BLA Clinical Review Memorandum

Application Type	BLA
STN	125739
CBER Received Date	November 30, 2021
PDUFA Goal Date	November 30, 2022
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Omolara Adewuni, MD MPH MBA
Review Completion Date / Stamped Date	November 30, 2022
Supervisory Concurrence	Meghan Ferris MD MPH Andrea Hulse MD
Applicant	Ferring Pharmaceuticals, Inc.
Established Name	Fecal Microbiota, Live
(Proposed) Trade Name	Rebyota
Pharmacologic Class	Live Therapeutics
Formulation(s), including Adjuvants, etc.	RBX2660 (Fecal Microbiota Transplantation, Frozen Preparation – Enema)
Dosage Form(s) and Route(s) of Administration	Suspension, For Rectal Use
Dosing Regimen	Single dose of 150 mL RBX2660 per rectum
Indication(s) and Intended Population(s)	Prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
ATLAS	age, temperature, leucocytes, albumin, systemic antibiotics
BIMO	Bioresearch Monitoring
BLA	biologics license application
CBER	Center for Biologics and Evaluation
CDAD	*Clostridioides difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CFR	Code of Federal Regulations
CFU	colony forming unit
CHF	congestive heart failure
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
DHS	donor human stool
DNA	deoxyribonucleic acid
EAC	Endpoint Adjudication Committee
EOP2	end of phase 2
FMT	fecal microbiota transplant
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICU	intensive care unit
IND	investigational new drug
ISS	integrated summary of safety
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OOPD	Office of Orphan Products Development
PCR	polymerase chain reaction
PEG	polyethylene glycol
PI	package insert
PP	Per-Protocol
PREA	Pediatric Research Equity Act
PT	preferred term
rCDI	recurrent *Clostridioides difficile* infection
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standardized MedDRA Query
SoC	standard of care
SOC	system organ class
TEAE	treatment emergent adverse event
(b) (4)	
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRE	vancomycin resistant enterococcus

1. EXECUTIVE SUMMARY

Ferring Pharmaceuticals, Inc. (the Applicant), submitted a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) to support licensure of RBX2660 (proprietary name Rebyota), a fecal microbiota suspension prepared from human stool collected from prescreened, qualified donors and tested for prespecified pathogens and other infectious agents. The proposed indication for RBX2660 is to "prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for CDI." RBX2660 is supplied as a pre-packaged single-dose of 150 mL fecal microbiota suspension in an enema bag.

Recurrent CDI (rCDI) is defined as an episode of CDI occurring within eight weeks of a previous episode of CDI and can be serious or life threatening (Surawicz et al. 2013). rCDI may be due to relapse of a previous episode of CDI by the same strain or reinfection by a different strain (Tang-Feldman et al. 2003). Risk factors for rCDI include age >65 years, antibiotics use, gastric acid suppression, hypervirulent strain (NAP1/BI/027 – produces larger amount of toxins A and B), renal insufficiency, history of previous CDI, previous severe CDI, prolonged hospital stays and lack of adaptive immune responses to toxins A and B (Song et al. 2019). rCDI occurs in about 20-35% of individuals who experience an initial episode of CDI, and approximately 40-60% of those with a first recurrence will experience a second recurrence (Hopkins et al. 2018). rCDI complications include dehydration, hypotension, kidney failure, severe diarrhea and rarely, toxic megacolon, colonic rupture, septicemia and death. rCDI is associated with significantly increased mortality independent of baseline characteristics, comorbidities and treatments received. Olsen et al (2015) reported that rCDI was associated with significantly higher hazards of death within 180 days, adjusting for demographics, comorbidities and medications received during the index CDI hospitalization (hazard ratio 1.33; 95% confidence interval 1.12–1.58).

Treatment options for rCDI are limited, and the current standard of care (SoC) antibiotic treatment regimens can be complex and prolonged. Bezlotoxumab, a human monoclonal antibody directed against *C. difficile* toxin B administered intravenously, is currently the only US licensed product indicated for reduction in 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.

This BLA included data from six clinical studies: two placebo-controlled studies (Phase 2 study 2014-01 and Phase 3 study 2017-01); three prospective open-label studies (2013-001, 2015-01, and 2019-01), and one retrospective study (2019-02). 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 the placebo-controlled Phase 2 study (2014-01) into study 2017-01. This Bayesian analysis provided the primary evidence of effectiveness for RBX2660 for the proposed indication.

Study 2014-01 was a Phase 2, double-blind, randomized, placebo-controlled trial in adults ≥18 years old with documented rCDI. A total of 133 subjects 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 rCDI; a total of 289 subjects were randomized 2:1 to receive one dose of RBX2660 or one dose of placebo. 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 intent-to-treat (mITT) population was pre-specified as the primary analysis population. The 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 active and placebo group per the planned design. In order to better align the analysis population definitions between the two studies, the Bayesian analysis was conducted with the analysis population definition of study 2017-01 applied to study 2014-01. In both studies, treatment with open-label RBX2660 was an option in the event of treatment failure.

The Bayesian primary efficacy endpoint analysis for the Phase 3 study 2017-01 (mITT population) resulted in an estimated difference in treatment success rates of 13.1% (95% credible interval: 2.3%, 24.0%). The posterior probability that RBX2660 was superior to placebo was 0.991. The efficacy results met a less stringent specified success threshold for posterior probability of superiority exceeding 0.9750338, equivalent to a frequentist one-sided Type 1 error rate <0.025. However, the efficacy results did not meet a more stringent success threshold for posterior probability of superiority 0.9993275, equivalent to a frequentist one-sided Type 1 error rate <0.00125.

Additional supportive effectiveness data was provided from RBX2660 treatment success rates in the prospective open-label studies, using the same definition as in the placebo-controlled trials, which ranged from 50.0% to 78.9% following a single dose of RBX2660. While contributory to the overall evaluation of effectiveness, interpretation of treatment success rates in the open-label studies was limited by lack of a concurrent control group.

In an analysis of treatment emergent adverse events (TEAEs) occurring within 8 weeks after blinded RBX2660 or placebo treatment in the largest placebo-controlled trial (2017-01), the most common adverse reactions (defined as AEs assessed as definitely, possibly, or probably related to RBX2660 by the investigator) reported by ≥3% of RBX2660 recipients and at a rate greater than that reported by placebo recipients included: abdominal pain, (8.9% vs. 6.9%), diarrhea (7.2% vs. 3.4%), abdominal distention (3.9% vs. 2.3%), flatulence (3.3% vs. 0%), and nausea (3.3% vs. 1%). Most related 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 related adverse reactions were reported. Most adverse reactions were mild to moderate in severity and none were life-threatening.

Safety data from studies 2013-001, 2014-01, 2015-01, 2017-01 and 2019-01 were pooled in an integrated summary of safety (ISS), including 6 months of follow-up after the last dose of study treatment across all studies. Safety was assessed by examining the incidence of all 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 ISS included an analysis of data from subjects enrolled in double-blind, placebo-controlled studies (n=312 RBX2660 recipients and 83 placebo recipients) and an analysis of data

from all studies (n=749 RBX2660 recipients and 83 placebo recipients), including non-randomized studies and subjects who received open-label RBX2660. The safety review specifically focused on the subjects who received one dose of RBX2660 (dosing regimen proposed for licensure; n=429), subjects who received blinded RBX2660 (n=193), subjects who received any dose of RBX2660, regardless of blinding or regimen (Any RBX2660; n=749), and placebo recipients (n=83).

A safety update was submitted in an amendment to the BLA in May 2022 that added 229 subjects exposed to open-label RBX2660 in Study 2019-01, bringing the total pre-licensure clinical trial safety database to 978 subjects. A review of adverse events reported by these additional subjects did not reveal any new safety signals, so the CBER review of the Full ISS remained limited to the 749 subjects included in the initial BLA submission. Safety data for the additional 229 subjects were reviewed separately.

In the Full ISS, the proportions of participants reporting TEAEs were 61.8% in the one-dose RBX2660 group, 69.9% in the blinded RBX2660 group, and 69.6% in the Any RBX2660 group compared to 60.2% in the placebo group. In all groups, the most commonly reported events were gastrointestinal. The severity of TEAEs was mostly mild or moderate, and most were related to pre-existing conditions. For both the one-dose and blinded RBX2660 groups compared to placebo, numerical imbalances in events of abdominal pain, nausea, flatulence, and abdominal distention were observed. The proportion of participants reporting related TEAEs was 22.6% in the one-dose RBX2660 group, 26.4% in the blinded RBX2660 group, and 23.3% in the Any RBX2660 group compared to 19.3% in the placebo group. The proportion of participants reporting severe and life-threatening TEAEs was 9.3% and 2.1%, respectively, in the one-dose RBX2660 group, 9.8% and 3.1%, respectively, in the blinded RBX2660 group, and 12.7% and 2.9%, respectively, in the Any RBX2660 group compared to 8.4% and 1.2%, respectively, in the placebo group.

The proportions of participants reporting serious TEAEs were 8.4% in the one-dose RBX2660 group, 10.4% in the blinded RBX2660 group, and 14.2% 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 subjects in the two, three, and four-dose RBX2660 groups, respectively). The most frequently reported serious TEAEs were in the MedDRA System Organ Classes of *Infections and infestations*, *Gastrointestinal disorders*, and *Respiratory, thoracic and mediastinal disorders*. A total of five subjects who received one or two doses of RBX2660 reported serious TEAEs that were considered possibly related to RBX2660 by the investigator, including three subjects in study 2014-01 (acute myeloid leukemia relapse, abdominal pain and recurrent CDI, and worsening chronic constipation) and two subjects in study 2015-01 (recurrent CDI and diarrhea and ileus, leukocytosis, CDI, and pyrexia). Following review of all of the individual case narratives, this reviewer did not consider any serious TEAEs to be plausibly related to RBX2660.

The proportions of participants reporting fatal TEAEs were 1.2% in the one-dose RBX2660 group, 2.6% in the blinded RBX2660 group, and 2.4% in the Any RBX2660 group, compared to 0% in the placebo group. The proportion of subjects reporting any TEAE leading to death increased as the number of treatment exposures increased, ranging from 3.4% in subjects who received two doses of RBX2660 to 16.7% of subjects who received 4 doses of RBX2660. Of the 18 fatal TEAEs observed in the RBX2660 clinical program, 17 were adjudicated as being unrelated to treatment. This reviewer

agrees with the assessment of causality for these cases. One death due to relapsed CDI on Day 21 (study 2015-01) was considered possibly related to RBX2660 and the enema procedure and definitely related to CDI by the investigator. Following review of the narrative and case report form, this reviewer considered the event not to be causally related to RBX2660 but rather related to recurrent CDI.

Conclusions

Recurrent CDI is a serious condition that can be associated with high rates of morbidity and mortality. There is an unmet medical need for the condition because currently available treatment options are limited and can be complex and prolonged.

Data submitted to the BLA establish that RBX2660 is effective in preventing recurrence of CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. Available data as summarized above, and in greater detail in this review memorandum, support the effectiveness of RBX2660 when administered 24-72 hours after completion of antibiotic therapy for the previous episode of rCDI. The primary evidence of effectiveness (superiority to placebo) is provided by a Bayesian analysis of efficacy data from two placebo-controlled studies, with additional supportive effectiveness data provided by multiple uncontrolled studies. While the estimated treatment effect is modest (13.1%, with a 95% credible interval lower bound of 2.3% in the Bayesian analysis), it is clinically meaningful for the population of patients with rCDI, who have limited FDA approved options for prevention of further episodes of rCDI. Evidence of effectiveness from the Bayesian analysis is further supported by effectiveness evidence from prospective open-label studies of RBX2660 and effectiveness estimates from randomized controlled trials of other FMT products reported in the literature, and together this evidence is considered in the context of rCDI being a serious disease with limited treatment options.

As summarized above, and in greater detail in this review memorandum, most adverse reactions associated with RBX2660 in clinical trials were gastrointestinal events that occurred soon after exposure to the product, and most reported adverse events, including all reported serious adverse events and deaths, were most likely associated with rCDI or underlying comorbid illnesses or treatments. While transmission of pathogens is a safety concern for FMT products, the risk of pathogen transmission appears to be low for RBX2660. Rigorous screening and testing of stool donors and stool will be an ongoing part of risk mitigation and post-licensure product quality controls. If RBX2660 were approved for use in individuals 18 years of age and older with recurrent CDI, the proposed measures of donor and stool screening and testing for pathogens, product labeling, and routine pharmacovigilance would be adequate to manage the risks.

In summary, this reviewer concludes that the benefit-risk balance for RBX2660 is favorable for the intended use being requested by the Applicant.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The clinical development program included five prospective studies, which enrolled a total of 978 subjects who received blinded or open-label RBX2660 and 83 subjects who received only blinded placebo. The majority of the subjects in the RBX2660 group were White (93.6%), not Hispanic or Latino 95.1%), female (65.4%) and <65 years of age

(52.1%). The numbers of subjects in other racial groups were too small to perform meaningful efficacy and safety analyses by race.

Subgroup analysis of treatment success within 8 weeks: Studies 2017-01 and 2014-01
In the ITT populations from Study 2014-01 and Study 2017-01, subgroup analysis of the primary efficacy endpoint by race, ethnicity, sex, and age group (<65 years, ≥65 years) did not yield statistically significant differences between subgroups. Numerical differences in success rate point estimates were observed in the following subgroups:

- White (9.1%) and non-white (8.3%)
- Hispanic or Latino (50.0%) and non-Hispanic or Latino (7.9%)
- Male (18.7%) and female (4.4%)
- <65 years (7.3%) and ≥65 years (12.7%)

Similar and non-statistically significant differences were observed in the per protocol populations.

Safety analyses by race, sex, and ethnicity (pooled safety population)
TEAEs were analyzed by age group, sex, number of previous CDI episodes, ethnicity and race group; there were no notable differences across the exposure groups in the predefined subgroup categories.

The frequency of TEAEs was higher in the older than the younger age group, including the frequency of serious TEAEs and TEAEs leading to death. Among subjects ≥65 years old, the proportions of subjects with severe and potentially life threatening TEAEs were 50/359 (13.9%) and 16/359 (4.5%), respectively, while among subjects <65 years old they were 45/390 (11.5%) and 6/390 (1.5%), respectively. Severe and potentially life threatening TEAEs occurred more frequently in subjects ≥75 years of age: 13/193 (6.7%).

The proportions of subjects with serious TEAEs were 24.4%, 18.1% and 10.5% in groups of subjects ages ≥75 years, ≥65 years, and <65 years, respectively. Similarly, a greater proportion of subjects ≥75 years old reported TEAEs leading to death. In the ISS, of 18 subjects with TEAEs leading to death, 3 (16.7%) subjects were <65 years, while 12 (66.7%) were ≥75 years or older. The increased rates of serious TEAEs and deaths in the older subjects may reflect the underlying medical conditions that predisposed the subjects to severe CDI.

The frequencies of TEAEs and serious TEAEs assessed by the investigator as related to RBX2660 were similar across age groups and this reviewer agreed with the assessment.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.2, 6.3
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Reviewer Comment: The Applicant included evaluation of health-related quality of life for CDI as measured by the Cdiff32 questionnaire in the exploratory objectives. The review memo focuses on discussion of safety and of primary and relevant secondary efficacy objectives related to the indication and prescribing information to be approved.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Introduction

Clostridioides difficile (formerly *Clostridium difficile*), also known as *C. difficile or C. diff*, is a Gram-positive, spore forming, anaerobic rod-shaped bacterium that colonizes patients through the fecal-oral route and causes *C. difficile* infection (CDI). CDI is a well-recognized cause of colitis-associated with morbidity and mortality, particularly in

subjects who are hospitalized and in long-term care facilities. There is a growing trend of community-associated CDI while the rate of healthcare associated CDI is decreasing.[1]

Epidemiology

CDI is a leading cause of healthcare associated infection and a significant threat to public health globally. In the United States, CDI is associated with 15,000 to 30,000 deaths annually, with acute inpatient costs exceeding $4.8 billion.[1] Population-based surveillance of CDI in ten US sites identified 15,512 cases in 2017, including 7,973 healthcare–associated and 7,539 community-associated cases.[2] The Centers for Disease Control and Prevention (CDC) consider CDI to be an urgent, antibiotic resistance threat (CDC 2019).[3] Globally, CDI incidence rate ranges from 1.1 to 631.8 per 100,000 population per year.[4]

Approximately 10% to 30% of patients will develop recurrent CDI (rCDI) after an initial episode of CDI, and each recurrence increases the risk for subsequent recurrence, with reported recurrence rates of 65% after three episodes of CDI.[5] rCDI is defined as an episode of CDI occurring within 8 weeks of a previous episode.[6] rCDI may be due to relapse of previous CDI by the same strain or reinfection by a different strain.[7] The high recurrence rate of CDI contributes to burden of disease and increased healthcare cost.[8]

The most frequently reported risk factors for rCDI include age >65 years,[9] antibiotic use for non-*C. difficile* infection after CDI diagnosis leading to disruption of the native intestinal microbiome, gastric acid suppression, infection with a hypervirulent strain (e.g., NAP1/BI/027, which produces a larger amount of toxins A and B), severe underlying disease, renal insufficiency, immunosuppression, inflammatory bowel disease, history of previous CDI, previous CDI severity, prolonged hospital stays, and lack of adaptive immune responses to toxins A and B.[10]

Clinical Manifestations, Diagnosis and Treatment

CDI symptoms may range from mild diarrhea to significant colitis. The most common signs and symptoms of moderate CDI are watery diarrhea >3 times a day for more than one day, mild abdominal cramping and tenderness. Symptoms are often associated with fever and leukocytosis. Severe infection can be associated with significant colitis, with signs and symptoms of more voluminous watery diarrhea as often as 10-15 times a day,

1 Fu Y, Luo Y, Grinspan AM. Epidemiology of community-acquired and recurrent *Clostridioides difficile* infection. Therapeutic advances in gastroenterology, 14, 17562848211016248. https://doi.org/10.1177/17562848211016248
2 Guh, A. Y., et. al. *Clostridioides difficile* Infection Working Group (2020). Trends in U.S. Burden of *Clostridioides difficile* Infection and Outcomes. The New England journal of medicine, 382(14), 1320–1330. https://doi.org/10.1056/NEJMoa1910215
3 CDC (2019). *Clostridioides difficile* (fact sheet based on the 2019 Antibiotic Resistance Threat Report). https://www.cdc.gov/drugresistance/pdf/threats-report/clostridioides-difficile-508.pdf
4 Balsells E et al. Global burden of *Clostridioides difficile* infections: a systematic review of meta-analysis. J Glob Health. June 2019;9:010407.https://jogh.org/documents/issue201901/jogh-09-010407.pdf
5 McDonald, L. C., et. al. (2018). Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children
6 Surawicz CM et al. Guidelines for diagnosis, treatment and prevention of *C. difficile* infections. Am J Gastroenterol 2013; 108:478-498
7 Tang-Feldman, Y. et. al. (2003). Molecular analysis of *Clostridium difficile* strains isolated from 18 cases of recurrent *C. difficile*-associated diarrhea. Journal of clinical microbiology, 41(7), 3413–3414. https://doi.org/10.1128/JCM.41.7.3413-3414.2003
8 Ghantoji, S. S. et. al. (2010). Economic healthcare costs of *C. difficile* infection: a systematic review. The Journal of hospital infection, 74(4), 309–318. https://doi.org/10.1016/j.jhin.2009.10.016
9 Deshpande, A., et. al. (2015). Risk factors for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. Infection control and hospital epidemiology, 36(4), 452–460. https://doi.org/10.1017/ice.2014.88
10 Song, J. H., & Kim, Y. S. (2019). Recurrent *Clostridium difficile* Infection: Risk Factors, Treatment, and Prevention. Gut and liver, 13(1), 16–24. https://doi.org/10.5009/gnl18071

mild to severe abdominal cramping/pain, fever, nausea and leukocytosis. CDI complications include dehydration and kidney failure from significant loss of fluids and electrolytes due to severe diarrhea, which can result in hypotension. Although rare, toxic megacolon is a total or segmental nonobstructive colonic dilatation that can lead to colonic rupture, septicemia, and death if left untreated. Other complications include bowel perforation or peritonitis, and death from even mild to moderate infection if not treated promptly. Surgical intervention with colectomy may be required when aggressive medical management is unsuccessful.

Diagnosis

The diagnostic criteria for CDI include new-onset diarrhea (≥3 unformed stools in 24 hours without an alternative etiology), and positive stool test for toxicogenic *C. difficile* or toxins, or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis. An algorithmic approach to testing is recommended, including highly sensitive tests, such as glutamate dehydrogenase followed by confirmation with more specific tests, including enzyme immunoassays (EIAs) to detect toxins A and B and nucleic acid amplification testing.[11,12]

Treatment

An initial episode of CDI is often successfully managed by fluid replacement, discontinuation of antibiotics if possible, and initiation of first-line antimicrobial therapy with oral vancomycin or fidaxomicin (and occasionally intravenous metronidazole or rectally delivered metronidazole or vancomycin). Second-line agents include metronidazole, nitazoxanide, rifamycin, and cytotoxin binding agents such as cholestyramine or colestipol.

Options for the treatment of rCDI depend on the initial course of therapy and may include a 10-day course of fidaxomicin or vancomycin or a tapered and pulsed fidaxomicin or vancomycin regimen. Treatment options are similar for patients with more than one recurrence, although they may also include a course of rifaximin if a standard course of vancomycin is used.[13] Bezlotoxumab (Zinplava), a human monoclonal antibody directed against *C. difficile* toxin B, was approved in 2016 and 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. While no fecal microbiota transplant (FMT) product is yet FDA-approved as safe and effective for prevention of rCDI, FMT has been recommended by various infectious diseases and gastroenterology practice guidelines and used widely, especially in the past ~10 years, as an unapproved product for this purpose, and FMT has been available as an unapproved therapy for rCDI under FDA's investigational new drug (IND) enforcement discretion policy since July 2013.

