the ITT population, percentage is calculated using the numbers of ITT subjects in each treatment arm excluding those who exited prior to receiving blinded treatment (N=87 placebo and N=180 RBX2660) as the denominator.
b. Subjects that exited the study prior to 8 weeks due to CDI-related symptoms are imputed as failure

- Study 2014-01 Data Borrowed for Study 2017-01 Primary Efficacy Analysis

Table 12 provides the aligned Phase 2 study 2014-01 data for borrowing in the refined Bayesian analysis. There were no qualitative changes in the results with alignment of the treatment success definition and primary endpoint assessment period. Applying study 2017-01 analysis population definitions to study 2014-01 decreased the number of 2014-01 subjects in the ITT population by five subjects, increased the number of subjects in the mITT population by two subjects, and increased the number of subjects in the PP population by 38 subjects.

Table 12. Aligned Study 2014-01 Data for Borrowing in the Refined Bayesian Analysis

Endpoint	mITT Group C 1-Dose RBX2660 1-Dose Placebo	mITT Group B 2-Dose Placebo	ITT Group C 1-Dose RBX2660 1-Dose Placebo	ITT Group B 2-Dose Placebo	PP Group C 1-Dose RBX2660 1-Dose Placebo	PP Group B 2-Dose Placebo
Number of subjects (n)	39	43	43	44	37	43
Treatment success (n)	25	19	25	19	25	19
Treatment failure (n)	14	24	18	25	12	24
Success rate	0.64	0.44	0.58	0.43	0.68	0.44

Source: Adapted from Table 5, 8, 9 and 10 in applicant's response to CBER information request #15 (IR#15) dated July 1, 2022 (STN 125739/0.25).
mITT= Modified intent to treat, ITT= intent to treat, PP= Per protocol

- Primary Efficacy Endpoint Analysis Results

Table 13 shows analysis results of the primary efficacy endpoint for the different analysis populations (mITT, ITT, and PP) in Study 2017-01 that borrowed final data from the corresponding study populations (mITT, ITT, and PP) from study 2014-01. The primary efficacy analysis using the mITT population resulted in an estimated treatment success rate of 0.71 in the RBX2660 group and 0.57 in the placebo group; the difference in treatment success rates was 0.13 (95% credible interval: 0.02 to 0.24). The posterior probability that RBX2660 was superior to placebo was 0.991, which met the second success threshold of 0.9750338 but did not meet the first success threshold of 0.9993275. The primary efficacy endpoint analysis using the ITT and the PP populations led to the same conclusion.

Table 13. Posterior Probability for Superiority and Posterior Estimates from the Bayesian Hierarchical Model with Study 2017-01 Analysis Population Definitions Applied to Study 2014-01

Population	Placebo Success Rate	RBX2660 (blinded) Success Rate	Treatment Effect
mITT	--	--	--
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
ITT	--	--	--
Mean	0.57	0.69	0.12
95% Credible Interval	0.47, 0.67	0.62, 0.76	0.01, 0.23
Posterior Probability			0.986
PP	--	--	--
Mean	0.56	0.72	0.15
95% Credible Interval	0.47, 0.66	0.65, 0.78	0.04, 0.26
Posterior Probability	--	--	0.997

Source: Adapted from STN 125739/0, Amendment 25, Final efficacy result Table 7
mITT= Modified intent to treat, ITT= intent to treat, PP= Per protocol
Note: This statistical analysis includes data from Phase 2 study (Protocol 2014-01) and Phase 3 (2017-01) studies

Reviewer Comments*: My analysis showed similar results. I conducted additional analysis to evaluate posterior probability of treatment effect being greater than other fixed levels. As shown in Figure 3, posterior probability of treatment effect > 1% was 0.985; posterior probability of treatment effect >2% was 0.978; posterior probability of treatment effect > 5% was 0.930.*

Figure 3 Posterior Distribution for Treatment Effect and Posterior Probability of Treatment Effect Being Greater Than Other Levels
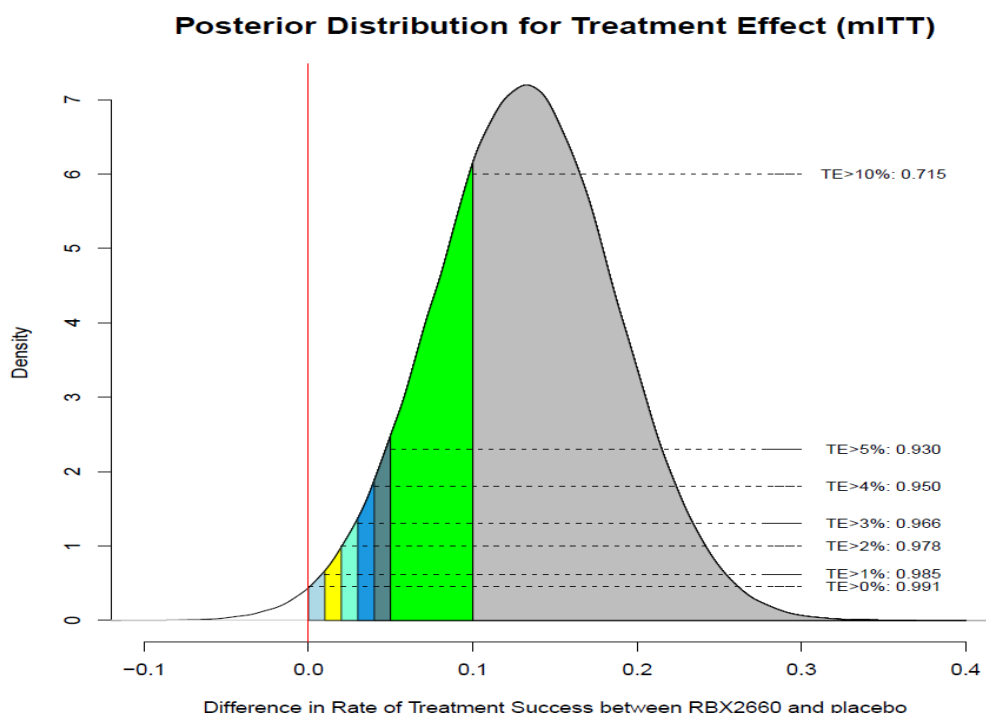
6.2.11.1.3 Additional/Sensitivity Analyses on Primary Efficacy Endpoint
- Analysis Using ITT and PP Populations