11 Kelly, CR et al. (2021). ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Official journal of the American College of Gastroenterology| ACG 116.6 (2021): 1124-1147
12 McDonald, L. C., et. al. (2018). Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 66(7), e1–e48. https://doi.org/10.1093/cid/cix1085
13 Johnson, S. et. al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *C. difficile* Infection in Adults. Clinical infectious diseases: Infectious Diseases Society of America, 73(5), e1029–e1044. https://doi.org/10.1093/cid/ciab549

Quality-of-life scores in patients with rCDI are lower compared to patients with a first episode of CDI, and consistently decrease with increasing number of CDI episodes.[14] In considering the benefits and harms of treatment for rCDI, 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 rCDI will invariably put a high value on avoidance of a subsequent CDI episode.[15]

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

Bezlotoxumab (Zinplava), a human monoclonal antibody directed against *C. difficile* toxin B, was approved on October 21, 2016, and is indicated for reduction in recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at high risk for CDI recurrence. Bezlotoxumab is administered by intravenous infusion as a single dose and is not indicated for the treatment of CDI.

The Warnings and Precautions section of the package insert for bezlotoxumab includes heart failure. Among subjects with a history of congestive heart failure (CHF) in the two Phase 2 clinical trials, serious adverse events of heart failure were reported more frequently in the bezlotoxumab group (15/118; 12.7%) than the placebo group (5/104; 4.8%) during the 12-week study period. Deaths were also more frequent in the bezlotoxumab group (19.5%) than the placebo group (12.5%) among subjects with a history of CHF. Causes of death in these subjects included cardiac failure, infections, and respiratory failure. Based on these observations, bezlotoxumab in patients with a history of CHF should be reserved for use when the benefit outweighs the risk.

2.3 Safety and Efficacy of Pharmacologically Related Products

Ongoing clinical development programs are assessing use of FMT for prevention or treatment of rCDI.

On July 2013, the Agency released guidance on the decision to exercise enforcement discretion regarding IND requirements for use of FMT to treat CDI not responsive to standard therapies. A draft guidance was released on March 2016, outlining IND requirements for use of FMT obtained from stool banks to treat CDI not responsive to standard therapies. The draft guidance was finalized in November 2022. No large-scale studies evaluating efficacy or safety of FMT administered to individuals under enforcement discretion have been submitted to the Agency for review. However, results

14 Garey, K. W. et. al. (2016). Development and Validation of a *Clostridium difficile* Health-related Quality-of-Life Questionnaire. Journal of clinical gastroenterology, 50(8), 631–637. https://doi.org/10.1097/MCG.0000000000000473
15 Johnson, S. et. al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *C. difficile* Infection in Adults. Clinical infectious diseases: Infectious Diseases Society of America, 73(5), e1029–e1044. https://doi.org/10.1093/cid/ciab549

of randomized, placebo-controlled trials of FMT products administered to individuals under enforcement discretion have been reported in the literature.[16,17,18,19,20]

FDA has issued multiple safety communications based on safety reports from specific investigational FMT products or safety concerns that resulted in revisions to donor screening and stool testing practices across all investigational FMT products. FDA safety communications to date include:

- June 13, 2019: risk of serious or life-threatening infections due to transmission of multi-drug resistant organisms (FDA 2019).
- March 12, 2020: risk of serious or life-threatening infections due to infections caused by enteropathogenic *Escherichia coli* and Shiga toxin-producing *Escherichia coli*, including events that occurred following investigational use of FMT, suspected to be due to transmission of these pathogenic organisms from the FMT product (FDA 2020a).
- March 23, 2020: potential risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) due to the documented presence of SARS-CoV-2 ribonucleic acid and/or SARS-CoV-2 virus in stool of infected individuals (FDA 2020b).
- August 22, 2022: potential risk of transmission of monkeypox virus due to the documented presence of monkeypox virus DNA in rectal swabs and/or stool samples from infected individuals (FDA 2022).

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

Not applicable.

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

20 DEC 2012	In a **pre-IND** meeting, CBER suggested that Rebiotix, Inc. (the Applicant) re-screen and re-test donors every 90 days due to concern of serious infections from asymptomatic carriers during fecal screening procedures. CBER asked the Applicant to propose a plan for testing each stool donation to assure safety from potential infectious diseases before it was given to subjects.
21 MAR 2013	The Applicant submitted IND 15349 to FDA.
17 MAY 2013	Clinical hold comments were communicated to the Applicant. Comments included incomplete investigator's brochure, insufficient study halting rules, adverse events monitoring and donor screening.
21 MAY 2013	Fast Track Designation was granted by FDA, based on published clinical experience with other FMT products.
12 JUL 2013	Clinical Hold was removed.

16 Hota, SS. et. al. (2017). Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial. Clin Infect Dis, 64(3), 265-271.
17 Hvas, CL et. al. (2019). Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection. Gastroenterology, 156(5), 1324-1332.
18 Kelly, CR, et. al. (2016). Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection: A Randomized Trial. Ann Intern Med, 165(9), 609-616.
19 Lee, CH. et. al. (2016). Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. JAMA, 315(2), 142-149.
20 van Nood, E, et. al. (2013). Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med, 368(5), 407-415.

04 MAR 2014	In a **Type C** meeting, the Applicant agreed with CBER to submit an amendment with the following: clear definition of recurring *C. difficile*, proposal for reasonable long-term follow-up, interim study report, and updated product data. CBER agreed to review the clinical study report from the Phase 2 study trial (2013-001) and give further advice at a future meeting with the Applicant.
10 MAR 2014	**Orphan Designation** (Designation Request #13-4210) was granted for "fecal microbiota for the treatment of recurrent *Clostridioides difficile* infection (*Clostridioides difficile* gastrointestinal disease)."
07 MAY 2014	The Applicant submitted responses to the non-hold comments from the Hold letter of May 17, 2013. CBER reviewed the submission and requested for additional information to include: a recommendation that the Applicant save a small aliquot from each donation. The Applicant was to clarify whether they have at least (b) (4) (b) (4) used to determine the total colony forming units (CFU) counts as part of the final product release testing. CBER acknowledged limitations of (b) (4) as a tool to identify microbes in human stool.
25 AUG 2014	CBER communicated comments regarding: • Phase 2 protocol and statistical analysis plan indicating that CBER continued to request 2-3 years follow-up to include SAEs and agreement with the primary endpoint of treatment success defined as absence of *Clostridioides difficile*-associated diarrhea (CDAD) without need for retreatment with *C. difficile* anti-infective therapy or fecal transplant at 56 days after last assigned study enema. • Concurrence with the primary endpoint for the Phase 3 study depending, in part, on the result of the Phase 2 study and agreement to discuss at the End-of-Phase 2 (EOP2) meeting. • Non-concurrence with the Applicant's statement that they did not consider use of SoC antibiotics to be considered a pre-treatment for RBX2660.
06 APR 2015	In a **Type C** meeting, discussions and responses included: Agreements that the Applicant change their (b) (4)-based potency test to a (b) (4)-based assay, with submission of appropriate assay and data for review. Agreement for the Applicant to modify their exclusion criteria to exclude potential donors who may be at a higher risk of multi-drug resistant organisms carriage and submit data on recipient's health status and utility of the diagnostic tests in healthy donors.
08 OCT 2015	**Breakthrough Therapy Designation** was granted based on preliminary clinical data for treatment response to RBX2660 in ongoing studies.
06 JAN 2016	In a **Type B** meeting, discussions and responses included: • Applicant agreed to continue accumulating data from numerous donors to demonstrate long term consistency of the drug product. • CBER reiterated that the indication for RBX2660 in the Phase 1/2 and ongoing Phase 2 clinical studies appeared more

	consistent with secondary prophylaxis against rCDI rather than with treatment or adjunctive treatment. CBER advised the Applicant to clarify their desired indication and noted that the Applicant could change the indication prior to the Phase 3 studies, which should be designed with the proposed indication in mind. • Applicant asked if the BLA could include an initial safety database of 300 subjects followed by a safety update to include an additional 300 subjects during the BLA review period. CBER did not agree but considered it a review issue to be discussed at EOP2 meeting.
22 DEC 2016	**Clinical EOP2 meeting:** • Applicant agreed to revise their proposed indication by removing the statement, ”standard of care course of antibiotics.” CBER suggested that the proposed indication should include the absence of active symptoms in describing those individuals for whom the drug is licensed, and the Applicant tentatively accepted the proposal. • CBER did not agree with the Applicant’s proposed dosing regimen that included a (b) (4) second dose of RBX2660. CBER and the Applicant agreed that the Phase 3 study should be designed to evaluate the to-be-marketed regimen (either a one- or two-dose regimen).
27 SEP 2017	CBER’s Advertising and Promotional Labeling Branch (CBER/APLB) determined that the Applicant’s suggested proprietary name of Rebyota was acceptable.
09 NOV 2017	**Orphan Drug Designation** #DRU-2013-4210 was amended to change the designated indication from “treatment of recurrent *Clostridioides difficile* infection” to “prevention of recurrent *Clostridioides difficil*e infection in individuals with recurrent *Clostridioides difficile* infection.”
22 OCT 2018	In a **Type C Meeting,** discussions included: Due to recruitment difficulties in the Phase 3 program, CBER considered flexible approaches to facilitate product development. CBER’s recommendation to the Applicant included incorporating the result of the Phase 2b Study 2014-01 into the single Phase 3 Study 2017-01, exploring design options such as formal borrowing of external data in a Bayesian framework or an appropriate integrated analysis with the ultimate provision of a proposal that would demonstrate a clinically meaningful treatment effect without lowering the statistical requirement for claiming study success. CBER agreed that one well-designed placebo-controlled Phase 3 study with the Phase 2 studies (2013-001, 2014-01 and 2015-01) could be sufficient for the BLA, if the results of the Phase 3 study were statistically very persuasive and demonstrated a clinically meaningful treatment effect. CBER reiterated the expectation that the BLA include a safety database with a sufficient number of subjects exposed to RBX2660 to adequately assess risks, with a total safety database of 600 subjects (not all of whom needed to be enrolled in controlled trials) considered to be generally

	adequate, provided that no safety signals arose that warranted further investigation.
15 FEB 2019	Statistical advice was provided in follow-up to the October 22, 2018 Type C meeting. CBER requested that the Applicant should revise the historical data borrowing strategy in the Bayesian adaptive design to exclude group A (2 doses of RBX2660) in Phase 2 study (2014-01) and to exclude different dosing regimens in the Phase 3 trial (2017-01) that may cause systematic differences from the intended use. CBER recommended that Applicant consider more stringent success criteria to ensure a positive trial result reflected a statistically persuasive finding, as previously recommended in the October 22, 2018 Type C meeting. CBER recommended that the Applicant take the 10% drop-out rate in Study 2017-01 (version 5.0) into consideration in the Bayesian adaptive design report.
11 SEP 2020	CBER provided responses to the Applicant's questions regarding the ISS SAP. CBER requested a rationale for the Applicant's plan to include Summary of Clinical Efficacy but not to integrate efficacy data across studies. CBER asked the Applicant to clarify how they intended to address the pooling of studies with different durations of follow-up (12 months in Study 2014-01 vs. 24 months in 2017-01). CBER requested that the Applicant provide separate safety analyses for subjects within comparative treatment groups as follows (blinded RBX2660 only, blinded placebo only, blinded RBX2660 followed by open-label RBX2660 and blinded placebo followed by open-label RBX2660). CBER requested that the Applicant provide a separate summary for Study 2019-02 (subjects receiving RBX2660 under Enforcement Discretion) and exclude the study from any pooled assessments, given the variability in safety documentation.
27 JAN 2021	CBER recommended that the Applicant perform additional time-to-event analysis in which subjects who discontinued for CDI-related symptoms prior to assessment of efficacy are counted as having CDI recurrence on date of last assessment, and address whether the Applicant plans to incorporate safety data obtained from the follow-up forms, and if so, how will the results be interpreted.
23 MAR 2021	In a **Pre-BLA Clinical Meeting,** discussions and responses included: CBER's agreement that the totality of data supported BLA submission, with Study 2014-01 formally integrated in the primary analysis of Study 2017-01 in a Bayesian framework. A total safety database of at least 600 subjects who had received at least a single dose of RBX2660 for recurrent CDI was considered by CBER to be adequate, provided no safety signals were found. CBER agreed that no pharmacology, pharmacokinetics, or toxicity studies were required, and none would be included for the BLA submission. CBER's decision to grant Priority Review designation was to be made at the time of BLA filing. CBER determined that a Vaccines and Related Biological Products Advisory Committee (VRBPAC) would be convened for this product. Agreement was reached on a rolling BLA submission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a clinical review without unreasonable difficulty; however, CBER identified several issues during the review.

A study data validation report identified multiple issues with the provided datasets, including data mapping to unexpected domains, missing variables, differences in adverse event report across datasets and inconsistent values for laboratory reports or adverse events.

Reviewer Comment: Some of the identified issues with the datasets were addressed with Information Requests to the Applicant to resolve discrepancies (see Section 5.2) or were explained in the Analysis Data Reviewer's Guide for each study. The remaining issues with the datasets did not preclude the use of the datasets to perform clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the clinical studies 2013-001, 2014-01, 2015-01, 2017-01 and 2019-01 were conducted in accordance with the study protocols and submitted according to relevant regulations in 21 CFR Part 11, 50, 54, 56 and 312 and 45 CFR 160 and 164, and the International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guidance; and applicable Health Canada regulations for the protection of human subjects, and with the ethical principles that have their origin in the Declaration of Helsinki.

The Applicant stated that an institutional review board ensured the ethical, scientific, and medical appropriateness of the retrospective 2019-02 study as per Good Clinical Practice, before it was conducted and approved all relevant documentation.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of five study sites with four clinical investigators (two in Canada). Table 1 lists inspection sites and BIMO inspection classification.

Table 1. Bioresearch Monitoring (BIMO) Inspection Classification

Firm (Type)	Location	Number of Enrolled Subjects	Inspection History	Status of Inspection
Christine Lee (CI) Protocol 2014-01	Hamilton, ON CANADA	30	none	VAI
Christine Lee (CI) Protocol 2017-01	Victoria, BC CANADA	22	none	VAI
Clint Behrend (CI)	Idaho Falls, ID	8 (2014-01) 26 (2017-01)	none	NAI
Sahil Khanna (CI)	Rochester, MN	9 (2014-01) 18 (2017-01)	none	NAI
Robert Orenstein (CI)	Phoenix, AZ	9 (2014-01) 6 (2017-01)	04/2015 VAI	NAI

Source: STN 125739/0 BIMO Late Cycle Reviewer Report, July 21, 2022, Established Inspection Report STN 125739

FMD 145 Cover letter August 8, 2022
CI: Clinical investigator; VAI: Voluntary action indicated; NAI: No active issues

BIMO inspections did not identify any deficiencies that would preclude approval.

Dr. Christine Lee received a final inspection finding of voluntary action indicated based on the Established Inspection Report that noted the following: Instances of protocols not being followed, ineligible subjects enrolled in both protocols, RBX2660 administered to the wrong subject, and instances where a subject was not properly consented. However, none of these discrepancies affected the final efficacy and safety analyses. Please refer to the BIMO reviewer's memo (Kanaeko Ravenell, MS) for details.

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 and list of investigators for the clinical studies submitted to the BLA, and certified that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the studies. The Applicant certified further that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21 CFR 54.2 were reported.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The source material for RBX2660 is defined as Donor Human Stool (DHS). Drug substance is DHS mixed with polyethylene glycol and sodium chloride irrigation prior to filling into the final container to become the drug product as part of a (b) (4) manufacturing process. The drug substance is not stored and has no company code, laboratory code or other non-proprietary name. Composition of the drug substance is presented in Table 2.

Table 2. Composition of the Drug Substance

Component	Quality Standard	Function	Quantity
Source Material (Donor Human Stool)	In-House Reference	Active Ingredient	(b) (4)
Excipient Solution ((b) (4) of PEG/Saline) Polyethylene Glycol 3350 (PEG) 0.9% Sodium Chloride Irrigation (Saline)	(b) (4) (PEG) (b) (4) (Saline	Cryoprotectant (PEG) Processing Aid (Saline)	(b) (4)

Source: STN 125739/0, Quality Overall Summary, page 5/34

The drug product is provided as a single 150-mL dose of fecal microbiota suspension in a 250-mL ethylene vinyl acetate bag with a tube set for rectal administration provided separately. Each 150-mL dose of RBX2660 contains between $1x10^8$ and $5x10^{10}$ colony forming units (CFU) per mL of fecal microbes including $>1x10^5$ CFU/mL of *Bacteroides*. The drug product is referred to below as fecal microbiota suspension and by its laboratory code, RBX2660.

There are two excipients used in the RBX2660 drug substance manufacturing, including sodium chloride irrigation that is sterile, commercially sourced and meets (b) (4)

(b) (4) grade and polyethylene glycol that meets the (b) (4) specification.

Stool donor health is screened through a qualification process that includes initial screening and ongoing monitoring. The initial screening includes informed consent, a Donor Qualification Questionnaire and SARS-CoV-2 Sample Collection Questionnaire. Pathogen testing included blood pathogen testing, DHS testing and testing for SARS-CoV-2 using a nasopharyngeal swab.

The initial blood draw is sent to a Clinical Laboratory Improvement Amendment certified laboratory for testing. Donor blood must conform to the donor specification provided in Table 3.

Table 3. Donor Blood Specification

Test	Method	Method Description	Acceptance Criteria
Treponema Antibodies	(b) (4)	(b) (4)	Nonreactive
(b) (4)			Nonreactive *or* Immunized
Hepatitis B Surface Antigen			Nonreactive *or* Immunized
Hepatitis C Antibody			Nonreactive
Human Immunodeficiency Virus (HIV) (b) (4)			Nonreactive

Source: STN 125739/0, Drug substance quality overall summary, page 7/15

Donors with no immunization record that show a positive (b) (4) response are to complete a second confirmatory blood test with a positive response to the (b) (4). The donor is terminated for a positive hepatitis B surface antigen with no corresponding immunization record, a positive antibody hepatitis C or human immunodeficiency virus (HIV) antibody, a positive treponema antibody response in the absence of subsequent retesting. The donor is terminated if the subsequent treponema retest was positive.

Specification of screening for DHS collected from donors is listed in Table 4.

Table 4. Donor Human Stool Specification

Test	Test Method	Test Description	Acceptance Criteria
(b) (4)			

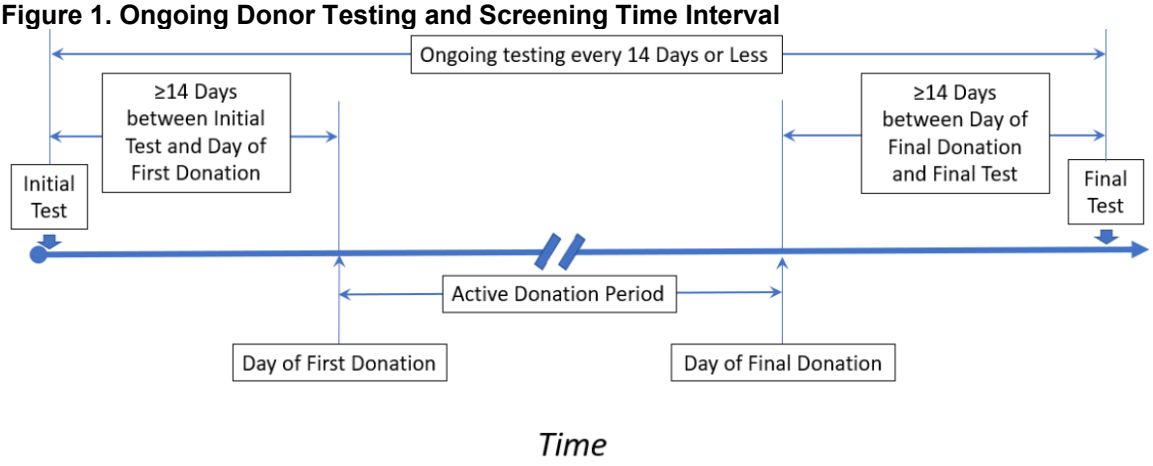
Test	Test Method	Test Description	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Enteropathogenic *E. coli*	(b) (4)	(b) (4)	Negative
Shiga toxin-producing *E. coli*	(b) (4)	(b) (4)	Negative
(b) (4)			
Vancomycin-resistant enterococci (VRE)	(b) (4)	(b) (4)	No VRE isolated
(b) (4)			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	(b) (4)	(b) (4)	No MRSA isolated
(b) (4)			
Extended-spectrum β-lactamase (ESBL)	(b) (4)	(b) (4)	No ESBL-producing organisms isolated
Carbapenem-resistant organism (CRE)	(b) (4)	(b) (4)	No carbapenem non-susceptible organisms isolated

Source: STN 125739/0, Drug substance Quality Overall Summary, page 8-9/15

Donor blood is periodically collected and tested for pathogens following initial qualification. Donors are tested at intervals no greater than 14 days following initial

qualification test for SARS-CoV-2. DHS is rejected if the donor was not tested at least 14 days before donation, 14 days after donation and at intervals no greater than 14 days as shown in Figure 1.

Figure 1. Ongoing Donor Testing and Screening Time Interval



Source: STN 125739/0, Drug substance Quality Overall Summary, page 11/15

Donors positive for SARS-CoV-2 are not able to donate stool for (b)(4) weeks from the date of the positive sample collection. Drug product manufactured from DHS donated (b)(4) weeks prior to the date of positive sample collection is rejected.

Donors do not have dietary restrictions with respect to potential food allergens.

DHS that passed inspection is sampled for pathogen testing and stored at (b) (4) . Samples from (b) (4) DHS lots from a single donor collected over no more than (b) (4) could be (b) (4) into a (b) (4) container for pathogen testing. No (b) (4) of DHS lots occurs for the manufacturing of the drug substance. Drug substance is not stored, and no drug substance stability data were provided.

The CMC reviewers identified potential review issues related to donor screening, release specifications and product stability, and the Applicant addressed these concerns. At the time the clinical review was completed, the CMC reviewers had identified no other issues that would preclude approval. Please see the CMC review for additional information.

4.2 Assay Validation

Each lot of the drug product was assessed according to the specific characteristic of the drug product. The test for a viable bacteria count was included to ensure total bacterial viability of the drug. The Applicant stated the proposed acceptance criteria were based on viability results for clinical batches, statistical evaluation of batch data at long-term frozen storage conditions (-60°C to -90°C), and evaluation at refrigerated storage conditions (2°C to 8°C) utilized to thaw the drug product and store the thawed product until administration.

The CMC reviewers have identified no issues that would preclude approval. Please see the CMC review for additional information.

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical studies were conducted ahead of human studies.

Therefore, in a Written Response to the Pre-BLA clinical meeting request on March 23, 2021, CBER agreed with the Applicant that Module 4 was not needed for the BLA.

4.4 Clinical Pharmacology

RBX2660 is human stool that is biologically sourced and not systemically absorbed. Therefore, no traditional clinical pharmacology studies were conducted.

4.4.1 Mechanism of Action

The exact mechanism of action is not fully understood, but it is thought to involve repopulation and restoration of the composition and diversity of the gut microbiome to suppress *C. difficile* outgrowth and CDI recurrence.

4.5 Statistical

The statistical reviewer verified the Bayesian hierarchical analysis that included formal borrowing of the Study 2014-01 efficacy results into the efficacy results of Study 2017-01. Please refer to the CBER statistical reviewer's memo for details.

4.6 Pharmacovigilance

The Applicant proposed to address the potential risks of infection transmission from the donor to individuals exposed to Rebyota by supplementing routine pharmacovigilance with enhanced screening of pathogens in Rebyota and its source donors, while also evaluating and refining product quality.

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).

Reviewer Comment: The safety profile of RBX2660 did not reveal any safety trends or unexpected severe or serious adverse events in a population that included older

subjects with multiple comorbid conditions at baseline. Please see the pharmacovigilance review for more details.

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

5.1 Review Strategy

The clinical development program for RBX2660 consisted of six studies, all of which were conducted in the United States and Canada and enrolled adults ≥18 years of age with documented rCDI. The totality of evidence submitted to support licensure included two placebo-controlled studies (a Phase 2 Study 2014-01 and Phase 3 Study 2017-01), three open-label studies (Phase 2 studies 2013-001 and 2015-01 and the ongoing Phase 3 Study 2019-01), and one retrospective study (Study 2019-02). All of the prospective studies required subjects to have completed standard-of-care (SoC) oral antibiotic therapy with resolution of symptoms prior to receiving RBX2660. In all studies except 2015-01, an open-label course of RBX2660 was allowed if a subject experienced a CDI recurrence after exposure to the protocol-specified dose(s) of either placebo or RBX2660.

Efficacy: The Applicant initially planned to conduct two independent placebo-controlled Phase 3 trials of approximately 300 subjects each to support licensure. The original primary efficacy analysis in each of the Phase 3 studies was a comparison of the efficacy of RBX2660 versus placebo, allowing for a 20% loss-to-follow-up rate. In July 2013, FDA released draft guidance on the decision to exercise enforcement discretion regarding the requirement of an IND application for use of FMT to treat CDI not responsive to standard therapies. Following CBER's decision to exercise enforcement discretion, the Applicant reported enrollment challenges in the first Phase 3 study (2017-01). In the face of these enrollment challenges, the Applicant anticipated similar challenges in enrolling a second placebo-controlled Phase 3 study and proposed using a single placebo-controlled Phase 3 study as the basis for approval.

The Applicant proposed use of a Bayesian model, the goal of which was to demonstrate a clinically meaningful treatment effect with persuasive statistical evidence, by integrating the data from two double-blinded, randomized, placebo-controlled studies of participants ≥18 years old with documented rCDI and who received the same single-dose regimen intended for licensure. The two studies included in this approach are the Phase 3 study, 2017-01 and the Phase 2 study, 2014-01. Use of an integrated Bayesian efficacy analysis is supported by similarity of the studies, including in study design (both randomized, placebo-controlled, and blinded), study population, product formulation, dosing regimen, and treatment success definitions. Therefore, CBER agreed that the 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, statistical success criteria were established to reflect the levels of statistical persuasiveness as part of the support for demonstrating substantial evidence of clinical effectiveness.

Supportive descriptive efficacy data on recurrence rates at 8 weeks was evaluated in several open-label studies (2013-001, 2015-01, 2019-01) and in a retrospective study, 2019-02. However, interpretation of data from these studies was limited by the lack of concurrent placebo control, inclusion of a different dosing regimen (two doses) than that

intended for licensure, and differences between study populations in the open-label and placebo-controlled studies.

Safety: The integrated summary of safety (ISS) included safety data from pooled analyses of all subjects exposed to at least one dose of RBX2660 in any of the five prospective studies (three Phase 2 studies: 2013-001, 2014-01, 2015-01, or two Phase 3 studies: 2017-01 and 2019-01). Subjects who were enrolled but not treated were not included in the ISS. In addition, 110 subjects who enrolled into the historical control arm of Study 2015-01 and all 78 subjects from the retrospective Study 2019-02 were not included in the safety population. Based on the differences in the study design, the ISS was organized by study groupings as follows:

- Full ISS: Included any subject who was exposed to at least one dose of RBX2660 (blinded or open-label) or placebo from the five prospective studies (2013-001, 2014-01, 2015-01, 2017-01 and 2019-01. See Table 5 and Table 6 for summaries of studies included in the ISS). The Full ISS population was comprised of 749 subjects exposed to at least one dose of RBX2660 and 83 subjects exposed only to placebo. An additional focus of the safety review included the 429 subjects who received one dose of RBX2660 (dosing regimen proposed for licensure). Of the 429 subjects who received one dose of RBX2660, most were enrolled in the ongoing open-label Phase 3 Study 2019-01 (n=211; 49.2%) and the placebo-controlled Phase 3 Study 2017-01 (n=163; 38.0%). The majority of the placebo recipients were enrolled in 2017-01 (n=63; 75.9%).

  Considerations in the interpretation of comparisons between the placebo and RBX2660 groups in the Full ISS population included:
  - The open-label nature of many of the RBX2660 doses
  - Subjects crossing over from placebo to receive open-label RBX2660 due to recurrence of CDI, which may reflect increased risk for adverse events due to underlying risk factors that predispose to rCDI or co-morbidities attributable to the CDI
  - Longer duration of follow-up for subjects who received multiple RBX2660 doses, due to subjects being followed for 6 months after the last dose of study treatment.

  A safety update was submitted in an amendment to the BLA in May 2022 that added 229 subjects exposed to open-label RBX2660 in Study 2019-01, bringing the total pre-licensure clinical trial safety database to 978 subjects. A review of adverse events reported by these additional subjects did not reveal any new safety signals, so the CBER review of the Full ISS remained limited to the 749 subjects included in the initial BLA submission. Safety data for the additional 229 subjects were reviewed separately.

- Blinded ISS: Included any subject exposed to RBX2660 or placebo in the randomized, double-blind, placebo-controlled studies 2014-01 and 2017-01. Subjects in the placebo group who experienced a CDI recurrence and received open-label RBX2660 were removed from the placebo group and counted as being exposed to RBX2660 in the safety analyses. This population was comprised of 83 subjects exposed to placebo and 312 subjects exposed to RBX2660, including 193 who received blinded RBX2660, 48 who received blinded placebo followed by RBX2660, and 71 who received blinded and then

open-label RBX2660. The safety review specifically focused on the 193 subjects who received one or two doses of blinded RBX2660.

A consideration in the interpretation of comparisons between the placebo and RBX2660 groups in the Blinded ISS population is that randomization was no longer preserved between the blinded placebo and RBX2660 groups due to exclusion of subjects who received open-label RBX2660 for CDI recurrence. The observed safety profiles may not be representative of those expected in the placebo or RBX2660 groups.

For each ISS group, safety data were analyzed by treatment (blinding and sequence) and by number of exposures (1 to 4 doses of RBX2660).

All studies included 6 months of safety follow-up from the last dose. Two studies (2014-01 and 2015-01) included follow up through 24 months; data from 6 months through 24 months of follow up were analyzed separately.

The coding dictionary for all studies in the ISS for the AEs was Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. CBER utilized safety review tools, including JMP® (SAS Institute Inc.) and a safety analytic software tool developed by FDA, to evaluate safety data by MedDRA hierarchies and Standardized MedDRA Queries (SMQs).

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

Presented below are the amendments, modules and content that were assigned to and reviewed by the clinical reviewer. The cover letters for each amendment were also reviewed.

- **STN 125739/0** (received May 03, 2021): Part 1 of 3 of the rolling BLA
  - Sections 1.3 (Administrative information including Debarment Certification and Financial Disclosure), 1.4 (Statement of Right to Reference), 1.6 (Meetings), 1.7 (Fast Track), 1.9 (Pediatric Administrative Information; Request for Waiver of Pediatric Studies), 1.12 (Other Correspondence – Request for Comments and Advice, Environmental Analysis and Orphan Drug Designation), 1.18 (Proprietary Names), 2.3 (Quality Overall Summary), 3.2 (Body of Data), 3.3 (Literature References)
- **STN 125739/1** (received July 01, 2021): Part 2 of 3 of the rolling BLA
  - Sections 1.6.3 (Type C Facilities Meeting), 3.2 (Body of Data)
- **STN 125739/4** (received November 30, 2021): Part 3 of 3 of the rolling BLA
  - Sections 1.3 (Administrative information including Field Copy Certification and Financial Certification and Disclosure), 1.6 (Meetings), 1.12 (Other Correspondence – Orphan Drug Designation), 1.14 (Labeling), 1.16 (Risk Management Plan), 2.2 (Introduction), 2.4 (Nonclinical Overview), 2.5 (Clinical Overview), 2.7 (Clinical Summary), 3.2 (Body of Data), 5.2 (Tabular Listing of all Clinical Studies), 5.3 (Clinical Study Reports), 5.4 (Literature References)
- **STN 125739/5** (received December 06, 2021)
  - Sections 1.18 (Proprietary Names)
- **STN 125739/6** (received December 14, 2021)
  - Sections 1.16 (Risk Management Plan)
- **STN 125739/7** (received December 21, 2021)

  - Sections 1.11.3 (Clinical Information Amendment, Responses to CBER Information Request (IR) dated December 16, 2021), 5.4 (Literature References)
- **STN 125739/8** (Received January 14, 2022)
  - Sections 1.3.1.2 (Change in Contact/Agent), 1.11.3 (Statistical Information Amendment, Part 1 Response to CBER Statistical IR dated January 11, 2022), 5.3.5.1 (Study 2017-01 Analysis Datasets)
- **STN 125739/9** (Received January 14, 2022)
  - Sections 5.3.5.1 (Correction to Study 2017-01 Program Files, Response to CBER IR dated January 11, 2022)
- **STN 125739/10** (Received January 20, 2022)
  - Sections 1.11.3 (Statistical Information Amendment, Part 2 response to CBER IR of January 11, 2022), 5.3.5 (Datasets for Study 2013-001, 2014-01, 2015-01 and 2017-01)
- **STN 125739/12** (Received March 07, 2022)
  - Section 1.14.1.3 (Draft Labeling Text), Response to CBER IR February 14, 2022; change of proposed indication in the prescribing information that is consistent with Orphan Designation
- **STN 125739/13** (Received March 20, 2022)
  - Sections 1.11.3 (Clinical Information Amendment), Statistical Information Amendment, Response to CBER IR dated March 16, 2022 – Explanation of discrepancies in primary efficacy analysis in the population used in Bayesian hierarchical model, 5.3.5.1 (Study 2017-01 Bayesian analysis report and Program Files)
- **STN 125739/16** (Received May 13, 2022)
  - Sections 5.3.5.2 (Study Reports of Uncontrolled Clinical Studies). Safety update report covering April 20, 2022 through March 25, 2022 for the ongoing open-label Study 2019-01. Safety data now included 483 treated subjects, with 229 additional subjects treated since the clinical data was filed with the original BLA
- **STN 125739/18** (Received May 18, 2022)
  - Sections 1.11.3 (Clinical Information Amendment), Response to CBER IR, dated April 29, 2022 – Study data standardization and National Drug Code numbers, 1.14 (Draft Labeling), 5.3.5 (Study 2014-01, 2015-01, 2017-01 and 2019-01 Narratives), 5.3.5.3 (ISS Datasets)
- **STN 125739/19** (Received May 20, 2022)
  - Sections 1.11.3 (Clinical Information Amendment), Updated Table for Treatment Emergent Adverse Events previously provided in the CBER Response dated December 21, 2021 and 5.3.5.3 (Updated ISS)
- **STN 125739/20** (Received May 25, 2022)
  - Sections 1.11.4 (Multiple Module Information Amendment). Response to CBER IR, dated April 8, 2022 – Related to Non-proprietary name suffixes
- **STN 125739/21** (Received May 27, 2022)
  - Sections 1.11.3 (Clinical Information Amendment), Section 5.3.5 (Reports of Efficacy and Safety Studies). Statistical Information Amendment, Response to CBER IR dated May 13, 2022 - Adjudication results and datasets for Study 2017-01
- **STN 125739/23** (Received June 22, 2022)

  - Section 1.11.3 (Clinical Information Amendment), Response to IR #14 dated June 08, 2022, Aggregate numbers of cases of Preferred Terms for all adverse events, all serious adverse events and all deaths
- **STN 125739/24** (Received June 30, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to Mid-Cycle communication teleconference held on May 31, 2022. Section 5.3.5 (Reports of Efficacy and Safety Studies), New safety analysis for Study 2017-01 with censoring at CDI recurrence and new safety analysis for ISS, split by treatment course
- **STN 125739/25** (Received July 01, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR dated June 17, 2022, requesting aggregate number of cases of Preferred Terms for all adverse event, serious adverse events and deaths in the assessment of the pharmacovigilance plan. Integrated Bayesian analysis with covariate adjustment. Section 5.3.5 (Reports of Efficacy and Safety Studies), Study 2014-01 and Study 2017-01 analysis datasets
- **STN 125739/28** (Received July 27, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #18 dated July 21, 2022. Section 1.16 (Risk Management Plan), Pharmacovigilance plan. Section 5.3.5 (Reports of Efficacy and Safety Studies). ISS updated Table of Preferred Terms for adverse events, serious adverse events and deaths
- **STN 125739/32** (Received August 12, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #21 dated August 09, 2022. Updated secondary efficacy analysis based on the definition of sustained clinical response during 6 months of follow-up.
- **STN 125739/33** (Received August 18, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #22 dated August 09, 2022. Explanations on inspection violations for clinical sites issued on form FDA 483. Assessments of the potential impact of the observations on the accuracy of efficacy and safety data analyses in studies 2014-01 and 2017-01.
- **STN 125739/38** (Received September 28, 2022)
  - Section 1.12 (Cover Letters), The Applicant submitted notification of change in ownership from Rebiotix, Inc. to Ferring Pharmaceuticals Inc., effective September 23, 2022.
- **STN 125739/39** (Received September 29, 2022)
  - Section 1.12 (Cover Letters), Ferring Pharmaceutics Inc., accepted ownership of contents in BLA 125739, effective September 23, 2022.
- **STN 125739/40** (Received September 30, 2022)
  - Section 1.12 (Clinical Information Amendment), Response to item #8 of IR #25, dated September 13, 2022. Response included recommendations on changes to donor screening to mitigate potential risks of monkeypox infections associated with FMT in ongoing RBX2660 studies.
  - Section 5.3.5 (Reports of Efficacy and Safety Studies). Updated study 2014-01 Tabulated datasets and updated study 2019-01 informed consent form.
- **STN 125739/41** (Received October 03, 2022)
  - Section 1.11.4 (Multiple Module Information Amendment), Response to IR dated September 23, 2022. Response to the Agency's request to

provide aggregate numbers of cases of Preferred Terms for all AEs, all TEAEs, all serious TEAEs and all TEAEs.

- **STN 125739/43** (Received October 7, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #28 dated September 23, 2022. Section 5.3.5 (Reports of Efficacy and Safety Studies). Safety analysis for study 2017-01 that included AEs within 8 weeks and 6 months of receiving RBX2660. Combined safety analysis of study 2014-01 and study 2017-01 was included.
- **STN 125739/44** (Received October 11, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to item # 8 of IR #25, dated September 28, 2022. The Agency granted an extension to # 8 of IR #25 at the time the Applicant responded to IR #25. This is the response to item #8 of IR #25, dated September 28, 2022. Section 5.3.5. (Reports of Efficacy and Safety Studies). Clarification of the AE dataset, specifically the solicited AEs, what was included and under which analysis file they were listed.
- **STN 125739/46** (Received October 21, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #30, dated October 14, 2022. Protocol synopsis for a voluntary safety surveillance postmarketing study that will further characterize the safety profile of RBX2660.
- **STN 125739/49** (Received November 01, 2022)
  - Section 1.6 (Risk Management Plan), revised Pharmacovigilance plan.
- **STN 125739/51** (Received November 03, 2022)
  - Section 1.14 (Labeling), Response to Draft Labeling Revisions #1.
- **STN 125739/52** (Received November 04, 2022)
  - Section 1.11.3 (Clinical Information Amendment, Response to IR #36, dated November 02, 2022. Clarification on the number of study sites listed in study 2017-01 clinical study report.
- **STN 125739/53** (Received November 04, 2022)
  - Section 1.14 (Labeling), Response to Carton and Container Labeling Revisions #1.
- **STN 125739/55** (Received November 07, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR # 35, dated November 2, 2022. Revised protocol synopsis for the voluntary safety surveillance postmarketing study.
- **STN 125739/56** (Received November 14, 2022)
  - Section 1.11.3 (Clinical Information Amendment), Response to IR #38, dated November 09, 2022. The Applicant was informed of the FDA regulations under 21 CFR 600.80, which required that the Applicant submit periodic safety reports (Periodic Adverse Experience Reports; PAERs). The Applicant acknowledged receipt of the information.
- **STN 125739/57** (Received November 21, 2022)
  - Section 1.14 (Labeling). Response to Draft Labeling Revisions #2, dated November 16, 2022.
- **STN 125739/58** (Received November 21, 2022)
  - Section 1.14 (Labeling). Response to Draft Carton and Container Labeling Revisions #2.
- **STN 125739/59** (Received November 21, 2022)

- Section 3.2.S.2.3 (Control of Materials). Donor Qualification Questionnaire Review and Donation Questionnaire Review documents were revised to comply with CBER requests regarding monkeypox.

5.3 Table of Studies/Clinical Trials

All studies were conducted in the United States and Canada in adults ≥18 years of age with documented rCDI. All the prospective studies required subjects to have received SoC oral antibiotic therapy and be CDI-symptom-controlled prior to initial treatment with RBX2660 or placebo. In all studies except 2015-01, a second course of treatment (i.e., open-label RBX2660) was allowed if the subject experienced a CDI recurrence after the first course of treatment. Features of each study design are presented in Table 5 and Table 6.