The primary efficacy analysis was repeated for the ITT and PP population, respectively, borrowing data from the corresponding analysis population in study 2014-01 (Table 12). For the ITT population, the Treatment Success rates of RBX2660 vs placebo estimated from the model were 0.69 vs 0.57; the posterior probability of superiority was 0.986. For the PP population, the Treatment Success rates of RBX2660 vs placebo were 0.72 vs 0.56; the posterior probability of superiority was 0.997. Similar to the primary analysis, the results met the second success threshold but missed the more stringent first success threshold.

- Applicant's Initial Analysis

The applicant used non-final ITT data from Study 2014-01 as historical data during the evaluation of trial operating characteristics at the design stage. The applicant later discovered that six subjects who were randomized but not dosed were erroneously excluded from the non-final Study 2014-01 ITT population. The applicant corrected the issue in the final Study 2014-01 Clinical Study Report. Nevertheless, following the

Statistical Analysis Plan, the applicant presented this analysis using non-final ITT data from Study 2014-01 as the primary efficacy analysis (Table 14) in the Study 2017-01 Clinical Study Report (not shown). The analysis led to the same conclusion as the refined primary efficacy analysis requested by the FDA, i.e., the results met the second success criterion but missed the more stringent first success criterion.

Table 14. Posterior Probability for Superiority and Posterior Estimates from the Bayesian Hierarchical Model, mITT, ITT, and PP Populations (Integrated Bayesian Analysis Borrowing Non-Final 2014-01 ITT Data Which was Used at the Design Stage)

Population	Placebo Success Rate	RBX2660 (blinded) Success Rate	Treatment Effect
mITT	--	--	--
Mean	0.58	0.70	0.12
95% Credible Interval	0.48, 0.68	0.64, 0.77	0.01, 0.23
Posterior Probability	--	--	0.986
ITT	--	--	--
Mean	0.57	0.69	0.13
95% Credible Interval	0.47, 0.67	0.63, 0.76	0.02, 0.23
Posterior Probability	--	--	0.987
PP	--	--	--
Mean	0.57	0.71	0.14
95% Credible Interval	0.47, 0.68	0.64, 0.77	0.02, 0.25
Posterior Probability	--	--	0.991

Source: Adapted from Table 11 in Study 2017-01 CSR and Protocol 2017-01 for RBX2660 Final Analysis Report, November 20, 2020 (STN 125739/0.4).
mITT= Modified intent to treat, ITT= intent to treat, PP= Per protocol

- Adjusted Analysis for Age and Previous Number of CDI Episodes

There appear to be some differences in age and number of previous episodes of CDI at Baseline, between Studies 2014-01 and 2017-01 and between treatment groups in Study 2017-01. Per CBER request (Information Request #15, June 17, 2022), the applicant performed additional analysis to further evaluate whether the between-study differences have a potential impact on the primary efficacy endpoint analysis. The integrated Bayesian analysis was repeated using age (dichotomized as age < 65 years and age $\geq$ 65 years) and previous number of CDI episodes at baseline (CDI=1, CDI=2, and CDI $\geq$ 3) as covariates. The results were generally similar to those of the primary efficacy analysis (Table 15).

Table 15. Posterior Probability for Superiority and Posterior Estimates from the Bayesian Hierarchical Model Adjusting for Age and Previous Number of CDI Episodes (mITT, ITT, and PP)

Population	Placebo Success Rate	RBX2660 (blinded) Success Rate	Treatment Effect
mITT			
Mean	0.57	0.71	0.14
95% Credible Interval	0.48, 0.66	0.65, 0.77	0.03, 0.24
Posterior Probability			0.995
ITT			
Mean	0.56	0.69	0.13
95% Credible Interval	0.47, 0.65	0.63, 0.76	0.03, 0.24
Posterior Probability			0.993
PP			

Population	Placebo Success Rate	RBX2660 (blinded) Success Rate	Treatment Effect
Mean	0.56	0.72	0.16
95% Credible Interval	0.47, 0.65	0.66, 0.78	0.05, 0.27
Posterior Probability			0.998

Source: Adapted from Table 17 and 19 in applicant's Response to Information Request #15 (IR#15), July 1, 2022 (STN 125739.0/25)

6.2.11.2 Analyses of Secondary Endpoint

Sustained clinical response is defined as Treatment Success of the presenting CDI recurrence and no new CDI episodes for greater than 8 weeks after completing the blinded treatment during the 6 months of follow-up. The applicant's initial analysis was based on the time frame from 8 weeks through 6 months. The results did not show a statistically significant difference in sustained clinical response rate between the RBX2660 (92.1%) and placebo (90.6%) arms in the mITT population (Table 16). CBER requested the applicant conduct secondary endpoint analysis from baseline through 6 months because this is better aligned with the definition of sustained clinical response and would enable causal conclusions as randomization is preserved. The results again did not show a statistically significant difference in sustained clinical response rate difference between the RBX2660 (65.5%) and placebo (56.5%) arms in the mITT population (Table 16). Similar findings were observed for the ITT populations.

Table 16. Comparison of Sustained Clinical Response in the RBX2660 Group and the Placebo Group in Study 2017-01

	ITT RBX2660 N=180	ITT Placebo N=87	mITT RBX2660 N=177	mITT Placebo N=85	PP RBX2660 N=167	PP Placebo N=78
Through 8 weeks						
Success, n (%)	126 (70.0)	53 (60.9)	126 (71.2)	53 (62.4)	120 (71.9)	48 (61.5)
Through 6 months						
Success, n (%)	116 (64.4)	48 (55.2)	116 (65.5)	48 (56.5)	110 (65.9)	43 (55.1)
Failure, n (%)	64 (35.6)	39 (44.8)	61 (34.5)	37 (43.5)	57 (34.1)	35 (44.9)
Difference [a] 95% CI [b]	9.3 -3.3 to 21.9		9.1 -3.6 to 21.7		10.7 -2.4 to 23.9	
p-value	0.145		0.156		0.106	
From 8 weeks through 6 months[a]						
Yes, n (%)	116 (92.1)	48 (90.6)	116 (92.1)	48 (90.6)	110 (91.7)	43 (89.6)
No, n (%)	10 (7.9)	5 (9.4)	10 (7.9)	5 (9.4)	10 (8.3)	5 (10.4)

[a] The denominator is the number of patients with Treatment Success at 8 weeks
Source: Adapted from Table 1 in response to CBER information request IR#21 (STN 125739/0.32) and Table 14 in Study 2017-01 CSR

The applicant conducted additional analysis on time to CDI occurrence through 6 months after blinded treatment. Although the Kaplan-Meier curves (Figure 4) showed some separation between two groups, a log-rank test was not statistically significant.

Figure 4 Kaplan-Meier Curve for Time to CDI Occurrence by Treatment Group (mITT)
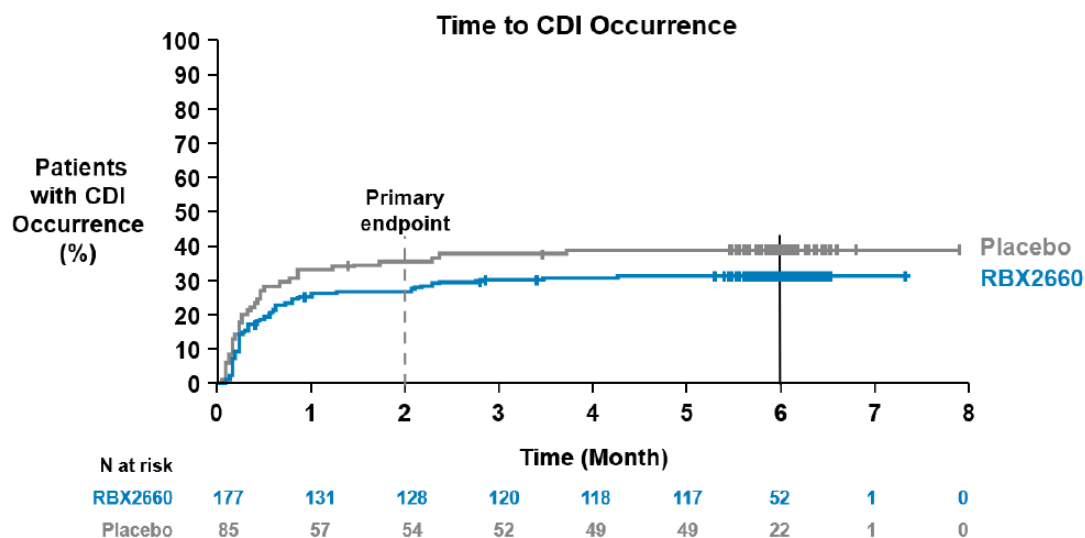
Source: Figure 17 in the applicant's VRBPAC Briefing Document

6.2.11.3 Subpopulation Analyses

Table 17 shows subgroup analyses based on the mITT population data in Study 2017-01 only. The trend of treatment success rate being higher in the RBX2660 group than the placebo group was observed across the subgroups. It should be noted that the subgroup analyses are descriptive in nature and caution is needed for interpretation.