Table 5. Double-Blind, Randomized, Placebo-Controlled Clinical Studies Submitted to RBX2660 BLA

Design Feature	Study 2014-01	Study 2017-01
NCT number	02299570	03244644
Number of RBX2660 exposures	1-4	1-2
Phase	2	3
Study design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Sites, countries	21 sites US/Canada	44 sites US/Canada
Initiation date	10 Dec 2014	31 Jul 2017
Completion date	13 Nov 2015	03 Aug 2020
Enrolled	150	320
Treated	128	267
Completed study	91	234
Number of previous CDIs, including qualifying events	At least 2 recurrences after a primary episode (i.e., at least 3 episodes, completed at least 2 rounds of SoC antibiotics therapy OR at least 2 severe CDI resulting in hospitalization	At least 1 recurrence after a primary episode (i.e., at least 2 episodes, completed at least 1 round of SoC antibiotics therapy OR at least 2 severe CDI resulting in hospitalization
Primary efficacy endpoint: treatment success	The absence of CDAD[a] 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.	The recurrence of CDI diarrhea within 8 weeks of blinded treatment.
Antibiotic washout (hours)	24-48	24-72
Efficacy endpoint adjudication	Data safety monitoring board	EAC
Treatment received	Placebo or RBX2660	Placebo or RBX2660
Randomization treatment groups: doses treatment regimen	1:1:1 ratio Group A: 2 doses RBX2660 Group B: 2 doses Placebo Group C: 1 RBX2660 dose/ 1 placebo dose 7±2 days apart	2:1 ratio 1 dose RBX2660 1 dose placebo
Optional second treatment course	Yes, up to 2 doses	Yes, 1 dose
Efficacy analysis	8 weeks[b]	8 weeks and 6 months

Design Feature	Study 2014-01	Study 2017-01
Safety follow-up (months)	24	6
Key contribution to clinical development program	Dose-finding Integrated data for efficacy, Historical data for 2017-01 analysis using Bayesian hierarchical model Safety	Primary evidence of efficacy Sustained clinical response through 6 months Safety

Source: Reviewer's Table, Adapted from STN 125739/0, Clinical Overview
Abbreviations: CDI=*Clostridioides difficile* infection, rCDI=recurrent *Clostridioides difficile* infection, SoC=Standard of care, EAC=Endpoint Adjudication Committee, IBD=Inflammatory Bowel Disease (include ulcerative colitis, Crohn's Disease), IBS=Irritable Bowel Syndrome (includes microscopic colitis, celiac disease and immunocompromised conditions), US=United States.
a. *Clostridioides difficile*-associated diarrhea (CDAD) is defined as the passage of three or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days.
b. After second enema

Table 6. Non-Randomized Clinical Studies Submitted to RBX2660 BLA

Design Feature	Study 2013-001	Study 2015-01	Study 2019-01	Study 2019-02
NCT number	01925417	02589847	03931941	Not applicable
Number of RBX2660 exposures	1-2	1-2	1-2	1-2
Phase	2	2	3	Not Applicable
Study design	Open-label, uncontrolled	Open-label, historical controlled	Open-label, uncontrolled	Retrospective, open-label, uncontrolled, Enforcement Discretion
Sites, countries	11 sites US	29 sites US/Canada	29 sites US/Canada	5 sites US
Initiation date	15 Aug 2013	15 Oct 2015	30 Jul 2019	11 Nov 2015
Completion date	16 Dec 2013	03 Mar 2017	Ongoing; Data cutoff: 20 Apr 2021	01 Mar 2020
Enrolled	40	162	293	94
Treated	34	149	254	94
Completed study	31	107	123 (data cutoff April 2021)	64
Number of previous CDI/CDADs, including qualifying events	At least 2 recurrences after a primary episode (i.e., at least 3 episodes, completed at least 2 rounds of SoC antibiotics therapy OR at least 2 severe CDAD[a] resulting in hospitalization	At least 2 recurrences after a primary episode (i.e., at least 3 episodes, completed at least 2 rounds of SoC antibiotics therapy OR at least 2 severe CDI resulting in hospitalization	rCDI not defined, relied on investigator opinion. Broad population including IBS, IBD, immunocompromised conditions to reflect clinical practice	CDI event that prompted first RBX2660 under Enforcement Discretion defined as "qualifying CDI event." rCDI defined as "on study CDI event" identified in the subject's medical record by a positive laboratory stool test for CDI, microbiota therapy or anti-infective therapy for CDI treatment or suspected CDI diarrhea

Design Feature	**Study 2013-001**	**Study 2015-01**	**Study 2019-01**	**Study 2019-02**
Primary efficacy endpoint: treatment success	The resolution of subject's symptoms of CDAD[a] 56 days after receipt of RBX2660	The recurrence-free rate of CDI diarrhea without the need for retreatment with *C. difficile* anti-infective therapy or FT through 56 days after completion of study treatment with RBX2660 compared to the recurrence-free rate observed in the study population to the recurrence-free rate from antibiotic-treated historical controls	The absence of CDI through 8 weeks after treatment	The absence of CDI through 8 weeks after treatment
Antibiotic washout (hours)	24-48	24-48	24-72	Not applicable
Efficacy endpoint adjudication	None	None	EAC	None
Treatment received	1 dose RBX2660	2 doses RBX26607±2 days apart	1 dose RBX2660	1 or 2 doses RBX2660
Optional second treatment course?	Yes	No	Yes	Investigator discretion
Efficacy analysis	8 weeks	8 weeks[b]	8 weeks and 6 months	8 weeks and 6 months
Safety follow-up (months)	6	24	6	6
Key contribution to clinical development program	Clinical proof of concept and safety	Supportive evidence of efficacy and safety	Supportive efficacy, persistence of efficacy, and safety Expanded rCDI patient population (e.g., IBD, IBS, and immunocompromised)	Supportive efficacy, persistence of efficacy Expanded rCDI patient population

Source: Reviewer's Table, Adapted from STN 125739/0, Clinical Overview
Abbreviations: CDI=*Clostridioides difficile* infection, CDAD=*Clostridioides difficile* associated diarrhea, rCDI=recurrent *Clostridioides difficile* infection, SoC=Standard of care, EAC=Endpoint Adjudication Committee, IBD=Inflammatory Bowel Disease (include ulcerative colitis, Crohn's Disease), IBS=Irritable Bowel Syndrome (includes microscopic colitis, celiac disease and immunocompromised conditions), US=United States.
a. CDAD defined as the presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days and at least one
positive stool test for the presence of toxigenic *C. difficile* or its toxins, or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.
b. Efficacy outcomes were only evaluated up to 8 weeks after the last enema

5.4 Consultations

CBER consulted the Office of Orphan Products Development (OOPD) on January 13, 2022, to provide input on the RBX2660 indication. The Applicant submitted a package insert (PI) with the following indication: "to reduce recurrence of *Clostridioides difficile* infection (CDI) in adults following antibiotic treatment for first or more recurrence of CDI." Per the Applicant's orphan designation letter granting orphan status and Form 365h the indication is "to reduce recurrence of *Clostridioides difficile* following antibiotic for recurrent *Clostridioides difficile* infection following antibiotic treatment for recurrent *C. difficile* infection." According to OOPD the proposed indication in the PI was not consistent with the RBX2660 indication that received orphan designation status.

CBER sent an Information Request to the Applicant on February 14, 2022, requesting that the Applicant revise the PI to include a proposed indication that is supported by the data submitted in the BLA. The Applicant submitted a PI with a revised indication that is both consistent with their orphan designation indication and supported by the data submitted in the BLA.

5.4.1 Advisory Committee Meeting

On September 22, 2022, the VRBPAC convened to discuss the safety and effectiveness of RBX2660. The two discussion items included in the agenda were: 1) the adequacy of the available data 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; and 2) the adequacy of the available data to support the safety of RBX2660 when administered in adults 18 years of age and older following antibiotic treatment for recurrent CDI.

Of the 17 voting VRBPAC members, 13 voted that the data supported the effectiveness of RBX2660, while 4 members voted that they did not. VRBPAC members generally expressed concerns with the limitations of the data supporting effectiveness, including the study design, estimated effectiveness, and lack of diversity among trial participants. Most members considered that the need for an additional treatment modality for individuals with rCDI was sufficient to vote yes, despite these limitations. Regarding safety, 12 members voted that the data supported safety of RBX2660, 4 voted that they did not, and 1 member abstained from voting. Members expressed concerns with the size of the safety database and some numerical imbalances in adverse events observed between RBX2660 and placebo groups, but the majority of voting members concluded that the safety data were sufficient in the context of the intended use, despite uncertainties.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1, Study 2014-01

Study Title: A Phase 2b prospective, randomized, double-blinded, placebo-controlled study to demonstrate the efficacy and safety of RBX2660 (fecal microbiota suspension) for the treatment of recurrent *Clostridium difficile* Infection (CDI).

Protocol ID: 2014-01
ClinicalTrials.gov ID: NCT02299570
Date First Subject Enrolled: December 10, 2014
Date Study Completion: January 05, 2018
Database Lock Point: September 30, 2020
Date of Final Study Report: March 26, 2020

6.1.1 Objectives

Primary objective: To assess the efficacy of two enemas of RBX2660 vs. two enemas of placebo.

Secondary objectives:

1. To evaluate the efficacy of 1 enema of RBX2660 vs. 1 enema of placebo vs. 2 enemas of placebo.
2. To evaluate the efficacy of 2 enemas of RBX2660 vs. 1 enema of RBX2660 and 1 enema of placebo.
3. To assess the safety of RBX2660
4. To assess the quality of life as measured by the SF-36 Form
5. To assess the efficacy of *C. difficile* infection therapies administered to confirmed treatment failures

6.1.2 Design Overview

Study 2014-01 was a Phase 2b, prospective, randomized, double-blinded, placebo-controlled, three-arm study. It was designed to assess the efficacy and safety of RBX2660 following two doses administered 7±2 days apart in adults ≥18 years old with rCDI. Subjects with rCDI at study entry had either a) had at least two recurrences after a primary episode and had completed at least two rounds of SoC oral antibiotic therapy or b) had at least two episodes of severe CDI resulting in hospitalization. A total of 150 subjects were enrolled, 133 of whom were randomized.

Of the 133 subjects, 106 were enrolled following implementation of version 4 of the protocol (dated January 20, 2015), which included the following changes:

- Definition of rCDI for study entry changed to "at least one positive stool sample for *C. difficile* within 60 days prior to or on the date of enrollment"
- Inclusion criterion #3 on antibiotic use prior to receiving study treatment clarified to "already taking or will start a course of antibiotics to control rCDI at time of enrollment"
- Inclusion criterion #4 on a positive stool test was changed from the presence of *C. difficile* from "within 30 days" to "within 60 days" prior to enrollment
- 24 to 48 hour wash-out period after completion of antibiotics requirement was added
- "Prescribe/continue antibiotics for CDI symptom control" was added
- Complete blood count (CBC) was added to baseline blood testing
- Window between randomization assignment and date of first treatment increased from two to four working days
- Specific criteria for the assessment of causality for adverse events was added
- Responsibility for review of AEs and assessment of triggering stopping rules changed from Medical Monitor to the Applicant's clinical development team

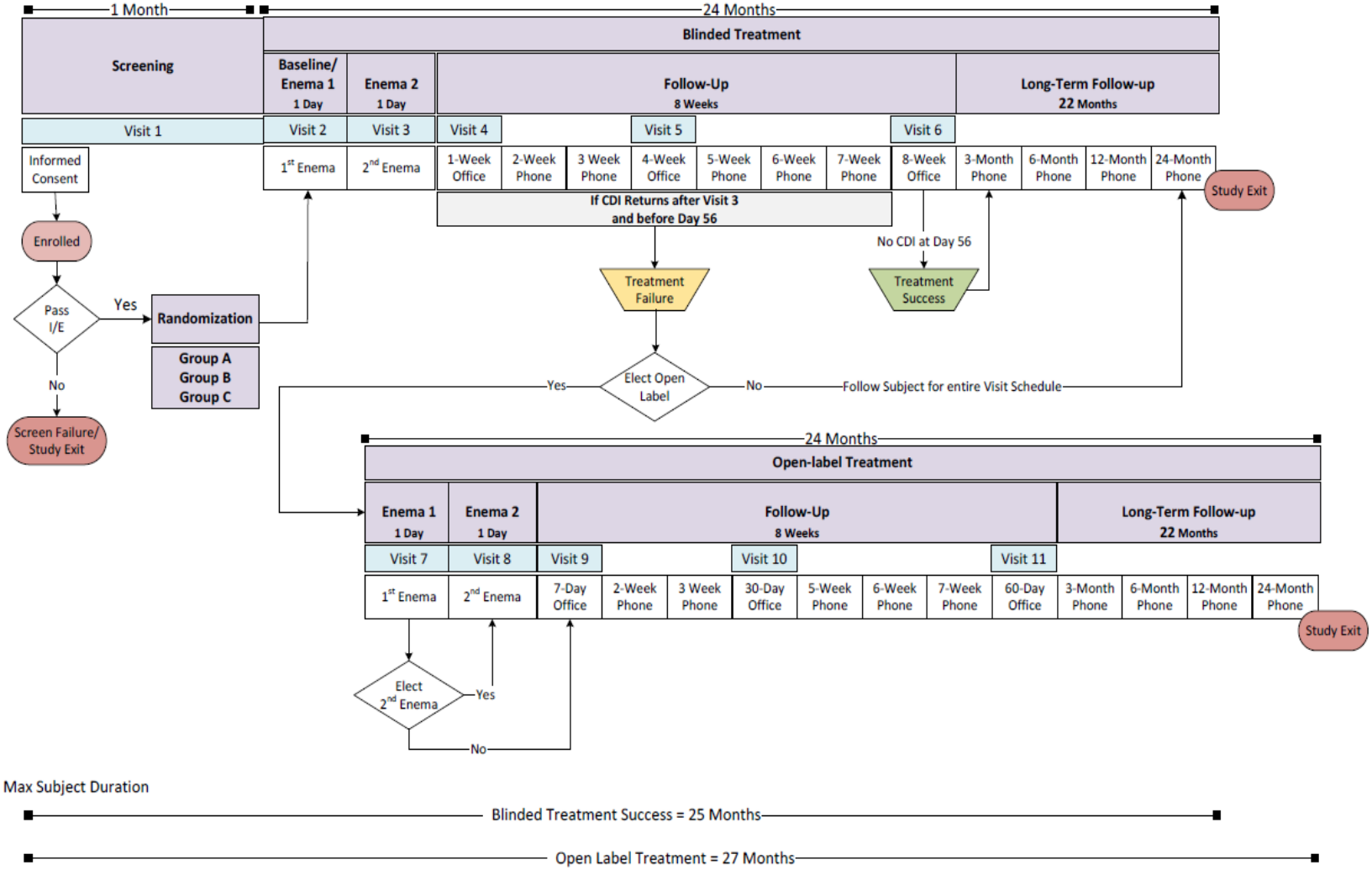
Subjects were on antibiotics to control rCDI symptoms at the time of enrollment, followed by a 24 to 48-hour washout period prior to receiving the first assigned study treatment. Symptom control, defined as the absence of CDI diarrhea, was required prior to being randomized to treatment. Subjects and site personnel who performed study follow-up procedures were blinded to the randomization assignment and delivered therapy.

Subjects were randomized 1:1:1 to:

- Group A: 2 enemas of RBX2660,
- Group B: 2 enemas of placebo, or
- Group C: 1 enema of RBX2660 and 1 enema of placebo

One complete assigned treatment course 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. The study design is shown in Figure 2.

Figure 2. Design of Study 2014-01



Source: STN 125739, Clinical Study Report Study 2014-01, page 24/2092

Treatment failures (as determined by the study investigator at the time of CDI recurrence) in any study group were eligible to receive open-label treatment with RBX2660, and these subjects could elect to receive up to two doses of RBX2660 enemas 7±2 days apart or another therapy deemed most appropriate by their study investigator. If a subject received treatment with RBX2660 during the open-label portion of the study, the follow-up visits, phone calls and completion of a new post-treatment subject diary occurred according to the same schedule as the blinded portion of the study.

6.1.3 Population

Key inclusion criteria:

- Adults ≥18 years old
- Medical record documentation of rCDI either: a) at least 2 recurrences 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
- Already taking or was starting a course of antibiotics to control rCDI symptoms at the time of enrollment. Subject's rCDI symptoms had to be controlled (<3 loose stools/day) while on antibiotics.
- A positive stool test for the presence of toxigenic *C. difficile* within 60 days prior to enrollment

Key exclusion criteria:

- A known history of continued *C. difficile* associated diarrhea (CDAD) despite being on a course of antibiotics prescribed for CDI treatment
- Antibiotic therapy required for a condition other than CDI
- Previous fecal transplant prior to study enrollment
- History of inflammatory bowel disease (IBD), e.g., ulcerative colitis, Crohn's disease or microscopic colitis
- Diagnosis of irritable bowel syndrome (IBS) as determined by Rome III criteria
- History of chronic diarrhea and celiac disease
- Disease symptoms caused by a confirmed intestinal pathogen other than C. difficile
- Colostomy
- Intraabdominal surgery within the last 60 days
- Evidence of active, severe colitis
- History of short gut syndrome or motility disorders
- Required regular use of medications to manage bowel hypermotility
- Life expectancy of <12 months
- Compromised immune system (e.g., HIV infection; AIDS-defining diagnosis or CD4 <200/mm^3; inherited/primary immune disorders; immunodeficient or immunosuppressed due to a medical condition or medication; current or recent (<90 days) treatment with chemotherapy; or current or recent (<90 days) treatment with immunosuppressant medications.
- Taking systemic steroids (≥20 mg a day or prednisone-equivalent) or is expected to be on steroids after enrollment through 8 weeks after completing the assigned study treatment.
- An absolute neutrophil count of <1000 cells/µL.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study treatments included RBX2660 (see Section 4.1 for a description of study drug product) and placebo (normal saline and cryoprotectant in the same proportions as in RBX2660), administered via enema.

6.1.5 Directions for Use

Each dose of RBX2660 or matched placebo was supplied in a brown enema bag within a brown opaque sleeve that was to remain in place over the bag and tubing during administration and disposal to preserve the blind. RBX2660 was shipped frozen to the site in a temperature-controlled carton and stored under the control of the investigator prior to administration.

The kit containing the study product was shipped to the site in a sealed carton that remained sealed at the site until opened at the time of administration by the investigator.

6.1.6 Sites and Centers

In Study 2014-01, if an investigative site was unable to enroll a sufficient number of subjects (where enrollment was too low to detect differences in treatment success in specified covariate analyses), it was combined with other smaller sites to create larger "similar" sites, which the Applicant termed "pseudo-sites." Eligible sites were pooled sequentially in ascending order of site number until a sufficient number of subjects was reached (at least 10).

A total of 97 subjects were enrolled at 19 study sites in the US, with a median of 5 subjects at each site (range 1-12 subjects). A total of 31 subjects were enrolled at 2 sites in Canada (7 and 24 subjects, respectively).

6.1.7 Surveillance/Monitoring

Table 7. Schedule of Events, Study 2014-01

Activity	Visit 1 Screen-ing	Visit 2 Baseline/ First Enema	Visit 3 Second Enema (1 week after Visit 2)	Visits 4-6 1- (±3 days), 4- and 8-Week Assess-ments	Phone call Weeks 2, 3, 5, 6, and 7[3]	Phone call for AEs at 3, 6, 12, and 24 months after Visit 3[4]	Visit 7[1] Open-label Enema (if CDI recurs at <56 days after Visit 3)	Visit 8[1] Open-label Enema((1 week after Visit 7)	Visits 9-11 1- (± 3 days), 4- and 8-Week Assessment	Phone call Weeks 2, 3, 5, 6 and 7[3]	Phone call for AEs at 3, 6, 12, and 24 months after Visit 8[4]
Informed consent	X										
Patient history	X										
Prescribe/continue ant biotics for CDI symptom control	X										
Modified physical exam		X									
Stool sent by subjects for testing and archiving	X			X		At 6, 12, and 24 months	X		X		At 6, 12, and 24 months
CBC testing	X[5]	X[5]									
C. difficile testing	X[6]						X[6]				
Stool and blood testing		X									
Pregnancy testing	X	X	X				X	X			
Form SF-36	X			X[1]			X[1]		X[1]		
Eligibility criteria confirmed	X	X									
Randomization assignment	X										
24-48hr washout confirmed		X									
Enema administered		X	X				X	X			
Recurrence of CDI symptoms assessed		X	X	X	X	X	X	X	X	X	X
Vital signs assessed	X	X	X				X	X			
Subject Diary reviewed	X	X	X	X			X	X	X		
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X
Adverse events assessed	X	X	X	X	X	X	X	X	X	X	X
SAEs assessed	X	X	X	X	X	X	X	X	X	X	X
Solicited AEs assessed[3]	X	X	X	X[2]			X	X	X[2]		

Source: STN 125739, 2014-01 Clinical Study Report, page 25-26/2092

1. Declared Treatment Failures may have elected to receive 1 or 2 enemas of open-label RBX2660. If one open-label enema was administered, follow-up schedule was based on the date of the single enema.
2. Solicited events were collected daily through 7 days after a treatment with the assigned study enema (blinded portion) or after a treatment with RBX2660 (open-label portion).
3. Weekly phone calls that occur out of window are not a protocol deviation; however, missed weekly calls were a protocol deviation.
4. 3-, 6-, 12-, and 24-month phone calls that were out of window or were missed were protocol deviations. Adverse events including serious adverse events and the onset of new chronic diseases were assessed at the 3-, 6-, and 12-month phone calls. The 24-month call assessed for SAEs and the new onset of chronic disease.
5. For absolute neutrophil count at Visit 1. Repeated CBC at Visit 2. 6. Performed within 60 days of enrollment and if CDI recurrence was suspected.

Safety assessments included:

1. Solicited events were collected daily via subject diary through 7 days after a treatment with the assigned study enema (blinded portion) or after a treatment with RBX2660 (open-label portion). Solicited events included gas (flatulence), abdominal distension or bloating, increased diarrhea, abdominal pain or cramping, constipation, rectal bleeding, irritation or pain, nausea, vomiting, fever ≥38.0° C (100.4°F), and chills. Solicited events reported as severe or life-threatening were reported as adverse events.
2. All adverse events (AEs), including serious adverse events (SAEs) were collected at weeks 1, 4 and 8 and on months 3, 6 and 12. SAEs were collected at month 24. An AE was considered serious if it was life threatening, resulted in death, in-patient hospitalization ≥24 hours or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or was a congenital anomaly/birth defect.
3. Frequency of major complications of CDAD including death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, or intensive care unit (ICU) admission.

Adverse events were graded by the site investigators for severity with the adapted Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events and Addendum 3: Rectal Grading Table for Use in Microbicide Studies (May 2012).

An independent Data Safety Monitoring Board (DSMB) was appointed to ensure safety of enrolled subjects and to make recommendations to the sponsors regarding the continuation, modification or termination of the study. The DSMB consisted of two physicians specialized in infectious diseases or gastroenterology who had experience managing subjects with rCDI and were not investigators in the study, plus a biostatistician who was not involved with study design or analyses.

6.1.8 Endpoints and Criteria for Study Success

Efficacy

The primary efficacy study endpoint was treatment success, defined as the absence of CDAD without the need for retreatment with *C. difficile* anti-infective therapy or fecal transplant at 56 days, comparing Group A (2 enemas RBX2660 administered 7±2 days apart) and Group B (2 enemas Placebo administered 7±2 days apart). CDAD was defined as the passage of three or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days. Treatment outcome was initially determined by the site investigator. The DSMB reviewed each case of investigator-declared outcome (blinded to individual treatment assignment) and was the final adjudicator of treatment outcome for the efficacy analyses.

Treatment failure (CDI recurrence) was defined as:

- The presence of CDI diarrhea, with or without other CDI symptoms, at <8 weeks after administration of the last assigned study dose
- A positive stool test for *C. difficile*
- Need for re-treatment for CDI, and
- No other cause for CDI symptoms was identified

Secondary and other efficacy endpoints:

- 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
- 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
- Time to CDAD recurrence after completion of the assigned study treatment for Group A vs. Group B
- Time to CDAD recurrence after completion of the assigned study treatment for Group C vs. Group B
- Time to CDAD recurrence after completion of the assigned study treatment for Group A vs. Group C
- Treatment success during the open-label period
- Time to CDAD recurrence during the open-label period

Reviewer Comment: CBER agreed with the Applicant that CDAD within 56 days of treatment would be considered a CDI recurrence, in line with the CDC definition that considers CDI cases with a positive C. difficile *stool between 2 to 8 weeks of the last positive infection to be recurrent episodes.*[21] *An additional secondary endpoint of SF-36 scores obtained at the 1, 4 and 8 week assessment visits during the blinded period as compared to baseline was included in the study but is not included in the clinical review, as the clinical review focused on safety and on primary and secondary efficacy endpoints CBER considered most pertinent to the indication and prescribing information to be approved.*

Safety

- The frequencies and severity grades of solicited AEs in each treatment group from the first day of assigned study treatment through seven days following the last enema of assigned study treatment
- Adverse events including serious adverse events and the onset of new chronic diseases categorized by frequency, severity, seriousness, and causality
- Frequencies of major complications of CDAD including death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, or ICU admission

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size

To demonstrate 80% success in the 2-enema RBX2660 group (Group A) vs. 40% success in the 2-enema placebo group (Group B), and a non-comparative evaluation of success in subjects who received 1-RBX2660 enema and 1 placebo enema (Group C), 105 subjects were required [power 90%; Type I error: 0.05 (two-sided)]. An additional 12 subjects were enrolled to allow for a 10% loss-to-follow up rate, for a total of approximately 117 subjects (39 per group). Enrolled subjects who withdrew from the study prior to randomization were replaced without counting toward the sample size cap.

Statistical Analysis Plan (SAP)

The final version of the statistical analysis plan (SAP) was submitted to CBER on December 5, 2015, with additional details related to the completion of the analysis of the primary endpoint and available safety data provided on March 30, 2016. According to the SAP, the primary analysis was to be completed by an unblinded team consisting of

[21] *Clostridioides difficile* Infection (CDI) Tracking | HAIC Activities | HAI | CDC. Accessed on April 15, 2022

an independent clinical consultant and statistical team using efficacy and safety data reported from the clinical sites and confirmed by the DSMB. An interim analysis of efficacy objectives using 127 treated subjects in the ITT population was conducted. The RBX2660 clinical study team remained blinded to individual treatment assignments through the database lock.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

There were four analysis populations in Study 2014-01 as presented in Table 8.

Table 8. Analysis Population Definitions for Study 2014-01

Analysis Population	Definition
Intent-to-Treat Population (ITT)	All randomized subjects, regardless of whether they completed their assigned study treatment. Subjects were analyzed according to their randomized treatment assignment rather than the actual treatment received.
Modified Intent-to-Treat Population (mITT)	Subjects who completed at least one dose of study treatment, regardless of which treatment received, excluding subjects who discontinued from the study during the blinded period prior to evaluation of treatment failure or success for any reason and excluding deviations from any inclusion/exclusion criteria.
Per-Protocol Population (PP)	All ITT subjects who received the treatment to which they were randomized and were evaluable for treatment success 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 success • expelled a moderate or large amount of dose • were adjudicated by the DSMB as treatment failures without meeting all 4 criteria for failure and • had major protocol deviations as determined by a clinical review of subject data prior to database lock • had eligibility criteria deviations
Safety Population	The population of randomized subjects who received any study treatment. Subjects were analyzed according to the treatment they actually received.

Source: STN 125739, Adapted from Summary of Clinical Efficacy, page 16-17/68

The primary and the first two secondary efficacy analyses were completed on the ITT, mITT and Per-Protocol (PP) populations. All other efficacy analyses were completed on the mITT and PP population.

6.1.10.1.1 Demographics

Table 9 shows the demographic characteristics of subjects in Study 2014-01. At baseline, the study population was mostly White, not Hispanic, and were being treated with vancomycin at screening. Slightly more females than males participated in the study. Overall, most subjects (89.8%) were reported to have received vancomycin alone for their qualifying rCDI episode, with a smaller percentage receiving vancomycin in combination (0.8% of subjects), fidaxomicin (4.7% of subjects), or other treatments. No major imbalances between the treatment groups were identified.

Table 9. Demographic and Baseline Characteristics, Study 2014-01, Safety Population

Characteristic	Group A 2 Dose RBX2660 N=42	Group B 2 Dose Placebo N=44	Group C 1 Dose RBX2660 1 Dose Placebo N=42
Age	--	--	--
Mean years [range]	62.8 [24 – 89]	58.8 [19 – 92]	61.4 [18 – 88]
<65, n (%)	19 (45.2)	25 (56.8)	24 (57.1)
≥65, n (%)	23 (54.8)	19 (43.2)	18 (42.9)
Sex, n (%)	--	--	--
Male	17 (40.5)	14 (31.8)	18 (42.9)
Female	25 (59.5)	30 (68.2)	24 (57.1)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	1 (2.4)	2 (4.5)	1 (2.4)
Not Hispanic or Latino	40 (95.2)	42 (95.5)	40 (95.2)
Not Reported	1 (2.4)	0 (0)	1 (2.4)
Race, n (%)	--	--	--
Black/African American	0 (0)	1(2.3)	2 (4.8)
White	42 (100)	43 (97.7)	40 (95.2)
Other	0 (0)	0 (0)	0 (0)
Antibiotic use at screening, n (%)	--	--	--
Vancomycin	39 (92.9)	40 (90.9)	36 (85.7)
Fidaxomicin	1 (2.4)	3 (6.8)	2 (4.8)
Other	2 (4.8)	1 (2.3)	4 (9.5)

Source: STN 125739, Clinical Study Report for Study 2014-01, Table 8, page 54/2092

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

An average of four CDI episodes was reported per subject. The disease history for some subjects was missing and reported to be permanently unavailable by the Applicant, given the length of time from some early CDI episodes with diagnosis and treatment given at different hospitals.

Reviewer Comment: In general, there were no clinically significant differences noted in disease history across the randomized treatment groups. However, a full assessment of the comparability of medical history across the treatment groups is precluded by missing data.

6.1.10.1.3 Subject Disposition

A total of 150 subjects were enrolled at 21 clinical sites in the United States (US) and Canada. Of the enrolled subjects, 11.3% (n=17) did not proceed to randomization (screen failures) and exited from the study. Of the 133 randomized subjects, five subjects withdrew prior to treatment for the following reasons: “withdrawal by subject or investigator” (n=4) and death (n=1). One of the subjects who withdrew prior to treatment was re-enrolled, randomized, treated, and analyzed according to the second randomized assignment. In total, 128 subjects received blinded treatment, comprising the safety population. Of these 128 subjects, four were lost to follow up, two were ineligible, and one had an unsuccessful enema, resulting in a mITT population of 121 subjects. Of these 121 subjects, 38 were excluded (n=1 unintended dose switch, n=3 prohibited medications, n=14 single enemas, n=15 moderate/large expulsion, n=5 indeterminate) from the PP population (n=83).

Protocol deviations

A total of 553 deviations were reported for 122 subjects, some of whom had protocol deviations in multiple categories. The most common protocol deviations related to

missed or out of window follow up visits or phone calls (n=271) and study procedures (labs, diaries, medications, antibiotics, out of window IP administration) not done per protocol (n=278). Other protocol deviations included eligibility criteria not met (n=3), informed consent issue (n=10), AE/SAE reported out of window (n=6), and other (n=54).

Reviewer Comment: Of the 10 informed consent issues, seven involved subjects signing the incorrect version of the form (corrected by obtaining signature on correct version), three involved not dating the HIPAA form, and one form was missing study site staff name, signature, or date. All subjects with eligibility criteria deviations were included in the SP and ITT analysis of efficacy but are removed from the mITT and PP efficacy analyses. The remaining deviations would not be expected to affect subject safety.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The efficacy results are summarized in Table 10. In the ITT population, the treatment success rate in Group A, the 2-dose RBX2660 group, was 55.6% (n/N=25/45), compared to 43.2% (n/N=19/44) in Group B, the 2-dose placebo group. The difference was not statistically significant (p=0.243).

Table 10. Efficacy Analysis Results, Study 2014-01, ITT and mITT Populations

Endpoint	Group A ITT 2 Doses RBX2660 N=45	Group C ITT 1 Dose RBX2660 N=44	Group B ITT 2 Doses Placebo N=44	Group A mITT 2 Doses RBX2660 N=40	Group C mITT 1 Dose RBX2660 N=38	Group B mITT 2 Doses Placebo N=43
Treatment success, n (%)	25 (55.6)	25 (56.8)	19 (43.2)	25 (62.5)	25 (65.8)	19 (44.2)
Treatment failure, n (%)	20 (44.4)	19 (43.2)	25 (56.8)	15 (37.5)	13 (34.2)	24 (55.8)
Difference in success rate (compared with placebo) 95% CI	12.4 (-8.2, 33.0)	13.6 (-7.1, 34.3)	--	18.3 (-2.8, 39.4)	21.6 (0.4, 42.8)	--
p-value	0.243	0.201	--	0.095	0.051	--

Source: STN 125739/0, Clinical Study Report 2014-01
mITT=modified Intent to Treat; ITT=Intent to Treat
Note: Randomized subjects who did not complete the assigned study treatment were considered Treatment Failures. Subjects who discontinued the study prior to 56 days after administration of the last assigned study enema during the blinded period for any reason were considered Treatment Failures. 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.

Reviewer Comment: No treatment difference was identified between the 1- vs. 2-dose regimen of RBX2660, supporting the plan to proceed with clinical development of one dose of RBX2660. The ITT population was used for the primary efficacy analysis, and the analysis was repeated using the mITT and PP populations. No statistically significant differences in treatment success rates (RBX2660 vs placebo) were observed in the ITT, mITT or PP populations.

6.1.11.2 Analyses of Secondary Endpoints

Secondary efficacy analyses included the following:

- Comparison of treatment success rates in Group C (1 RBX2660 enema and 1 placebo enema 7±2 days apart) to Group B (2-dose placebo group): As shown in Table 10, the differences in treatment success rates for both the ITT and mITT population were not statistically significant. However, the PP efficacy analysis did

show a statistically significant difference in treatment success rate of 29.4% (87.5% in Group C and 58.1% in Group B, *p=0.017*.
- Comparison of treatment success rates in Group A (2-dose RBX2660 group) and Group C: As shown in Table 10, there was no difference in treatment success rates between the groups (55.6% and 56.8%, respectively).
- Time to CDI Recurrence: The log-rank test was performed to evaluate the survival distributions of three treatment groups (Group A vs. Group B, Group A vs. Group C, and Group C vs. Group B). For the ITT population, there was no difference between either Groups A or C compared to Group B or between Groups A and C.

Reviewer Comment: While the difference in treatment success between Group C and B was clinically significant in the PP population, it was not statistically significant in the primary efficacy analysis population (ITT). The overall treatment success rate after one or two doses of RBX2660 was similar, data which were used to support the Applicant's decision to focus on one dose of RBX2660 for further clinical development.

6.1.11.3 Subpopulation Analyses

Additional analyses of treatment success between Group A (2-dose RBX2660 group) and Group B (2-dose placebo group) were completed for the following subgroups in the ITT:

- Antibiotic used at screening (vancomycin, fidaxomicin, other)
- Race (White, non-White)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, unreported)
- Sex (female, male): Analyzed using ITT, mITT and PP and population
- Age group (<65 years, ≥65 years): Analyzed using ITT, mITT and PP population
- Number of previous episodes of CDI recurrence at baseline
- Pseudo-site

For each specific subgroup analysis, no significant differences in treatment success were noted between the Group A and Group B ITT populations.

Reviewer Comment: Interpretation of subgroup analyses is limited by the small sample sizes.

6.1.11.4 Dropouts and/or Discontinuations

Table 11 summarizes subjects who discontinued from Study 2014-01 during the double-blind, the open-label portions, and long-term follow-up portions of the study.

Table 11. Reasons for Discontinuation, Study 2014-01 (All Enrolled Subjects)

Discontinuation	Group A 2 Dose RBX2660 N=45 n (%)	Group B 2 Dose Placebo N=44 n (%)	Group C 1 Dose RBX2660 1 Dose Placebo N=44 n (%)	Total N=133 n (%)
Subjects who discontinued study	14 (31.1)	9 (20.5)	19 (43.2)	42 (31.6)
Primary reason for discontinuation	--	--	--	--
Death	8 (17.8)	2 (4.5)	6 (13.6)	16 (12.0)
Investigator withdrawal	1 (2.2)	0	1 (2.3)	2 (1.5)
Lost to follow-up	1 (2.2)	1 (2.3)	5 (11.4)	7 (5.3)
Withdrawal by subject	2 (4.4)	2 (4.6)	4 (9.1)	8 (6.0)
Screen failure	0	0	0	0
Study terminated by sponsor	0	0	0	0
Other	2 (4.4)	4 (9.1)	3 (6.8)	9 (6.8)

Source: STN 125739/0, Adapted from Clinical study report, page 98/2092, Table 14.1.1.1
Note: Numbers based on ITT population, all randomized subjects, regardless of whether they complete treatment

The most common reason for subject discontinuation was death, followed by withdrawal by subject and lost to follow-up. Of the 37 subjects who discontinued following study treatment, four discontinued <56 days after treatment and 33 discontinued ≥56 days after treatment.

Reviewer Comment: Of the 16 subjects who discontinued due to deaths, 1 subject was randomized but died due to complications of severe CDI prior to receiving study enema. The remaining 15 subjects died a median of 280.5 days (range: 57 – 670 days) after receipt of the first enema dose. Narratives were provided and reviewed, and no deaths were considered related to RBX2660 or the enema procedure by the investigator or this reviewer. All deaths had plausible alternate etiologies compounding a pre-existing condition.

Randomized subjects who did not complete the assigned study treatment were considered as treatment failures. Subjects who discontinued the study prior to 56 days after administration of the last assigned study enema during the blinded period for any reason were considered treatment failures in the primary and secondary efficacy analysis.

The DSMB adjudicated treatment success and failure for all subjects during the blinded portion, and there were no adjustments needed for efficacy analyses beyond the agreement to include indeterminates as treatment failures for the purpose of efficacy analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses were conducted for treatment success during the open-label period and time to CDI recurrence after completion of the assigned study treatment during the open-label period. The results of treatment success during the open-label period are not discussed in this memo because data from additional doses of RBX2660 do not directly support the indication and use requested for approval.

The Applicant collected optional stool samples for analysis by (b) (4) as part of their research and development effort. The stool samples continue to be analyzed, and the Applicant will provide the final report of the results upon completion.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population (N=128) was defined as any subject who received at least one blinded enema, or attempted a study enema, whether placebo or RBX2660 and was used for the safety analyses.

Adverse events were categorized by severity, seriousness, and relatedness by site investigator.

Adverse events were independently reviewed by a medical monitor with additional oversight by a DSMB for evaluation of safety trends and stopping rules.

All adverse event terms were coded using MedDRA version 17.0.

6.1.12.2 Overview of Adverse Events

Solicited events

A subject diary was used to solicit the incidence and severity of anticipated events for the first 7 days after treatment. The solicited events included gas or flatulence, abdominal distension or bloating, rectal irritation or pain, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, rectal bleeding, nausea, vomiting, and fever ≥38.0° C (100.4°F).

Subjects were asked to maintain a diary both pre- and post-treatment, including the time from enrollment to the first blinded enema (pre-treatment) and the time from after the first blinded enema through seven days after the second blinded enema (post-treatment). Compliance with returning the pre- and post-treatment diaries was 100%.

Table 12 summarizes solicited event data following the first and second blinded enema.

Table 12. Subjects with Solicited Events, Study 2014-01, Safety Population

Timing of Event	Group A 2 Dose RBX2660 N=42 n (%)	Group B 2 Dose Placebo N=44 n (%)	Group C 1 Dose RBX2660, 1 Dose Placebo N=42 n (%)
After 1st blinded enema	38 (90.5)	42 (95.5)	38 (90.5)
After 2nd blinded enema	34 (81.0)	35 (79.5)	29 (69.0)

Source: STN 125739/0, Clinical study report, Table 29, page 84/2092

Reviewer Comment: Nearly all subjects in each treatment group experienced solicited events after the first blinded enema. Fewer subjects in each treatment group experienced solicited events after the second blinded enema. Because some solicited events may be due to sequelae of the recent CDI, it is unclear whether this difference reflects the effects of treatment or resolving disease.

Table 13 summarizes the number of subjects who reported each solicited event by the maximum severity reported post-treatment. Severity data was missing for 3, 2, and 4 subjects in Groups A, B, and C, respectively.

Table 13. Solicited Events by Maximum Post-Treatment Severity, Study 2014-01, Safety Population

Solicited Event	Group A 2 Dose RBX2660 (N=42) n (%)	Group B 2 Dose Placebo (N=44) n (%)	Group C 1 Dose RBX2660 1 Dose Placebo (N=42) n (%)
Subjects with at least one solicited event	42 (100.0)	44 (100.0)	42 (100.0)
Gas flatulence*	--	--	--
Mild	19 (45.2)	18 (40.9)	20 (47.6)
Moderate	12 (28.6)	16 (36.4)	12 (28.6)
Abdominal distension or bloating	--	--	--
Mild	14 (33.3)	13 (29.5)	12 (28.6)
Moderate	7 (16.7)	7 (15.9)	12 (28.6)
Severe	3 (7.1)	7 (15.9)	1 (2.4)
Increased diarrhea	--	--	--
Mild	11 (26.2)	6 (13.6)	11 (26.2)
Moderate	8 (19.0)	9 (20.5)	9 (21.4)
Severe	4 (9.5)	6 (13.6)	5 (11.9)
Potentially life threatening	1 (2.4)	1 (2.3)	0 (0.0)
Abdominal pain or cramping	--	--	--
Mild	10 (23.8)	11 (25.0)	10 (23.8)
Moderate	8 (19.0)	7 (15.9)	13 (31.0)
Severe	4 (9.5)	10 (22.7)	5 (11.9)
Constipation	--	--	--
Mild	5 (11.9)	7 (15.9)	14 (33.3)
Moderate	3 (7.1)	0 (0.0)	5 (11.9)
Severe	0 (0.0)	4 (9.1)	0 (0.0)
Fever ≥100.4 degrees F*	--	--	--
Mild	0 (0.0)	2 (4.5)	2 (4.8)
Moderate	0 (0.0)	1 (2.3)	0 (0.0)
Chills/severe shivering	--	--	--
Mild	4 (9.5)	9 (20.5)	8 (19.0)
Moderate	4 (9.5)	4 (9.1)	4 (9.5)
Severe	1 (2.4)	6 (13.6)	1 (2.4)
Rectal irritation or pain	--	--	--
Mild	7 (16.7)	14 (31.8)	10 (23.8)
Moderate	7 (16.7)	6 (13.6)	6 (14.3)
Severe	0 (0.0)	3 (6.8)	0 (0.0)
Rectal bleeding	--	--	--
Mild	4 (9.5)	7 (15.9)	3 (7.1)
Moderate	1 (2.4)	2 (4.5)	1 (2.4)
Severe	1 (2.4)	1 (2.3)	0 (0.0)
Nausea	--	--	--
Mild	5 (11.9)	8 (19.0)	11 (26.2)
Moderate	6 (14.3)	3 (6.8)	2 (4.8)
Severe	1 (2.4)	4 (9.5)	3 (7.1)
Potentially life threatening	0 (0.0)	2 (4.8)	1 (2.4)

Solicited Event	Group A 2 Dose RBX2660 (N=42) n (%)	Group B 2 Dose Placebo (N=44) n (%)	Group C 1 Dose RBX2660 1 Dose Placebo (N=42) n (%)
Vomiting	--	--	--
Mild	1 (2.4)	2 (4.8)	5 (11.9)
Moderate	0 (0.0)	1 (2.4)	0 (0.0)
Severe	1 (2.4)	1 (2.4)	0 (0.0)
Potentially life threatening	0 (0.0)	1 (2.4)	0 (0.0)

Source: STN 125739/ Clinical study report, pages 1892-1902/2092, Table 14.3.3.3
*No severe events reported

Reviewer Comment: The most common solicited events were gas (flatulence), abdominal cramping and bloating. Most reported solicited events were mild/moderate in severity. Events reported by more subjects in both of the RBX2660 groups compared to placebo included increased diarrhea and constipation.

Treatment emergent adverse events

Treatment emergent adverse events (TEAEs), including all non-solicited AEs and solicited events that were categorized as AEs (see Section 6.1.7), were reported in 105/126 (83.3%) of subjects in the safety population, the majority of which were mild or moderate and occurred within the 8-week follow-up of blinded treatment. The overall summary of TEAEs in the Study 2014-01 safety population through 24 months after the last RBX2660 dose (including blinded and open label periods) is presented in Table 14.

Table 14. Overall Summary of Treatment Emergent Adverse Events Through 24 Months, Study 2014-01, Safety Population

TEAE Category	Group A 2 Dose RBX2660 N=42 n (%)	Group B 2 Dose Placebo N=44 n (%)	Group C 1 Dose RBX2660 1 Dose Placebo N=42 n (%)	Total N=128 n (%)
Any TEAEs	34 (81.0)	38 (86.4)	33 (78.6)	105 (82.0)
Severe TEAEs	7 (16.7)	4 (9.1)	5 (11.9)	16 (12.5)
TEAEs leading to discontinuation	14 (31.1)	9 (20.5)	19 (43.2)	42 (31.6)
Serious TEAEs	22 (52.4)	16 (36.4)	15 (35.7)	53 (41.4)
Serious TEAEs related to RBX2660	3 (7.1)	0 (0)	0 (0)	3 (2.3)
Deaths	7 (16.7)	2 (4.5)	6 (14.3)	15 (11.7)

Source: STN 125739/0, Table 14.1.1.1, 14.3.1.1.1, Clinical Study Report, page 1189/2092 JMP Reviewer ADAM Dataset Analysis

The most commonly reported TEAEs across treatment groups were in the MedDRA SOC *Gastrointestinal disorders*. Of the most commonly reported TEAEs (≥5% of subjects in any arm) during the blinded portion through 24 months after receiving the last study enema or until receipt of open-label RBX2660, the following events were reported more frequently in either of the RBX2660 groups compared to placebo: anemia, diarrhea, abdominal pain, constipation, nausea, flatulence, hematochezia, pyrexia, fatigue, urinary tract infection, pneumonia, fall, headache, dyspnea, and orthostatic hypotension (Table 15).