Table 17. Subgroup Analyses of Treatment Success within 8 Weeks (mITT)

Subgroup / Analysis Population	Placebo n/N (%)	RBX2660 n/N (%)	Difference between RBX2660 and Placebo % (95% CI)
Age group			
< 65 years	35/53 (66.0)	66/90 (73.3)	7.3 (-8.4, 23.0)
≥65 years	18/32 (56.3)	60/87 (69.0)	12.7 (-7.0, 32.5)
Sex			
Male	15/26 (57.7)	42/55 (76.4)	18.7 (-3.4, 40.7)
Female	38/59 (64.4)	84/122 (68.9)	4.4 (-10.3, 19.2)
Race			
White	47/76 (61.8)	117/165 (70.9)	9.1 (-3.9, 22.0)
Non-White	6/9 (66.7)	9/12 (75.0)	8.3 (-31.0, 47.7)
Ethnicity			
Hispanic or Latino	2/4 (50.0)	2/2 (100.0)	50.0 (1.0, 99.0)
Not Hispanic or Latino	51/81 (63.0)	124/175 (70.9)	7.9 (-4.6, 20.4)
Number of previous episodes of CDI recurrence at baseline*			
≤3	38/57 (66.7)	80/111 (72.1)	5.4 (-9.4, 20.2)
>3	15/28 (53.6)	46/66 (69.7)	16.1 (-5.4, 37.7)
Number of previous episodes of CDI recurrence at baseline **			
<3	20/33 (60.6)	42/53 (79.2)	18.6 (-1.3, 28.6)
≥3	33/52 (63.5)	84/124 (67.7)	4.3 (-11.1, 19.7)
Vancomycin use duration for qualifying CDI episode			

Subgroup / Analysis Population	Placebo n/N (%)	RBX2660 n/N (%)	Difference between RBX2660 and Placebo % (95% CI)
≤14 days	18/26 (69.2)	32/45 (71.1)	1.9 (-20.3, 24.0)
>14 days	28/50 (56.0)	75/109 (68.8)	12.8 (-3.5, 29.1)

Source: Table 12 in VRBPAC FDA Briefing Document
mITT= modified Intent to Treat

6.2.11.4 Dropouts and/or Discontinuations
Please refer to section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses
N/A

6.2.12 Safety Analyses

- Study 2017-01 Double-Blind Period

Table 18 provides a summary of the solicited AEs collected during the first 7 days post treatment during the blinded period. The majority of the subjects – 94.4% and 96.6% in the RBX2660 and placebo groups, respectively - reported at least one of the solicited events. The majority of solicited AEs reported by subjects were assessed as mild or moderate. The observed event rates in the placebo group were higher than those in the RBX2660 group for gas, abdominal distension or bloating, increased diarrhea, abdominal pain or cramping, constipation, rectal irritation or pain, rectal bleeding, and nausea. The event rates for fever, chills/severe shivering, and vomiting were similar between the two treatment groups.

Table 18. Summary of Solicited Adverse Events by Maximum Post-Treatment Severity During Blinded Period (SP)

Solicited Event Maximum Post-treatment Severity	Placebo (N=87) Subjects n (%)	RBX2660 (N=180) Subjects n (%)
Subjects with at least one solicited adverse event	84 (96.6)	170 (94.4)
Gas (flatulence)		
None	8 (9.2)	24 (13.3)
Mild	33 (37.9)	84 (46.7)
Moderate	44 (50.6)	69 (38.3)
Abdominal distension or bloating		
None	16 (18.4)	63 (35.0)
Mild	26 (29.9)	65 (36.1)
Moderate	33 (37.9)	37 (20.6)
Severe	10 (11.5)	12 (6.7)
Increased diarrhea		
None	27 (31.0)	74 (41.1)
Mild	25 (28.7)	41 (22.8)
Moderate	22 (25.3)	40 (22.2)
Severe	9 (10.3)	21 (11.7)
Potentially life-threatening	2 (2.3)	1 (0.6)
Abdominal pain or cramping		
None	15 (17.2)	58 (32.2)

Solicited Event Maximum Post-treatment Severity	Placebo (N=87) Subjects n (%)	RBX2660 (N=180) Subjects n (%)
Mild	28 (32.2)	60 (33.3)
Moderate	22 (25.3)	42 (23.3)
Severe	17 (19.5)	16 (8.9)
Potentially life-threatening	3 (3.4)	1 (0.6)
Constipation		
None	61 (70.1)	147 (81.7)
Mild	12 (13.8)	21 (11.7)
Moderate	7 (8.0)	8 (4.4)
Severe	3 (3.4)	1 (0.6)
Potentially life-threatening	2 (2.3)	0 (0.0)
Fever		
None	73 (83.9)	150 (83.3)
Mild	9 (10.3)	17 (9.4)
Moderate	3 (3.4)	7 (3.9)
Severe	0 (0.0)	2 (1.1)
Potentially life-threatening	0 (0.0)	1 (0.6)
Chills/severe shivering		
None	60 (69.0)	123 (68.3)
Mild	19 (21.8)	36 (20.0)
Moderate	5 (5.7)	14 (7.8)
Severe	1 (1.1)	4 (2.2)
Potentially life-threatening	0 (0.0)	0 (0.0)
Rectal irritation or pain		
None	39 (44.8)	97 (53.9)
Mild	22 (25.3)	57 (31.7)
Moderate	19 (21.8)	17 (9.4)
Severe	5 (5.7)	5 (2.8)
Potentially life-threatening	0 (0.0)	1 (0.6)
Rectal bleeding		
None	68 (78.2)	151 (83.9)
Mild	12 (13.8)	23 (12.8)
Moderate	3 (3.4)	3 (1.7)
Severe	1 (1.1)	0 (0.0)
Potentially life-threatening	1 (1.1)	0 (0.0)
Nausea		
None	46 (52.9)	113 (62.8)
Mild	22 (25.3)	36 (20.0)
Moderate	11 (12.6)	23 (12.8)
Severe	5 (5.7)	4 (2.2)
Potentially life-threatening	1 (1.1)	1 (0.6)
Vomiting		
None	79 (90.8)	161 (89.4)
Mild	4 (4.6)	12 (6.7)
Moderate	0 (0.0)	3 (1.7)
Severe	1 (1.1)	1 (0.6)
Potentially life-threatening	1 (1.1)	0 (0.0)

Source: Table 29 in Study 2017-01 CSR

Reviewer's Comment: It's untypical to observe generally higher solicited event rates in the placebo group than those in the investigational treatment group. I defer to the clinical reviewer regarding the explanation of the observed findings above.

As shown in Table 19, the rate of any AEs during the 8-week double-blind period was higher in the RBX2660 group (47.8%) compared to the placebo group (39.1%). While the rates of moderate and severe AEs were relatively similar between the treatment groups, the rates of mild AEs and SAEs were higher in the RBX2660 group than the placebo group. No subjects were discontinued due to an AE or SAE. There was one death in the RBX2660 group.

Table 19. Adverse Events During Study 2017-01 8-Week Double-Blind Period

	Blinded RBX2660 N = 180	Placebo N = 87
All AEs	86 (47.8%)	34 (39.1%)
Number of AEs	262	87
AEs by maximum severity*		
Mild	40 (22.2%)	13 (14.9%)
Moderate	37 (20.6%)	18 (20.7%)
Severe	8 (4.4%)	3 (3.4%)
Potentially life-threatening**	1 (0.6%)	0
Patient discontinued from study due to AE**	1 (0.6%)	0
All SAEs	4 (2.2%)	1 (1.1%)
Deaths**	1 (0.6%)	0

Source: Table 12 in applicant's VRBPAC Briefing Document
Note: Treatment failures are censored at time of CDI recurrence.
* AEs reported by maximum severity as assessed by investigator using Common Terminology Criteria for Adverse Events (CTCAE) criteria.
** Same patient represented in each category.

CBER requested the applicant to evaluate AEs within 8 weeks after the first course of treatment between the RBX2660 and placebo groups, using data for subjects from Day 0 up until the earliest time of the following: end of 8 weeks post the first enema; time of open label RBX2660 treatment received; or time of loss-to-follow up/withdrawal. The rate of AEs during the at-risk period was higher in the RBX2660 group (52.8%) compared to placebo (46.0%). The rate of SAEs during the at-risk period was 5.0% in the RBX2660 group as compared with 4.6% in the placebo group.

- Study 2017-01 Overview of Adverse Events Through 6 Months

Safety results through 6 months after blinded treatment are presented in Table 20. Similar to the safety findings during the 8-week double-blind period, a higher rate of any AEs was reported in the RBX2660 group (55.6%) compared to the placebo group (44.8%), which was driven primarily by patients experiencing a mild or moderate event by maximum severity. Serious AEs were reported for 3.9% of blinded RBX2660 patients through 6 months, compared with 2.3% in the blinded placebo group. The same patient who experienced an AE leading to death in the first 8 weeks of double-blind treatment remained the only patient who died through 6 months in this analysis.

Table 20. Study 2017-01 Safety Overview Through 6 Months

	Blinded RBX2660 N = 180	Blinded Placebo N = 87
Any AEs	100 (55.6%)	39 (44.8%)
Number of AEs	368	131
AEs by maximum severity*		
Mild	42 (23.3%)	9 (10.3%)
Moderate	47 (26.1%)	25 (28.7%)
Severe	10 (5.6%)	5 (5.7%)
Potentially life-threatening**	1 (0.6%)	0 (0.0)
Patient discontinued from study due to AE**	1 (0.6%)	0 (0.0)
SAEs	7 (3.9%)	2 (2.3%)
Deaths**	1 (0.6%)	0 (0.0)

Source: Table 15 in applicant's VRBPAC Briefing Document
Note: Treatment failures are censored at time of CDI recurrence.
* AEs reported by maximum severity as assessed by investigator using Common Terminology Criteria for Adverse Events (CTCAE) criteria.
** Same patient represented in each category.