Table 15. TEAEs Occurring Overall in ≥5% of Subjects in any Arm During the Blinded Portion Through 24 Months After Receiving the Last Study Enema or Until Receipt of Open-Label RBX2660 (Safety Population)

System Organ Class ***Preferred Term***[a]	**Group A** **2 Dose** **RBX2660** **N=42** **n (%)**	**Group B** **2 Dose Placebo** **N=44** **n (%)**	**Group C** **1 Dose RBX2660** **1 Dose Placebo** **N=42** **n (%)**
Subjects with at least one AE[b]	31 (73.8)	29 (65.9)	32 (76.2)
Blood and lymphatic system disorders	--	--	--
Anemia	3 (7.1)	0	2 (4.8)
Gastrointestinal disorders	--	--	--
Diarrhea	17 (40.5)	7 (15.9)	5 (11.9)
Abdominal pain	11 (26.2)	8 (18.2)	8 (19.0)
Constipation	7 (16.7)	2 (4.5)	3 (7.1)
Nausea	4 (9.5)	1 (2.3)	4 (9.5)
Flatulence	4 (9.5)	2 (4.5)	4 (9.5)
Abdominal distension	3 (7.1)	4 (9.1)	2 (4.8)
Anorectal discomfort	3 (7.1)	3 (6.8)	2 (4.8)
Hematochezia	1 (2.4)	0	3 (7.1)
Proctalgia	0 (0)	3 (6.8)	1 (2.4)
General disorders and administration site conditions	--	--	--
Pyrexia	2 (4.8)	3 (6.8)	6 (14.3)
Chills	2 (4.8)	4 (9.1)	1 (2.4)
Fatigue	3 (7.1)	1 (2.3)	1 (2.4)
Infections and infestations			
Urinary tract infection	6 (14.3)	2 (4.5)	1 (2.4)
Pneumonia	2 (4.8)	0	3 (7.1)
Injury, poisoning and procedural complications	--	--	--
Fall	1 (2.4)	1 (2.3)	3 (7.1)
Contusion	0 (0)	3 (6.8)	1 (2.4)
Metabolism and nutrition disorders	--	--	--
Dehydration	3 (7.1)	3 (6.8)	1 (2.4)
Nervous system disorders	--	--	--
Headache	3 (7.1)	2 (4.5)	1 (2.4)
Respiratory, thoracic disorders, and mediastinal	--	--	--
Dyspnea	3 (7.1)	0	2 (4.8)
Vascular disorders	--	--	--
Orthostatic hypotension	3 (7.1)	0	0

Source: STN 125739/0, Table 18, Clinical Study Report, page 73
a. Adverse Events were coded using MedDRA version 17.0 and were reviewed by the Medical Monitor
b. Total number of subjects is inclusive of all AEs in the blinded portion; not only those subject to the >5% cutoff

In an analysis of all TEAEs in a more limited timeframe (blinded portion through week 1 after last study enema), the following events were reported by more than one subject in any group and more frequently in either of the RBX2660 groups compared to placebo: diarrhea, abdominal pain, constipation, nausea, flatulence, and pyrexia.

TEAEs were most commonly reported between the first dose of the RBX2660 enema and the one-week follow-up (33.6% of subjects), and the proportion of subjects reporting TEAEs decreased at later time points: 30.5% of subjects from day 7 to day 28, 18.8% of subjects at the Day 56 visit, 10.9% of subjects at the Month 3 visit, and 17.2% of subjects at the Month 6 visit.

The distribution of TEAEs by sex and age group (<65 years and ≥65 years) was comparable across the three randomized treatment groups. As 95.3% of subjects in the safety population self-reported as white and not Hispanic or Latino, it was not possible to conduct meaningful analyses of TEAEs by race.

Reviewer Comment: TEAEs were mostly mild to moderate in severity. Although some imbalances in specific events are noted when comparing RBX2660 groups to placebo, interpretation of these differences is confounded by small numbers of subjects in each group.

6.1.12.3 Deaths

Death was reported in 16 subjects, including one subject who was randomized but not treated. Three deaths (general health deterioration associated with multiple comorbidities, bacteremia and renal failure) occurred within 56 days of treatment. None of the deaths were considered to be related to RBX2660 by the investigator or the Applicant. Details of the 15 deaths reported post-treatment are described in Table 16.

Table 16. Deaths, Safety Population, Study 2014-01

Age (Years) Race Sex	**Preferred Term**	**Number of CDI Before RBX2660 Enema**	**TEAE Onset Day Relative to Enema Death (End) Day**	**Relationship to Treatment**
Group A: 2x RBX2660	--	--	--	--
76 White Male	Acute respiratory failure	6	31 74	Unrelated
87 White Female	Adenocarcinoma of colon Respiratory failure	11	217-218 223	Unrelated
53 White Male	Acute myeloid leukemia	4	69 358	Unrelated
69 White Female	Chronic Obstructive Pulmonary Disease Exacerbation	5	363 373	Unrelated
84 White Female	Renal failure *C. difficile* infection Sepsis	8	49-74 (discontinued dialysis) 50 64	Unrelated
59 White Female	Failure to thrive due to Advanced/progressive Parkinsonism	14	488 - 503	Unrelated

Age (Years) Race Sex	Preferred Term	Number of CDI Before RBX2660 Enema	TEAE Onset Day Relative to Enema Death (End) Day	Relationship to Treatment
Group B: 2x Placebo	--	--	--	--
46 White Male	Small cell carcinoma	4	208-260	Unrelated
68 White Female	Cerebrovascular accident Metastatic adenocarcinoma, leptomeningeal disease Embolic stroke	4	267-289 289-289 289-289 289-289	Unrelated Unrelated Unrelated Unrelated
73 White Female	Intestinal ischemia	3	Specific day not reported Died day 564 post enema	Unrelated
Group C: 1x Placebo, 1x RBX2660	--	--	--	--
88 White Male	General physical health deterioration	3	56 57	Unrelated
83 White Male	General physical health deterioration	3	88 100	Unrelated
63 White Male	MRSA Bacteremia from hemodialysis catheter, Sepsis, Respiratory failure	4	60 – 64 60 – 64 60 – 64	Unrelated
87 White Female	Sepsis (likely respiratory source) Palliative care	8	283 289	Unrelated
85 White Female	Angina pectoris Acute renal failure Congestive heart failure	4	249 - 252 249 - 252 249 - 252	Unrelated
86 White Female	Perforated appendicitis Respiratory failure Extradural hematoma Paraplegia	7	657 - 657 658 - 666 665 - 666 665 - 666	Unrelated

Source: STN 125739/0, Adapted from Clinical Study Report Body 2 narratives pages 4 – 132 and Reviewer's JMP ADAM Review Analysis of AE datasets

Reviewer Comment: Based on plausible alternative etiologies, pre-existing conditions, and/or the lack of a plausible alternative etiology, this reviewer agrees with the investigator's assessments that the deaths were unrelated to RBX2660.

6.1.12.4 All Serious Adverse Events

There were 53 subjects (41.4%) with reported serious TEAEs in Study 2014-01. Serious TEAEs were reported most commonly in Group A (2-dose RBX2660), including all 3 serious TEAEs considered to be related to RBX2660 by the investigator. However, this reviewer does not consider these 3 adverse events to be causally related to RBX2660 as described below:

- A 59-year-old white female with a history of Parkinson's disease and chronic constipation received two doses of RBX2660 and reported an SAE of worsening chronic constipation on day 45 post RBX2660. The investigator reported worsening chronic constipation as related to RBX2660. The event of worsening chronic constipation was not considered to be related to RBX2660 by this

reviewer due to a lack of temporal relationship (onset 45 days post RBX2660 exposure).

- A 44-year-old white female with history of Marfan syndrome, interstitial cystitis, hypertension, angina, fibromyalgia, depression, morbid obesity and rCDI (4 episodes) received 2 doses of RBX2660 and reported an SAE of abdominal pain on day 10 post RBX2660. The subject reported nausea, vomiting and eight bowel movements with abdominal pain worse after eating and was diagnosed with rCDI. The investigator reported the serious event of abdominal pain as related to RBX2660 and CDI. This reviewer considers that the rCDI provides a clear alternative etiology for the SAE.

- A 53-year-old white male with history of acute myeloid leukemia (AML) in remission following stem cell transplant received 2 doses of RBX2660 and reported an SAE of recurrent acute myeloid leukemia on day 69 post RBX2660. The investigator reported the recurrent AML as related to RBX2660 and to a pre-existing condition. The subject received multiple chemotherapy regimens and the event was noted to be resolved on day 253 post RBX2660. However, the subject was diagnosed with relapsed AML on day 357 post RBX2660 and subsequently died. The death was considered unrelated to RBX2660 by the investigator. This reviewer does not consider the event of AML relapse to be related to RBX2660 in this subject, given the pre-existing diagnosis and lack of temporal relationship of RBX2660 and onset of AML symptoms.

Reviewer Comment: Following review of the case reports and narratives for each SAE, none were considered related by this reviewer.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) were not specified for Study 2014-01.

6.1.12.6 Clinical Test Results

Blood samples were collected at screening and baseline. The screening results were used as part of study eligibility. Blood samples drawn at baseline prior to receiving the first dose were used to establish a baseline for standard values. There were no safety monitoring labs drawn as part of the study protocol. Stool samples were analyzed at local laboratories if a subject had a suspected CDI recurrence.

6.1.12.7 Dropouts and/or Discontinuations

There were no discontinuations due to AEs in the safety population of Study 2014-01.

6.1.13 Study Summary and Conclusions

The primary efficacy analysis compared the treatment success rate after two doses of RBX2660 vs two doses of placebo in the ITT population. The estimated difference in treatment effect of 12.4% was not statistically significant. The safety population of Study 2014-01 consisted of subjects who received at least one study enema. TEAEs were most commonly reported in the MedDRA SOC *Gastrointestinal disorders* and were mostly mild to moderate in severity. Small imbalances in some AEs were noted, most of which were gastrointestinal in nature. None of the SAEs or deaths were considered related to RBX2660 by this reviewer.

6.2 Trial #2, Study 2017-01

2017-01 was a Phase 3, prospective, randomized, multicenter, double-blinded, placebo-controlled study to evaluate the efficacy and safety of RBX2660 for the prevention of recurrent *Clostridium difficile* infection (rCDI) when administered as a single blinded study enema in subjects who had prior rCDI that was resolved following antibiotic treatment.

Protocol ID: 2017-01
ClinicalTrials.gov ID: NCT03244644
Date First Subject Enrolled: July 31, 2017
Date Last Subject Completed: August 03, 2020
Database Lock Point: September 30, 2020
Date of Final Study Report: November 20, 2020

6.2.1 Objectives

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

Secondary objective: To evaluate the sustained clinical response rate of RBX2660 as compared to placebo after blinded treatment

Other objectives:

1. To confirm the safety and tolerability of RBX2660
2. To identify baseline characteristics predictive of efficacy outcomes
3. To characterize the changes from baseline fecal microbial composition in subjects treated with RBX2660 as compared to placebo
4. To characterize the changes from baseline comorbidities in subjects treated with RBX2660 as compared to placebo
5. To evaluate health-related quality of life for CDI as measured by the Cdiff32 questionnaire
    - The Cdiff32 health-related quality of life instrument comprises 32 self-administered questions about the impact of CDI in 3 broad domains pertaining to the health of CDI patients (physical, mental and social). Some of the questions are scored '1 (best) to 5 (worst)' and others are score '1 (worst) – 5 (best).' For calculation of an overall Cdiff32 score, each of the raw scores for the 32 questions are standardized to '1 (worst) to 5 (best)', converted from '1 to 5' to '0 (worst score) to 100 (best score)' and then average. Changes from screening were summarized using descriptive statistics at 1 and 8 weeks, and 4 and 6 months after study treatment using the safety population.
6. To characterize the baseline severity of CDI in subjects with documented CDI recurrence
7. To evaluate treatment success of RBX2660 in placebo subjects who are documented study treatment failures then went on to receive RBX2660
8. To assess the ability of more than one dose of RBX2660 to prevent CDI recurrence
9. To assess the combined treatment success of all subjects receiving a single dose of RBX2660 during the study both to prevent recurrent CDI as well as prevent new CDI episodes

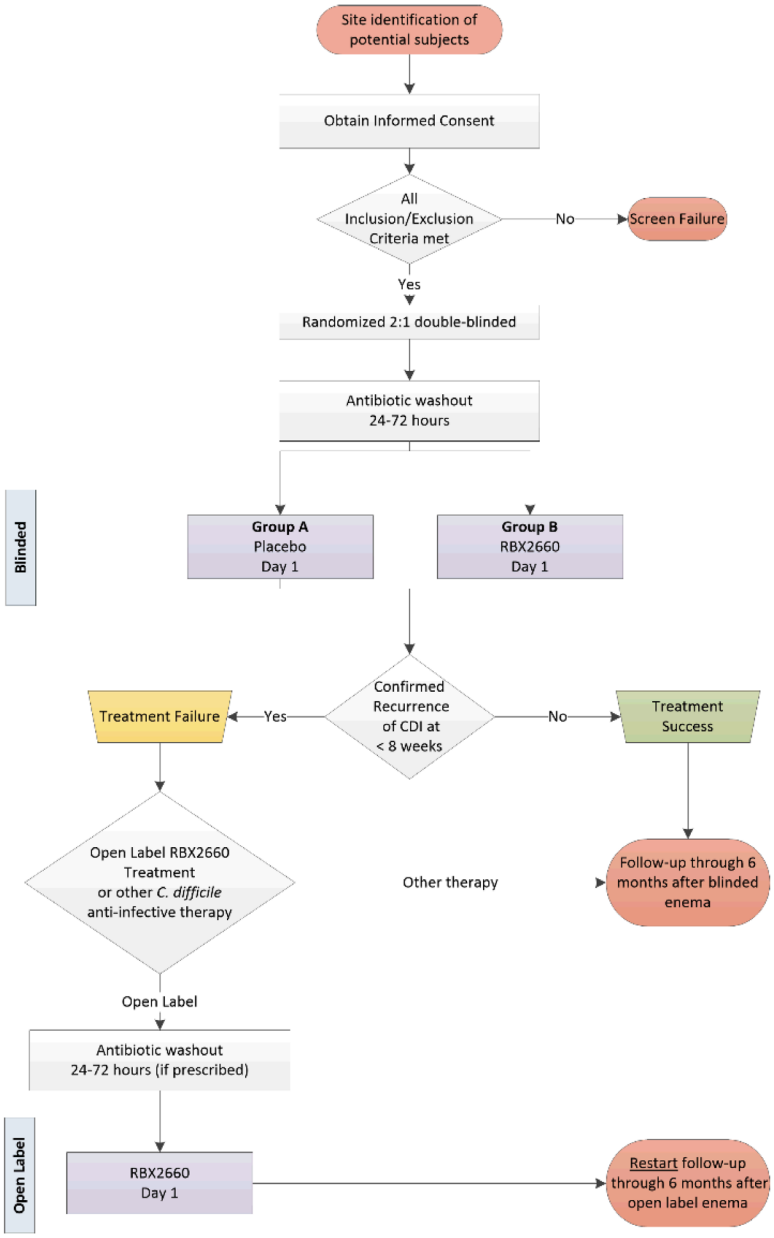
10. To assess the clearance rate of vancomycin-resistant enterococcus in subjects who are carriers at baseline
11. To assess the clearance of *C. difficile* following enema treatment at 4 and 8 weeks and 3 and 6 months after blinded study treatment in subjects receiving RBX2660 and those receiving placebo

Reviewer Comment: The review of efficacy data in this memo is limited to the primary and secondary objectives that CBER considered most pertinent to the indication and prescribing information to be approved.

6.2.2 Design Overview

2017-01 was a Phase 3, prospective, randomized, multicenter, double-blinded, placebo-controlled study to evaluate the efficacy and safety of RBX2660 for the prevention of rCDI. The study design schematic for Study 2019-01 is presented in Figure 3**.**

Figure 3. Study 2017-01 General Study Design



Source: STN 125739/0, 2017-01 Clinical Study Report, page 23/102

At the time of enrollment, subjects were already taking or had been prescribed antibiotics to control rCDI symptoms. Subjects were randomized 2:1 to receive RBX2660 or placebo after resolution of rCDI following antibiotic treatment.

The randomization schedule was created using randomized blocks within four strata based on antibiotics used at screening (vancomycin alone, vancomycin in combination, fidaxomicin, or other). Study treatment was administered within 21 days of the screening visit. Eligible subjects received a single blinded study enema following an antibiotic washout period of 24 to 72 hours and within 14 calendar days of randomization.

Open-label RBX2660 enema treatment was an option for subjects who were deemed to be treatment failures per the pre-specified treatment failure definition. This open-label enema was administered within 21 calendar days of treatment failure. If a subject received treatment with RBX2660 during the open-label portion of the study, the follow-up visits, phone calls and completion of a new post-treatment subject diary occurred according to the same schedule as of the blinded portion of the study.

6.2.3 Population

Inclusion Criteria
Key inclusion criteria included the following:

- Adults ≥18 years old
- Medical record documentation of rCDI 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
- Positive stool test for the presence of toxigenic *C. difficile* within 30 days prior to enrollment
- Currently taking or had just been prescribed antibiotics to control CDI-related diarrhea at the time of enrollment. *Note: Subject's CDI diarrhea had to be controlled (<3 unformed/loose [i.e., Bristol Stool Scale type 6-7] stools/day for 2 consecutive days) while taking antibiotics during screening.*

Exclusion Criteria
Key exclusion criteria included the following:

- Known history of refractory CDI
- Continued CDI diarrhea despite being on a course of antibiotics prescribed for CDI treatment
- Required antibiotic therapy for a condition other than CDI
- Previous fecal transplant, RBX2660 treatment, receipt of CDI vaccine, or treatment with CDI monoclonal antibodies prior to study enrollment
- History of inflammatory bowel disease, e.g., ulcerative colitis, Crohn's disease, microscopic colitis
- Diagnosis or irritable bowel syndrome as determined by Rome III criteria
- History of chronic diarrhea and celiac disease
- Disease symptoms (diarrhea) caused by a confirmed intestinal pathogen other than *C. difficile*
- Currently had a colostomy
- Intraabdominal surgery within the last 60 days
- Evidence of active, severe colitis
- History of short gut syndrome or motility disorders
- Required the regular use of medications to manage bowel hypermotility
- Planned therapy within 3 months that might cause diarrhea (e.g., chemotherapy)
- Planned surgery requiring perioperative antibiotics within 6 months of study enrollment
- Life expectancy of <6 months
- Compromised immune system (e.g., HIV infection with a cluster of differentiation 4 (CD4) count <200/mm^3; inherited/primary immune disorders; immunodeficient or immunosuppressed due to a medical condition or medication). *Note: Eligible*

HIV patients who had a CD4 count >200/mm^3 who were on stable, highly active anti-retroviral therapy were considered for enrollment.

- Taking systemic steroids >20 mg prednisone a day or prednisone-equivalent or was expected to be on steroids (>20 mg prednisone a day or equivalent) after enrollment through 8 weeks after completing the assigned study treatment. *Note: Eligible patients taking a steroid dose equivalent to prednisone 20 mg/day for >2 weeks, antimetabolites (e.g., azathioprine, 6-mercaptopurine, or low-dose methotrexate for autoimmune disease), calcineurin inhibitors (e.g., tacrolimus and cyclosporine), or mycophenolate mofetil may have been enrolled only after consultation with the Medical Monitor, and only if the doses had been stable (except for drug therapeutic monitoring adjustments for calcineurin inhibitors) for 90 days and had not been associated with diarrhea prior to the current episode of CDI.*
- An absolute neutrophil count of <1000 cells/μL during screening
  Note: Eligible HIV patients who had a CD4 count >200/mm^3 who were on stable, highly active anti-retroviral therapy were considered for enrollment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study treatments included RBX2660 (see Section 4.1 for a description of study drug product) and placebo (normal saline), administered via enema.

6.2.5 Directions for Use

Each dose of RBX2660 or placebo was supplied in a kit containing one enema bag of study drug, materials for preparation and administration, and a biohazard disposal bag. Each dose of RBX2660 or matched placebo was supplied in a brown enema bag within a brown opaque sleeve that was to remain in place over the bag and tubing during administration and disposal to preserve the blind. RBX2660 or placebo was stored at -80°C and shipped frozen to the clinical site, where it was thawed in the refrigerator for approximately 24 hours and kept refrigerated until administration or the expiration date. RBX2660 was not to be heated or re-frozen after receipt and was for rectal use only.

6.2.6 Sites and Centers

A total of 211 subjects were enrolled at 36 study sites in the US, with a median of 3 subjects at each site (range 1-24 subjects). A total of 78 subjects were enrolled at 5 sites in Canada, with a median of 7 subjects at each site (range: 1-36 subjects).

6.2.7 Surveillance/Monitoring

The schedule of study procedures is shown in Table 17.