Per CBER request, the applicant additionally evaluated the AEs within 6 months after the first course of treatment between the RBX2660 and placebo groups, using data for subjects from Day 0 up until the earliest time of the following: end of 6 months post the first enema; time of open label RBX2660 treatment received; or time of loss-to-follow up/withdrawal. The rate of any AEs during the at-risk period was higher in the RBX2660 group (61.1%) compared to placebo (52.9%). The rate of SAEs during the at-risk period was 6.7% in the RBX2660 group as compared with 6.9% in the placebo group.

Reviewer's Comment: In the summaries of unsolicited AEs presented in Tables 18 and 19, safety data after CDI recurrences for subjects who experienced a CDI recurrence were not included. Many of these subjects received open-label dose of RBX2660. As a result, the presented AE rates may be underestimated.

6.2.12.1 Methods
Safety analysis was performed with descriptive statistics.

6.2.12.3 Deaths
Two subjects died during the entirety of Study 2017-01. Both were in the RBX2660 group. One subject died due to cardio-respiratory arrest on Day 37 from last RBX2660 treatment, the other subject died due to multimorbidity on Day 151 from last RBX2660 treatment. The deaths were assessed as unrelated to study treatment by the investigators.

6.2.12.4 Nonfatal Serious Adverse Events
Please see section 6.2.12.

6.2.12.5 Adverse Events of Special Interest (AESI)
N/A

6.2.12.6 Clinical Test Results
N/A

6.2.12.7 Dropouts and/or Discontinuations
Please see section 6.2.12.

7. INTEGRATED OVERVIEW OF EFFICACY

In addition to the efficacy results from Study 2017-01, RBX2660 was evaluated in several open label studies (2013-001, 2015-01, 2019-01) and in a retrospective study, 2019-02. In these studies, the applicant collected the 8-week CDI recurrence data and analyzed them in a descriptive manner. The efficacy results of the three open-label clinical studies are summarized in Table 21. However, the interpretation of these open-label data is limited by the lack of concurrent placebo control, inclusion of a different dosing regimen (2 doses) than intended for licensure, and differences between study populations in the open-label and placebo-controlled studies.

Table 21. Summary of Study Design and Efficacy Results of Studies 2013-01, 2015-01, and 2019-01

Study	Study Design	Treatment	Study Subjects	Efficacy Results
2013-001	Phase 2, Open label, Prospective, Non-controlled	RBX2660; One Enema; Rectal.	34 RBX2660	The primary efficacy endpoint was treatment success, defined as the absence of CDAD (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 treatment with RBX2660. Sixteen (16) subjects or 50.0% (N=16/32) were considered a treatment success after their first treatment with RBX2660.
2015-01	Prospective, Historical Control	RBX2660; Two Enemas 7 ± 2 days apart; Rectal	149 RBX2660 (Historical Control N=110)	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 subjects (n=142) who received at least one enema, compared with a closely matched Historical Control arm (n=75) chosen from a retrospective chart review of subjects treated with antibiotics for rCDI who matched key eligibility criteria and had an evaluable treatment outcome. The proportion of subjects with Treatment Success, was higher in the RBX2660 arm (78.9%) as compared with the Historical Control arm (30.7%).
2019-01	Prospective, Non-controlled	RBX2660; One Enema; Rectal	254 RBX2660	Ad hoc efficacy analysis of study 2019-01 data available at the time of the cut-off date (20-Apr-2021) showed that, at 8 weeks post first RBX2660 treatment, 73.4% (113/154) of the mITT subjects experienced Treatment Success.

Source: Reviewer's summary based on the CSRs of Studies 2013-01, 2015-01 and 2019-01

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The ISS safety population comprised any subject who was exposed to treatment. Subjects who were enrolled but not treated were not included. In addition, 110 subjects enrolled into the historical control arm of Study 2015-01 and subjects from the retrospective Study 2019-02 are not included. The applicant used two study groupings: one includes all 5 prospective studies. The other is a subset of Group 1 and consists of only the prospective randomized double-blind, placebo-controlled studies.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

- Randomized, double-blind and placebo-controlled studies: Studies 2014-01 and 2017-01
- Open-label studies: Studies 2013-1, 2015-01, and 2019-01

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The integrated safety population included 978 patients in the RBX2660 group and 83 in the placebo group. Table 22 shows number of subjects in each treatment group across five studies. Table 23 shows subject disposition in the integrated safety population. Table 24 shows baseline demographics and characteristics of the integrated safety population.

Table 22. Integrated Safety Populations by Treatment Group

	Placebo Only (N = 83)	RBX2660 Only (N = 763)	Placebo / Open-Label RBX2660 (N = 48)	RBX2660 / Open-Label RBX2660 (N = 167)	All RBX2660 (N = 978)*
Study 2013-001 (Open-label)	0 (0.0)	19 (2.5%)	0 (0.0)	15 (9.0%)	34 (3.5%)
Study 2014-01 (DB, PBO Study)	20 (24.1%)	54 (7.1%)	24 (50.0%)	30 (18.0%)	108 (11.0%)
Study 2015-01 (Open-label)	0 (0.0)	149 (19.5%)	0 (0.0)	0 (0.0)	149 (15.2%)
Study 2017-01 (DB, PBO Study)	63 (75.9%)	139 (18.2%)	24 (50.0%)	41 (24.6%)	204 (20.9%)
Study 2019-01 (Open-label)	0 (0.0)	402 (52.7%)	0 (0.0)	81 (48.5%)	483 (49.4%)

Source: Table 19 in the applicant's VRBPAC Briefing Document
* In the initial BLA submission, there were 749 subjects in the All RBX2660 group. The applicant submitted additional safety data from ongoing Study 2019-01, making the total number of subjects in the All RBX2660 group to be 978.