Table 17. Schedule of Events, Study 2017-01

Activity	Screening (Enrollment)	Baseline / Enema Administration (≤ 21 days from Screening)	Follow-up Visits 1-, 4- and 8-Week (± 3 days) Assessments[a]	Weekly Phone Assessment Weeks 2, 3 and 6 (± 3 days)	Unscheduled Possible Recurrence Visit	Open-Label Enema Administration[a] (≤ 21 calendar days post-Tx Failure)	Phone Assessment at 3 and 6 months (± 14 days)
Informed consent obtained	X						
Demographics, medical history	X						
Prescribe/continue antibiotics for CDI symptom control	X						
Modified physical exam conducted		X					
Stool sent to Rebiotix by subjects for testing and archiving (optional)	X		X		X		X
Central lab CBC w/differential testing[b]	X[b]	X					
Central Lab CMP & CRP testing	X						
C. difficile testing[c]	X[c]				X[c]		
Central Lab stool and blood testing		X					
Urine pregnancy testing performed at site (if applicable)	X	X				X	
Cdiff32 questionnaire	X		X		X		X
Inclusion/exclusion criteria confirmed	X	X					
Randomization assignment	X[d]						

Activity	Screening (Enrollment)	Baseline / Enema Administration (≤ 21 days from Screening)	Follow-up Visits 1-, 4- and 8-Week (± 3 days) Assessments[a]	Weekly Phone Assessment Weeks 2, 3 and 6 (± 3 days)	Unscheduled Possible Recurrence Visit	Open-Label Enema Administration[a] (≤ 21 calendar days post-Tx Failure)	Phone Assessment at 3 and 6 months (± 14 days)
24-72 hr washout period confirmed		X				X	
Enema administered		X				X	
Product complaint (if applicable)		X				X	
Recurrence or new CDI symptoms assessed		X	X	X	X	X	X
Vital signs assessed	X	X			X	X	
Subject Diary discussed/reviewed	X	X	X[e]			X	
Employment status assessed	X		X[f]				X
Concomitant medications	X	X	X	X	X	X	X
Medical history assessment	X		X[f]		X		X
Adverse events assessed		X	X	X	X	X	X
Solicited events assessed[g]		X	X[g]			X[g]	
Protocol deviations (if applicable)	X	X	X	X	X	X	X

Source: STN 125739/0, 2017-01 Clinical Study Report, page 31-32/102
CDI=*C. difficile* infection, CMP=comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, a bumin, AST, ALT, alkaline phosphatase, bilirubin [direct, indirect and total], and glucose), CRP=C-reactive protein, Tx=treatment.
a. Documented Treatment Failures might have received an open-label RBX2660 enema. If an open-label enema was administered, the follow-up visit requirement re-started based on the date of last enema administration.
b. Exclusion criteria for absolute neutrophil count were assessed based on the CBC collected at the Screening visit.
c. Performed within 30 days prior to or at enrollment and if CDI recurrence was suspected.
d. Randomization occurred after Screening criteria was assessed and elig bility confirmed (4-14 calendar days from randomization to blinded study treatment).
e. Subject Diary was reviewed only at the 1-week follow-up visit.
f. Collected at the 8-week follow-up visit only.
g. Solicited events were collected in the Subject Diary from the day of administration of any study enema (blinded or open-label) until the day prior to the 1-week visit. The Subject Diary was collected and reviewed at the 1-week visit. Solicited events that increased in severity from Screening were assessed for a poss ble adverse event.

Safety assessments

Safety assessments included:

1. Solicited events were collected daily via subject diary through 7 days after a treatment with the assigned study enema (blinded portion) or after a treatment with RBX2660 (open-label portion). Solicited events included gas (flatulence), abdominal distension or bloating, abdominal pain or cramping, rectal irritation or pain, rectal bleeding, chills/severe shivering, increased diarrhea, constipation, nausea, vomiting and fever ≥37.8° C (100.0°F). A solicited event became an AE after the data entry had been reviewed by the site investigator to determine if the severity grade entered matched the severity definition provided in the diaries. Solicited AEs with increased severity from pre- to post- enema were captured as an AE or SAE as determined by the site's investigator.
2. All AEs, including SAEs, were collected at the in-person site visits, which included a discussion of symptoms with the subjects at weeks 1, 4, 8, and by phone at weeks 2, 3, 6 and months 3 and 6, with a review of the subject diary at baseline and at the 1-week follow-up visit. An AE was considered serious if it was life threatening, resulted in death, in-patient hospitalization ≥24 hours or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or was a congenital anomaly/birth defect.
3. Frequency of major complications of CDAD including death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, or intensive care unit (ICU) admission

Adverse events were graded by the site investigators for severity with the adapted Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events and NIH/NCI Common Terminology Criteria for Adverse Events.

Study Oversight

An independent DSMB, consisting of two physicians specializing in infectious diseases or gastroenterology who have experience managing subjects with rCDI and were not investigators in the study, was appointed to ensure the safety of enrolled subjects and to make recommendations to the sponsors regarding the continuation, modification or termination of the study. A biostatistician who was not involved with study design or analyses was also a member of the DSMB. Interim safety review for trends in unanticipated AEs and stopping rules was to be conducted once randomization reached approximately 50% and 75%. An independent medical monitor also conducted blinded review of SAEs or events reported by the site as related to the investigational product (IP) or enema procedure, to allow for early identification of any possible unanticipated events or events that might require immediate review by the DSMB.

An endpoint adjudication committee (EAC) provided independent blinded adjudication of treatment success or failure that were used for efficacy analyses. The EAC was comprised of 3 physicians specializing in infectious diseases or gastroenterology who have experience managing subjects with rCDI and were not investigators in the study.

6.2.8 Endpoints and Criteria for Study Success

Efficacy

The primary efficacy endpoint was recurrence of CDI within 8 weeks of blinded treatment. Definitions for the efficacy analysis included the following:

- 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.
- Treatment success was defined as the absence of CDI diarrhea through 8 weeks after completing the blinded study treatment.
- Treatment failure (CDI recurrence) was defined as the presence of CDI diarrhea within 8 weeks of administration of a study enema, which includes a positive stool test for *C. difficile* toxin at the time of the diarrhea.

The following additional criteria for treatment failure were used:

Intention-to-Treat (ITT) Analysis Population

- Randomized subjects who withdrew prior to receiving blinded treatment.
- Randomized subjects in whom blinded treatment was attempted but delivery of the enema was not successful.
- Randomized and treated subjects who exited prior to their 8-week efficacy assessment, even if protocol required treatment failure documentation was not on file.

Modified Intent-to-Treat (mITT) Analysis Population

- Subjects who withdrew prior to treatment.
- Subjects in whom blinded treatment was attempted but not completed.
- Subjects who discontinued from the study prior to evaluation of Treatment Failure/Success for the primary endpoint, if the reason for exit was not related to CDI symptoms.
    - Reasons for exit were captured on the exit form to allow for identification of such subjects.
- Subjects who exited prior to the 8-week efficacy assessment due to CDI-related symptoms, even if documentation, as required per protocol, was not on file.

Treatment outcome was initially determined by the site investigator. All outcomes were adjudicated by the EAC.

Prior to unblinding, the Statistical Analysis Plan (SAP) was revised to introduce a Bayesian hierarchical model for the analysis of the primary efficacy endpoint that formally integrated treatment success rates from study 2014-01 into study 2017-01, as described in Section 5.1. The extent of borrowing was dependent on the similarity of effect for both active and placebo groups per the planned design. The mITT population was pre-specified as the primary analysis population for reporting purposes, supported by the ITT analysis. The Bayesian analysis evaluated the posterior probability of superiority of RBX2660 compared to placebo. There were two thresholds for declaring superiority as follows:

- First (more stringent) threshold was met if the posterior probability of superiority exceeded 0.9993275, reflecting a frequentist one-sided Type I error rate <0.00125

- Second (less stringent) threshold was met if the posterior probability of superiority exceeded 0.9750338, reflecting a frequentist one-sided Type I error rate <0.025

The secondary efficacy endpoint was loss of sustained clinical response through six months after blinded treatment.

Safety

- Number of AEs per subject
- Timing of attributable AE post-treatment exposure (i.e., TEAE)
- Duration of TEAE
- Relatedness of TEAE
- Severity of TEAE
- Causality of TEAE to IP, enema, *C. difficile*, or prior condition
- Number of each of the following through 8 weeks post-blinded treatment: death, septic
- shock, toxic megacolon, colonic perforation, emergency colectomy, and intensive care unit (ICU) admission
- Onset of new chronic conditions relative to blinded treatment administration

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size

To demonstrate an assumed 69% success rate in the RBX2660 group vs. 47% success rate in the placebo group, 240 subjects were required (power >90%, nominal 2.5% type I error rate). Up to an additional 30 subjects could be enrolled to allow for a 10% loss to follow-up, for a total of approximately 270 subjects. Considering the 2:1 randomization, this would result in approximately 180 subjects in the RBX2660 arm and 90 subjects in the placebo arm. Enrolled subjects who signed consent and withdrew for any reason prior to administration of the first blinded enema were replaced without counting toward the sample size cap. Replacement subjects were randomized to ensure proper blinding.

Statistical Analysis Plan (SAP)

The original version of the SAP (dated July 18, 2017) was amended 7 times prior to unblinding. Key amendments are show in Table 18.

Table 18. Summary of Key Changes Implemented by Global SAP Amendments for Study 2017-01

Version	Date	Key Changes
2.0	September 25, 2017	Adjusted sample size and revised key secondary endpoints.
3.0	February 13, 2018	Adjusted sample size and revised secondary objective and all endpoints.
4.0	March 22, 2019	Adjusted sample size and introduced a detailed interim analysis plan. Bayesian hierarchical analysis was introduced.
5.0	August 07, 2019	Revised detailed interim analysis plan.
6.0	August 13, 2019	Added detail of statistical method to be used to analyze the secondary efficacy endpoint.

Version	Date	Key Changes
7.0	March 23, 2020	Clarified timing of primary efficacy analysis to occur when last subject reached 8 weeks, if enrollment must proceed up to 270 treatments. Added sensitivity analyses of primary endpoint. Clarified the role of the EAC.
8.0	September 25, 2020	Added analysis windows for adverse event analysis, clarified planned sensitivity analyses of the primary endpoint, added time to CDI occurrence, corrected the number of diary questions, and added an analysis of a new subgroup.

Source: STN 125739/0, 2017-01 Clinical Study Report, page 49/102
EAC=endpoint adjudication committee; CDI=*C. difficile* infection

The interim analyses evaluated the primary efficacy endpoint for either success or futility. Both interim analyses and the final primary efficacy analysis were performed, independent of the Applicant, by the Statistical Analysis Committee, DSMB, and EAC.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Table 19. 2017-01 Efficacy Analysis Population Definitions

Analysis Population	Definition
Intent-to-Treat Population (ITT)	All randomized subjects. Subjects were analyzed according to the randomized treatment rather than the actual treatment received regardless of treatment misallocations. Randomized subjects who exited prior to receiving blinded treatment were not included in the analysis.
Modified Intent-to-Treat Population (mITT)	All randomized subjects who successfully received blinded treatment but excluding subjects who: • withdrew prior to treatment • attempted but did not complete treatment; and • discontinued from the study prior to evaluation of Treatment Success for the primary endpoint, if the reason for exit was not related to CDI symptoms
Per-Protocol Population (PP)	All subjects who successfully received blinded treatment and were analyzed according to the treatment they received, excluding subjects who: • had documented deviations to inclusion or exclusion criteria • exited the study prior to the 8-week efficacy evaluation, if the reason for exit was not related to CDI symptoms
Safety Population	All randomized subjects who had any blinded treatment attempted or completed. Subjects were analyzed according to the treatment they actually received. The safety population was used in analysis of all safety endpoints.

Source: STN 125739, Adapted from Summary of Clinical Efficacy, page 16-17/68

The mITT population was used for the assessment of the primary and secondary efficacy analyses. Sensitivity analyses of the primary and secondary endpoints were conducted using the ITT and PP populations.

6.2.10.1.1 Demographics

The demographic and baseline characteristics of subjects in Study 2017-01 are presented in Table 20. The age range of subjects in Study 2017-01 was 19 – 93 years

old, with a median age of 63 years and 45.7% (122/267) of the subjects were ≥65 years of age. The subjects in Study 2017-01 were mostly White (92%), not Hispanic or Latino (93%), and female (69%).

Table 20. Demographic and Baseline Characteristics, Study 2017-01, Safety Population

Characteristic	Placebo N=87 n (%)	RBX2660 N=180 n (%)	Total N=267 n (%)
Age	--	--	--
Mean years [range]	57.7 [26 -86]	61.3 [19 – 93]	60.1 [19 – 93]
<65, n (%)	54 (62.1)	91 (50.6)	145 (54.3)
≥65, n (%)	33 (37.9)	89 (49.4)	122 (45.7)
Sex, n (%)	--	--	--
Male	27 (31.0)	57 (31.7)	84 (31.5)
Female	60 (69.0)	123 (68.3)	183 (68.5)
Ethnicity, n (%)	--	--	--
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)
Race, n (%)	--	--	--
Black/African American	6 (6.9)	8 (4.4)	14 (5.2)
White	78 (89.7)	168 (93.3)	246 (92.1)
Other	3 (3.4)	0 (0.0)	3 (1.1)
American Indian or Alaska Native	0 (0.0)	2 (1.1)	2 (0.7)
Asian	0 (0.0)	1 (0.6)	1 (0.4)
Multiple	0 (0.0)	1 (0.6)	1 (0.4)

Source: STN 125739, Adapted from STN 125739/0, Clinical Study Report 2017-01, Table 7

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 21. Baseline Disease Characteristics, Study 2017-01, Safety Population

Category	Placebo N=87 n (%)	RBX2660 N=180 n (%)	Total N=267 n (%)
Total number of CDI episodes before blinded treatment	--	--	--
1	0	0	0
2	33 (37.9)	53 (29.4)	86 (32.2)
≥3	54 (62.1)	127 (70.6)	181 (67.8)
Episode duration (days)			
Mean	25.6	26.3	26.1
Minimum - maximum	11 - 67	11 - 163	11 - 163
Antibiotics administration for qualifying CDAD/CDI episode, n (%)	--		
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)

Source: STN 125739, Adapted from Clinical Study Report 2017-01, Table 8

The ATLAS score (a severity scoring system to predict response to therapy) was comparable between the placebo and the RBX2660 arms with a score of 2.9 in the

placebo arm and 3.0 in the RBX2660 arm. According to published studies of clinical outcomes among patients with CDI, at 30 days post-diagnosis, patients with ATLAS score of ≤3 points had 100% survival while all of those with scores ≥8 died,[22] suggesting the subjects in Study 2017-01 did not have severe disease at baseline.

The most common medical history in the safety population was connective tissue disease in 28.5% (76/267) of subjects, chronic obstructive pulmonary disease in 16.9% (45/267) of subjects, peripheral vascular disease in 16.1% (43/267) of subjects, solid tumors in 14.2% (38/267) of subjects, diabetes mellitus in 12.4% (33/267) of subjects, myocardial infarction in 11.2% (30/267) of subjects, and chronic kidney disease in 10.1% (27/267) of subjects.

Reviewer Comment: The proportions of subjects reporting pre-existing conditions overall, by SOC, and by preferred terms (PTs) were comparable between placebo and RBX2660 groups and typical of a study population with rCDI.

6.2.10.1.3 Subject Disposition

Of the 320 enrolled subjects, there were 40 screen failures, 31 of whom exited the study prior to randomization. Of the remaining 9 screen failures, 5 subjects were randomized before being assessed as screen failures, and 4 subjects were rescreened and randomized. The most common reason for subject screen failure was “did not meet protocol inclusion or exclusion criteria.”

Of the 289 subjects randomized to the RBX2660 arm (n=193) and placebo arm (n=96), 267 were treated with blinded RBX2660 (n=180) or blinded placebo (n=87).

Of the 267 randomized and treated subjects, 33 (12.4%) discontinued the study (RBX2660: 21 subjects, placebo: 12 subjects), 20 of whom withdrew during the blinded period and 13 of whom withdrew during the open-label period. The most common reason for withdrawal was “withdrawal by subject” (33%). Two subjects in the RBX2660 arm discontinued from the study due to fatal TEAEs that were not related to RBX2660 (discussed further in Section 6.2.12.3).

Table 22 summarizes subject disposition in the analysis populations used to evaluate the primary and secondary efficacy endpoints.

Table 22. Subject Disposition, Study 2017-01

Population	Placebo N=96 n (%)	RBX2660 N=193 n (%)	Total N=289 n (%)
Randomized	96 (100)	193 (100)	289 (100)
Intent to Treat (ITT)	96 (100)	193 (100)	289 (100)
Safety population	87 (90.6)	180 (93.3)	267 (92.4)
Modified Intent to Treat (mITT)	85 (88.5)	177 (91.7)	262 (90.7)
Per Protocol (PP)	78 (81.3)	167 (86.5)	245 (84.8)

Source: STN 125739/0, Clinical study report Study 2017-01, Table 6

[22] Hernandez-Garcia R., Garza-Gonzalez E. et. al. Application of the ATLAS score for evaluating severity of C. difficile infection in teaching hospitals in Mexico. The Brazilian Journal of Infectious Diseases. Aug 2015: Vol 19 (4): 399-402

Exposure
All 267 randomized and treated subjects were included in the safety population. A total of 65 subjects, including 41 in the blinded RBX2660 arm and 24 in the blinded placebo arm, were designated as treatment failures during the blinded portion and received an open-label dose of RBX2660. Therefore, a total of 204 subjects were exposed to RBX2660 (blinded and/or open-label), including 163 subjects who received one dose and 41 subjects who received two doses.

Protocol deviations
A total of 46 (15.9%) subjects had at least 1 reportable protocol deviation, including 15 subjects in the placebo group (15.6%) and 31 subjects in the RBX2660 group (16.1%). Protocol deviations included: eligibility criterion (n=16), study procedure not done per protocol – restricted medication taken (n=8), informed consent (n=6), study procedure out of window (n=4), and other (n=13).

Based on a detailed review, the Applicant concluded that none of these protocol deviations had a significant impact on subject safety or study outcomes.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was performed with a Bayesian hierarchical model that formally integrated treatment success rates from Study 2014-01 into Study 2017-01. See Sections 5.1 and 6.2.8 for details on the statistical approach.

Two interim analyses were also considered in the design to allow early stopping due to futility or evidence of outstanding efficacy. The success criteria for the interim and final analyses (first threshold) were initially set at posterior probability of superiority 0.99943 (equivalent to a frequentist one-sided threshold of 0.00125); the second threshold for final analysis was set at 0.97706 (equivalent to a frequentist one-sided threshold of 0.025). The Applicant adjusted the success thresholds based on the actual information fraction at the end of the study, which resulted in the first threshold being set at posterior probability of superiority 0.9993275, and the second at posterior probability of superiority 0.9750338.

Treatment outcomes for the mITT, ITT, and PP analysis populations are described in Table 23 below. The mITT population included 262 subjects with adjudicated outcomes for the primary efficacy analysis in Study 2017-01.

Table 23. Primary Endpoint Outcomes by Treatment Arm and Analysis Population, Study 2017-01, mITT, ITT, and PP Populations

Endpoint	mITT Placebo N=85 n (%)	mITT RBX2660 N=177 n (%)	ITT[a] Placebo N=96 n (%)	ITT[a] RBX2660 N=193 n (%)	PP Placebo N=78 n (%)	PP RBX2660 N=167 n (%)
Not treated	0	0	9	13	0	0
Number with adjudicated outcome	85	177	87	180	78	167
Treatment successes	53 (62.4)	126 (71.2)	53 (60.9)	126 (70.0)	48 (61.5)	120 (71.9)
Treatment failures	32 (37.6)	49 (27.7)	32 (36.8)	49 (27.2)	30 (38.5)	46 (27.5)
Indeterminate	0 (0.0)	2 (1.1)	2 (2.3)	5 (2.8)	0 (0.0)	1 (0.60)
Imputed as failures[b]	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)	0 (0.0)	1 (0.60)

Source: 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

Studies 2014-01 and 2017-01 investigated the same product in dosage, route, and formulation (for a single dose) and were generally similar in study design and study population. However, there were differences in treatment success definition, endpoint assessment period, and analysis population definition between the two studies. In an effort to improve exchangeability between Studies 2014-01 and 2017-01 and therefore provide more interpretable information for regulatory decision making, FDA requested a refined analysis with the following alignments between the two studies during the BLA review:

- Alignment of the primary endpoint definitions for treatment success: the Applicant indicated that the two definitions were identical although the language varied slightly.
- Alignment of the primary efficacy endpoint assessment period: since there was one week between the two enemas in Study 2014-01, there were nine weeks of assessment period compared to eight 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 eight weeks in Study 2014-01, in line with Study 2017-01.
- Alignment of analysis population (ITT, mITT, and PP) definitions between the two studies by applying Study 2017-01 analysis population definitions to Study 2014-01: Study 2014-01 and Study 2017-01 have notable differences in their analysis population definitions:
    - mITT: The mITT population for Study 2014-01 was defined as all subjects who completed at least one dose of study treatment excluding subjects who discontinued for any reason, and subjects with protocol deviations. In Study 2017-01, the mITT population excluded subjects who withdrew prior to treatment, subjects in whom treatment was attempted but not completed, and subjects who discontinued from the study prior to evaluation of treatment failure/success for the primary endpoint if the reason for the exit was not related to CDI symptoms.
    - ITT: The ITT population of Study 2014-01 included all randomized subjects, regardless of whether they completed their assigned study treatment. In comparison, the ITT population of Study 2017-01 included all randomized subjects but excluded subjects who exited prior to receiving blinded treatment.
    - PP: In the PP population for Study 2014-01, the exclusion criteria for ITT subjects who received the treatment to which they were randomized and were evaluable for treatment success/failure at 56 days after assigned treatment were related to withdrawal of consent, lost to follow-up, retention of enema, and major protocol deviations. In comparison, the PP population of Study 2017-01 included all subjects who successfully received blinded treatment except for protocol deviations and subjects who exited prior to the 8-week efficacy evaluation, if the reason for exit was not related to CDI symptoms.

Applying Study 2017-01 analysis population definitions to Study 2014-01 decreased the number of 2014-01 subjects in the ITT population by five, increased the number of subjects in the mITT population by two, and increased the number of subjects in the PP population by 38. Table 24 shows 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.

Table 24. 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	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	0.641	0.442	0.581	0.432	0.676	0.442

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

Results from the Bayesian hierarchical model with Study 2017-01 analysis population definitions applied to Study 2014-01 for the different analysis populations (mITT, ITT, and PP) are presented in Table 25.

Table 25. 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

The primary efficacy analysis that used a Bayesian hierarchical model showed that RBX2660 demonstrated a treatment effect estimate of 13.1% (95% credible interval 2.3% to 24.0%) with a posterior probability of superiority of 0.991. The primary efficacy results met the less stringent threshold of posterior probability of superiority >0.9750 (frequentist one-sided Type I error rate <0.025) but did not exceed the more stringent threshold of >0.9993 (frequentist one-sided Type 1 error rate <0.00125). The primary efficacy analysis was repeated for the ITT and PP populations, and the results met the second success threshold but missed the more stringent first success threshold.