Table 23. Integrated Safety Population Disposition

	Placebo Only (N = 83)	RBX2660 Only (N = 763)	Placebo / Open Label RBX2660 (N = 48)	RBX2660 / Open-Label RBX2660 (N = 167)	All RBX2660 (N = 978)
Received treatment	83 (100.0%)	763 (100.0%)	48 (100.0%)	167 (100.0%)	978 (100.0%)
Completed 8-week follow-up (after first treatment)	78 (94.0%)	672 (88.1%)	42 (87.5%)	146 (87.4%)	860 (87.9%)
Completed 6-month follow-up (after first treatment)	75 (90.4%)	583 (76.4%)	42 (87.5%)	126 (75.4%)	751 (76.8%)
Completed 24-month follow-up (after first treatment)	16 (19.3%)	145 (19.0%)	19 (39.6%)	18 (10.8%)	182 (18.6%)
Ongoing in 2019-01	0 (0.0)	119 (15.6%)	0 (0.0)	25 (15.0%)	144 (14.7%)
Between treatment and 8-week follow-up	0 (0.0)	38 (31.9%)	0 (0.0)	6 (24.0%)	44 (30.6%)
Between 8-week and 6-month follow-up	0 (0.0)	68 (57.1%)	0 (0.0)	16 (64.0%)	84 (58.3%)

Source: Table 20 in the applicant's VRBPAC Briefing Document

Table 24. Integrated Safety Population – Baseline Demographics and Characteristics

	Placebo Only (N = 83)	RBX2660 Only (N = 763)	Placebo / Open-Label RBX2660 (N = 48)	RBX2660 / Open-Label RBX2660 (N = 167)	All RBX2660 (N = 978)
Age (years), mean (SD) Min, max	58.1 (16.48) 19.0, 90.0	61.4 (17.60) 18.0, 103.0	58.0 (18.19) 24.0, 92.0	62.8 (18.34) 18.0, 93.0	61.5 (17.77) 18.0, 103.0
Female, n (%)	60 (72.3%)	516 (67.6%)	30 (62.5%)	111 (66.5%)	657 (67.2%)
White, n (%)	75 (90.4%)	713 (93.4%)	46 (95.8%)	158 (94.6%)	917 (93.8%)
Duration of CDI (days), mean (SD)	24.3 (13.98)	32.3 (27.35)	25.7 (16.23)	32.3 (27.04)	31.9 (26.85)
Number of Previous Episodes of CDI ≥ 1 1-3 ≥ 3	83 (100.0) 60 (72.3) 57 (68.7)	757 (99.2) 450 (59.0) 595 (78.0)	48 (100.0) 23 (47.9) 40 (83.3)	167 (100.0) 98 (58.7) 133 (79.6)	972 (99.4) 571 (58.4) 768 (78.5)
Hospitalization					
Due to CDI episode, n (%)	17 (20.5%)	106 (13.9%)	5 (10.4%)	25 (15.0%)	136 (13.9%)
Duration (days), median (IQR)	5.0 (3.0)	5.0 (4.0)	5.0 (6.0)	7.5 (7.5)	5.0 (4.0)

Source: Table 31 in the applicant's VRBPAC Briefing Document

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Considerations in pooling of the studies and consequently interpretation of comparisons between the placebo and pooled treatment groups in the ISS include:
1) The open-label nature of many of the RBX2660 doses in the ISS population;
2) Subjects may 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 rCDI or morbidities attributable to the CDI;
3) The Placebo Only group does not include the subjects who experienced a CDI recurrence and received an open-label dose of RBX2660. As a result, AE rates may be underestimated in this group and may not represent subjects' experience

from receiving placebo only in the general population. The difference in AE rates between the RBX2660 groups and the Placebo Only group may be overestimated and tend to be conservative against favor of RBX2660.

4) 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.

5) As randomizations are no longer preserved in the pooled analysis, causal conclusions cannot be drawn. Therefore, the results in the ISS should be interpreted with caution.

8.4 Safety Results

8.4.1 Deaths

Across all studies, there were 18 deaths due to AEs with an onset within 6 months after the last treatment course. All deaths occurred in the RBX2660 group. None of the deaths were considered to be related to RBX2660 by the study investigator or FDA.

8.4.2 Nonfatal Serious Adverse Events

SAEs were reported in 13.8% of all the patients treated with RBX2660 (1-4 doses), 10.1% in the patients treated with 1 dose RBX2660, and 7.2% in the patients treated with placebo.

8.4.3 Study Dropouts/Discontinuations

Please refer to Table 23.

8.4.4 Common Adverse Events

Both pooled double-blind studies (Studies 2014-01 and 2017-01) and pooled five studies showed that the overall AE rates were higher in the RBX2660 groups compared to the placebo only group (Table 25 and Table 26). Across five studies, 18 deaths were reported in the All RBX2660 (1-4 does) group and none in the placebo only group; these deaths were considered to be not related to the product by study investigators.

Table 25. Integrated Safety Population - Overview of Adverse Events in Blinded Studies

Safety through 6-months after last treatment	Blinded RBX2660 Only (1 or 2 doses) N = 193	Placebo Only N = 83
Number of subjects with AEs	135 (69.9%)	50 (60.2%)
Number of AEs	632	174
AEs by maximum severity*		
Mild	56 (29.0%)	13 (15.7%)
Moderate	54 (28.0%)	29 (34.9%)
Severe	19 (9.8%)	7 (8.4%)
Potentially life-threatening	6 (3.1%)	1 (1.2%)
Subjects discontinued from study due to AE**	1 (0.5%)	0 (0.0)
All SAEs	20 (10.4%)	6 (7.2%)
Deaths	5 (2.6%)	0 (0.0)

Source: Table 21 in the applicant's VRBPAC Briefing Document
* AEs reported by maximum severity as assessed by investigator using Common Terminology Criteria for Adverse Events (CTCAE) criteria;
** AEs leading to discontinuation were only collected in Studies 2017-01 and 2019-01, which also includes deaths in these studies.

Table 26. Integrated Safety Population – Overview of Adverse Events in All Patients Treated with RBX2660

Safety through 6-months after last treatment*	All RBX2660 (1-4 Doses) N = 978	RBX2660 1 Dose Only N = 595	Placebo Only N = 83
Number of subjects with AEs	673 (68.8%)	378 (63.5%)	50 (60.2%)
Number of AEs	2881	1327	174
AEs by maximum severity**			
Mild	224 (22.9%)	124 (20.8%)	13 (15.7%)
Moderate	294 (30.1%)	176 (29.6%)	29 (34.9%)
Severe	126 (12.9%)	64 (10.8%)	7 (8.4%)
Potentially life-threatening	29 (3.0%)	14 (2.4%)	1 (1.2%)
Subjects discontinued from study due to AE***	8 (0.8%)	5 (0.8%)	0 (0.0)
All SAEs	135 (13.8%)	60 (10.1%)	6 (7.2%)
Deaths	18 (1.8%)	5 (0.8%)	0 (0.0)

Source: Table 22 in the applicant's VRBPAC Briefing Document
Note: Treatment failures are censored at time of CDI recurrence.
* AEs after the first treatment in patients who received a second treatment are included; the All RBX2660 group includes those with Treatment Failure on placebo who crossed over to RBX2660 treatment.
** AEs reported by maximum severity as assessed by investigator using Common Terminology Criteria for Adverse Events (CTCAE) criteria;
*** AEs leading to discontinuation were only collected in Studies 2017-01 and 2019-01, which also includes deaths in these studies.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy:

The primary efficacy endpoint analysis for the Phase 3 study 2017-01 (mITT population), conducted with a Bayesian analysis borrowing information from Phase 2 study 2014-01, resulted in a model-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. The efficacy results did not meet the first and more stringent success threshold (posterior probability of superiority 0.9993275) that would have been considered a statistically very persuasive finding in a single trial that could substitute for positive statistical evidence from two independent adequate and well-controlled trials. Nevertheless, the efficacy results met the second success threshold (posterior probability of superiority 0.9750338) that is considered equivalent to positive statistical evidence from a single adequate and well-controlled trial. Although the integrated Bayesian analysis did not meet the first and more stringent success threshold that could substitute for positive statistical evidence from two independent adequate and well-controlled trials, the evidence for efficacy needs to be evaluated in the context of therapeutic setting and risk. In certain settings, substantial evidence of effectiveness can be present with somewhat less certainty about effectiveness, when balanced against the risk of rejecting or delaying the marketing of an effective therapy for an unmet medical need. In my view, considering the severity and rarity of the disease and unmet medical need, the data submitted with this BLA can support the conclusion that there is substantial evidence of effectiveness of RBX2660 for preventing recurrence of CDI.

Safety:

The safety evaluation was conducted based on individual studies and integrated safety analysis. These safety analyses showed a generally similar trend. The rate of AEs was generally higher in the RBX2660 group compared to the placebo group. Imbalances were observed in gastrointestinal AEs and SAEs, including fatal events, between the RBX2660 groups and the placebo group. Across five studies, 18 deaths were reported in the All RBX2660 (1-4 does) group; these deaths were considered to be not related to the product by study investigators or FDA.

10.2 Conclusions and Recommendations

Overall, the primary efficacy analysis of Phase 3 study 2017-01 met the pre-specified statistical success threshold for a single adequate and well-controlled trial. While the rates of adverse events were generally higher among the subjects receiving RBX2660 than those receiving placebo, no major safety concern was identified from the studies. In my view, considering the severity and rarity of the disease and unmet medical need, the data submitted with this BLA can support the conclusion that there is substantial evidence of effectiveness of RBX2660 for preventing recurrence of CDI.