CBER requested additional analyses to address baseline differences in age and number of previous episodes of CDI between Studies 2014-01 and 2017-01 and between treatment groups in Study 2017-01. The integrated Bayesian analysis was repeated using age (dichotomized as age <65 years and age ≥65 years) and previous number of CDI episodes at baseline (CDI=1, CDI=2, and CDI ≥3) as covariates. The results were generally similar to those of the primary efficacy analysis.

6.2.11.2 Analyses of Secondary Endpoints

The secondary efficacy endpoint of sustained clinical response was defined as Treatment Success of the presenting CDI recurrence and no new CDI episodes from 8 weeks after completing the blinded treatment through 6 months of follow-up. In this analysis, the sustained clinical response rates were not statistically significantly different between the RBX2660 (92.1%) and placebo (90.1%) groups (mITT population).

In an additional analysis requested by CBER, based on the time frame from baseline through 6 months (to better align with the definition of sustained clinical response and preserve randomization), the difference in sustained clinical response rates between the RBX2660 (65.5%) and placebo (56.5%) groups (mITT population) was not statistically significant (9.1% difference, 95% CI: -3.6, 21.7). Similar findings were observed for the ITT and PP populations.

Reviewer Comment: No significant treatment effect on sustained clinical response was observed across multiple populations and time frames, suggesting that the treatment effects of RBX2660 may be limited to the primary efficacy analysis timeframe.

6.2.11.3 Subpopulation Analyses

Analyses of the primary efficacy endpoint (treatment success within 8 weeks of blinded treatment) was repeated in all the analysis populations (ITT, mITT and PP) to assess for potential differences in the following subgroups: age (<65 years, ≥65 years), sex (female, male), race group (white, non-white), ethnicity (Hispanic-Latino, not Hispanic-Latino), site geography (outside the US, Eastern US, Southern US, Northern US, and Western US), number of previous episodes of CDI recurrence at baseline, and vancomycin use duration for qualifying CDI episode. The trend of a higher treatment success rate was preserved across the subgroups, although the estimated treatment effect varied.

Table 26. Subgroup Analyses of Treatment Success Within 8 Weeks, Study 2017-01, mITT population

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)

Subgroup / Analysis Population	Placebo n/N (%)	RBX2660 n/N (%)	Difference between RBX2660 and Placebo % (95% CI)
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[a]	--	--	--
≤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[b]	--	--	--
<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	--	--	--
≤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: Adapted from Table 21 in Study 2017-01 CSR
mITT=modified Intent to Treat
a. Applicant's results submitted with the original BLA
b. Adapted from Table 11 and 12 in Applicant's response to CBER information request #15 (IR#15) dated July 1, 2022 (STN 125739/0.25).

Reviewer Comment: Interpretation of subgroup analyses is limited by the small sample sizes.

6.2.11.4 Dropouts and/or Discontinuations

Please see Section 6.2.10.1.3 for information on subjects who discontinued from the study.

Please see Section 6.2.8 for a description of how subjects who discontinued from the study were handled in the primary efficacy analysis.

6.2.11.5 Exploratory and Post Hoc Analyses

The results of exploratory analyses are not discussed in this memo because they do not directly support the indication and use requested for approval.

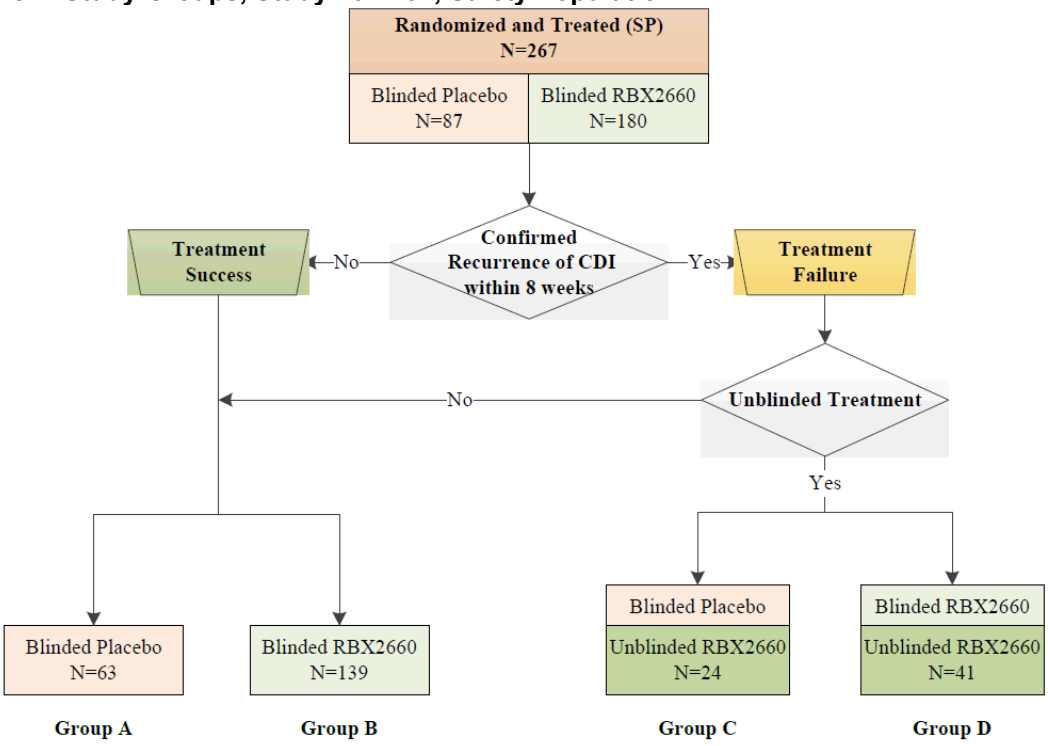
6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population was defined as the population of randomized subjects who had attempted or completed any blinded treatment. Subjects were analyzed according to the treatment they actually received in case misallocations occurred. The safety population was used in the analysis of all safety endpoints, unless otherwise specified. Safety data for participants who received open-label RBX2660 was summarized separately.

The blinded safety population consisted of 267 subjects who had any blinded treatment (87 subjects received one blinded placebo enema: 180 subjects received one blinded RBX2660 enema). Open label RBX2660 was administered to 41 subjects originally randomized to RBX2660 and 24 subjects originally randomized to placebo, as described in Figure 4 below.

Figure 4. Study Groups, Study 2017-01, Safety Population



Source: STN 125739, Clinical Study Report, page 77/102

Adverse events were categorized by severity, seriousness, and relatedness by site investigator.

Adverse events were independently reviewed by a blinded medical monitor with additional oversight by a blinded DSMB for evaluation of safety trends and stopping rules.

AEs were coded using MedDRA version 20.0.

Reviewer Comment: Analyses of TEAEs in the blinded period allow for comparison with placebo to better assess whether differences in observed TEAE rates between treatment groups might be due to RBX2660 exposure rather than chance alone.

6.2.12.2 Overview of Adverse Events

Solicited events

A subject diary was used to solicit the incidence and severity of anticipated events for the first 7 days after treatment. The solicited events included gas or flatulence, abdominal distension or bloating, rectal irritation or pain, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, rectal bleeding, nausea, vomiting, and fever ≥38.0° C (100.4°F).

During the open-label portion of the study, a separate diary was used to collect solicited event data for 7 days post open-label RBX2660. Compliance in returning subject diaries was summarized by calculating the proportion of subjects who answered all 14 daily questions for at least 80% of the expected number of diaries. Compliance with returning the diaries during the blinded treatment period was 95.6% (172/180) in the RBX2660

group and 92.0% (80/87) in the placebo arm) and during the open-label treatment period was 87.8% (36/41) among subjects originally randomized to RBX2660 vs. 87.5% (21/24) among subjects originally randomized to placebo.

Table 27 summarizes the number of subjects who reported each solicited event by the maximum severity reported post-treatment. The number of subjects for whom severity was missing was 2 in the placebo group, 3 in the RBX2660 group, for a total of 5.

Table 27. Solicited Events by Maximum Post-Treatment Severity During Blinded Period, Study 2017-01, Safety Population

Solicited Event Maximum Post-treatment Severity	Placebo (N=87) n (%)	RBX2660 (N=180) n (%)	Total (N=267) n (%)
Subjects with at least one solicited event	84 (96.6)	170 (94.4)	254 (95.1)
Gas flatulence*	--	--	--
Mild	33 (37.9)	84 (46.7)	117 (43.8)
Moderate	44 (50.6)	69 (38.3)	113 (42.3)
Abdominal distension or bloating	--	--	--
Mild	26 (29.9)	65 (36.1)	91 (34.1)
Moderate	33 (37.9)	37 (20.6)	70 (26.2)
Severe	10 (11.5)	12 (6.7)	22 (8.2)
Increased diarrhea	--	--	--
Mild	25 (28.7)	41 (22.8)	66 (24.7)
Moderate	22 (25.3)	40 (22.2)	62 (23.2)
Severe	9 (10.3)	21 (11.7)	30 (11.2)
Potentially life threatening	2 (2.3)	1 (0.6)	3 (1.1)
Abdominal pain or cramping	--	--	--
Mild	28 (32.2)	60 (33.3)	88 (33.0)
Moderate	22 (25.3)	42 (23.3)	64 (24.0)
Severe	17 (19.5)	16 (8.9)	33 (12.4)
Potentially life threatening	3 (3.4)	1 (0.6)	4 (1.5)
Constipation	--	--	--
Mild	12 (13.8)	21 (11.7)	33 (12.4)
Moderate	7 (8.0)	8 (4.4)	15 (5.6)
Severe	3 (3.4)	1 (0.6)	4 (1.5)
Potentially life threatening	2 (2.3)	0 (0.0)	2 (0.7)
Fever	--	--	--
Mild	9 (10.3)	17 (9.4)	26 (9.7)
Moderate	3 (3.4)	7 (3.9)	10 (3.7)
Severe	0 (0.0)	2 (1.1)	2 (0.7)
Potentially life threatening	0 (0.0)	1 (0.6)	1 (0.4)
Chills/severe shivering	--	--	--
Mild	19 (21.8)	36 (20.0)	55 (20.6)
Moderate	5 (5.7)	14 (7.8)	19 (7.1)
Severe	1 (1.1)	4 (2.2)	5 (1.9)
Potentially life threatening	0 (0.0)	0 (0.0)	0 (0.0)
Rectal irritation or pain	--	--	--
Mild	22 (25.3)	57 (31.7)	79 (29.6)
Moderate	19 (21.8)	17 (9.4)	36 (13.5)
Severe	5 (5.7)	5 (2.8)	10 (3.7)
Potentially life threatening	0 (0.0)	1 (0.6)	1 (0.4)

Solicited Event Maximum Post-treatment Severity	Placebo (N=87) n (%)	RBX2660 (N=180) n (%)	Total (N=267) n (%)
Rectal bleeding	--	--	--
Mild	12 (13.8)	23 (12.8)	35 (13.1)
Moderate	3 (3.4)	3 (1.7)	6 (2.2)
Severe	1 (1.1)	0 (0.0)	1 (0.4)
Potentially life threatening	1 (1.1)	0 (0.0)	1 (0.4)
Nausea	--	--	--
Mild	22 (25.3)	36 (20.0)	58 (21.7)
Moderate	11 (12.6)	23 (12.8)	34 (12.7)
Severe	5 (5.7)	4 (2.2)	9 (3.4)
Potentially life threatening	1 (1.1)	1 (0.6)	2 (0.7)
Vomiting	--	--	--
Mild	4 (4.6)	12 (6.7)	16 (6.0)
Moderate	0 (0.0)	3 (1.7)	3 (1.1)
Severe	1 (1.1)	1 (0.6)	2 (0.7)
Potentially life threatening	1 (1.1)	0 (0.0)	1 (0.4)

Source: STN 125739/0, Clinical Study Report, pages 88-89/102
*No severe events reported
Note: If a subject reported more than one severity score on the same date, the maximum severity was used. Percentage is calculated using the number of subjects in the column heading as the denominator.

Reviewer Comment: The most common solicited events were flatulence, abdominal distension/bloating and abdominal pain/cramping, and the majority of solicited AEs were 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. Severe solicited events of abdominal pain/cramping, increased diarrhea, and abdominal distension/bloating were more frequently reported in the placebo group compared to the RBX2660 group. While no conclusions could be drawn from these data, these imbalances may suggest that the solicited events are most reflective of the underlying recent CDI.

Treatment emergent adverse events (TEAEs)

TEAEs, including all non-solicited AEs and solicited events that were categorized as AEs (see Section 6.2.7), were reported in 66.7% (178/267) of subjects, most of which were mild or moderate, and the majority occurred within the 8-week follow-up of blinded treatment. The overall summary of TEAEs collected through 6 months is presented in Table 28 below.

Table 28. Overview Summary of Adverse Events, Study 2017-17, Safety Population, through 6 months

Category	Placebo N=87 n (%)	RBX2660 N=180 n (%)	Total N=267 n (%)
All TEAEs	52 (59.8)	126 (70.0)	178 (66.7)
Severe TEAEs	8 (9.2)	18 (10.0)	26 (9.7)
TEAEs leading to subject withdrawal	0	3 (1.7)	3 (1.1)
Serious TEAEs	6 (6.9)	15 (8.3)	21 (7.9)
Serious TEAEs related to RBX2660	0	0	0
Deaths	0	2 (1.1)	2 (0.7)

Source: Adapted from STN 125739, Clinical Study Report 2017-01, page 78/102, Table 14.3.3.1.1.1 and ADAE datasets

There were 708 TEAEs reported throughout Study 2017-01, the majority of which (n=401; 56.6%) occurred within the 8-week blinded follow-up period following treatment.

The overall summaries of TEAEs within the 8-week follow-up period are presented in Table 29 and Table 30 below for the blinded and open-label periods, respectively.

Table 29. Overview of Treatment Emergent Adverse Events Within 8-Week Follow-Up of Blinded Treatment, Study 2017-01, Safety Population

Category	Group A Placebo Only First Treatment N=63 n (%)	Group C Placebo/OL RBX2660 First Treatment N=24 n (%)	Group B Blinded RBX2660 First Treatment N=139 n (%)	Group D Blinded RBX2660/OL RBX2660 First Treatment N=41 n (%)
All TEAEs	30 (47.6)	8 (33.3)	79 (56.8)	15 (36.6)
Severe TEAEs	5 (7.9)	0	10 (7.2)	3 (7.3)
TEAEs leading to subject withdrawal	0	0	1 (0.7)	0
Serious TEAEs	3 (4.8)	1 (4.2)	6 (4.3)	3 (7.3)
Serious TEAEs related to RBX2660	0	0	0	0
Deaths	0	0	1 (0.7)	0

Source: Study 2017-01 Clinical Study Report, Table 14.3.1.1.3
Group A: Placebo randomized subjects who did not receive an unblinded RBX2660.
Group B: RBX2660 randomized subjects who did not receive an unblinded RBX2660.
Group C: Placebo randomized subjects who went on to receive an unblinded RBX2660.
Group D: RBX2660 randomized subjects who went on to receive an unblinded RBX2660.
For TEAEs counted in blinded treatment period, TEAEs are reported with an onset date after 8 weeks since blinded enema or up until the time the subject received the unblinded enema.

The most frequently occurring TEAEs within 8 weeks follow-up of blinded RBX2660 were related to events in the MedDRA SOC *Gastrointestinal disorders*. The preferred terms (PTs) most frequently reported within 8 weeks follow-up of blinded RBX2660 included diarrhea 35/267 (13.1%), abdominal pain 33/267 (12.4%) and nausea 18/267 (6.7%).

Reviewer Comment: No specific patterns or imbalances in TEAEs were noted in the 8-week blinded follow up period.

Table 30. Overview of Treatment Emergent Adverse Events Within 8-Week Follow-Up of Open-Label RBX-2660 Treatment, Study 2017-01, Safety Population

Category	Group C Placebo/OL RBX2660 N=24 n (%)	Group D Blinded RBX2660/OL RBX2660 N=41 n (%)
All TEAEs	11 (45.8)	23 (56.1)
Severe TEAEs	0 (0.0)	3 (7.3)
TEAEs leading to subject withdrawal	0 (0.0)	1 (2.4)
Serious TEAEs	1 (4.2)	3 (7.3)
Serious TEAEs related to RBX2660	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)

Source: Study 2017-01 Clinical Study Report, Table 14.3.1.1.4

The most frequently occurring TEAEs within 8-weeks follow-up of open-label RBX2660 were reported in the MedDRA SOC of *Gastrointestinal disorders*. The most commonly reported TEAEs within 8-week follow-up of open-label treatment (≥5% of subjects) included diarrhea (18.5%) and abdominal pain (7.7%).

Adverse reactions
In an analysis of TEAEs occurring within 8 weeks after blinded RBX2660 or placebo treatment, the most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to RBX2660 by the investigator), reported by ≥3% of RBX2660 recipients and at a rate greater than that reported by placebo recipients included: abdominal pain, (8.9% vs. 6.9%), diarrhea (7.2% vs. 3.4%), abdominal distention (3.9% vs. 2.3%), flatulence (3.3% vs. 0%), and nausea (3.3% vs. 1%). 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 and none were life-threatening.

6.2.12.3 Deaths

There were two deaths reported in Study 2017-01, neither of which was considered related to RBX2660 or the procedure. Brief narratives of the two deaths are as follows:

- A 79-year-old male was hospitalized for an SAE of congestive cardiac failure on Day 151 after RBX2660 and a nonserious event of chronic obstructive pulmonary disease. The subject died on Day 151 after the last (2nd) dose of RBX2660, due to multiple pre-existing comorbidities including chronic obstructive pulmonary disease, decubitus ulcer of the right heel and sacrum.
- A 75-year-old white male with a medical history of coronary artery bypass graft x4 experienced an event of cardiorespiratory arrest on Day 37 after receiving one dose of RBX2660.

Reviewer Comment: Both of the fatal events were reported as being related to pre-existing conditions by the investigator, and this reviewer agrees with the investigator and the Applicant that the deaths had other plausible etiologies.

6.2.12.4 All Serious Adverse Events

A total of 54 SAEs were reported by 26 subjects during Study 2017-01. Two of the 54 SAEs were fatal, as described above in Section 6.2.12.3. The most common SAE reported was CDI (CDI events that required hospitalization for ≥24 hours were classified as SAEs). Most of the serious TEAEs were related to CDI events (16/54; 29.6%) and pre-existing conditions (40/54; 74.1%). No serious TEAEs were reported to be related RBX2660 enema by the investigator and the Applicant.

Of the 54 SAEs, 28 were reported by 14 subjects within 8-weeks follow-up of blinded (n=20) or open-label (n=8) RBX2660. SAEs reported by more than one subject in Groups B-D included CDI (n=3), *C. difficile* colitis (n=2), and alcohol withdrawal syndrome (n=2). Table 31 summarizes the SAEs that occurred within 8-weeks follow up of blinded or unblinded RBX2660 by MedDRA SOC.

Table 31. Serious TEAEs Within 8 Weeks of Follow-Up of Blinded or Unblinded Treatment, by System Organ Class for Study 2017-01

System Organ Class	Group A Placebo Only N=63 n (%) events	Group B Blinded RBX2660 N=139 n (%) events	Group C Placebo/OL RBX2660 N=41 n (%) events	Group D Blinded RBX2660/OL RBX2660 N=24 n (%) events	Total N=267 n (%) events
Subjects with serious TEAEs	3 (4.8) 3	6 (4.3) 13	1 (4.2) 5	4 (9.8) 7	14 (5.2) 28
Cardiac disorders	0 (0.0)	1 (0.7) 1	0 (0.0)	0 (0.0)	1 (0.4) 1
Gastrointestinal disorders	0 (0.0)	2 (1.4) 4	1 (4.2) 3	0 (0.0)	3 (1.1) 7
General disorders and administration site conditions	0 (0.0)	1 (0.7) 1	0 (0.0)	0 (0.0)	1 (0.4) 1
Infections and infestations	2 (3.2) 2	3 (2.2) 3	0 (0.0)	3 (7.3) 5	8 (3.0) 10
Injury, poisoning and procedural complications	0 (0.0)	2 (1.4) 2	0 (0.0)	1 (2.4) 1	3 (1.1) 3
Metabolism and nutrition disorders	1 (1.6) 1	1 (0.7) 2	1 (4.2) 1	0 (0.0)	3 (1.1) 4
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (4.2) 1	1 (2.4) 1	2 (0.7) 2

Source: Reviewer's JMP Analysis review of ADAM and SDTM dataset, Study 2017-01 CSR, Table 14.3.1.7.1

The remaining 26 SAEs were reported after the 8-week follow-up period following blinded or open-label RBX2660. CDI was the only SAE reported by more than one subject in Groups B-D (n=2). Table 32 summarizes the serious TEAEs that occurred after 8-weeks follow up of blinded or unblinded RBX2660 by MedDRA SOC.

Table 32. Serious TEAEs After 8 Weeks of Follow-Up of Blinded or Unblinded Treatment, by SOC, Study 2017-01

System Organ Class	Group A Placebo Only N=63 n (%) events	Group B Blinded RBX2660 N=139 n (%) events	Group C Placebo/OL RBX2660 N=24 n (%) events	Group D Blinded RBX2660/OL RBX2660 N=41 n (%) events	Total N=267 n (%) events
Subjects with serious TEAEs	3 (4.8) 6	6 (4.3) 12	1 (4.2) 3	2 (4.9) 5	12 (4.5) 26
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4) 1	1 (0.4) 1
Gastrointestinal disorders	1 (1.6) 1	1 (0.7) 3	0 (0.0)	0 (0.0)	2 (0.7) 4
General disorders and administration site conditions	0 (0.0)	1 (0.7) 1	0 (0.0)	1 (2.4) 1	2 (0.7) 2
Infections and infestations	2 (3.2) 2	1 (0.7) 1	0 (0.0)	1 (2.4) 1	4 (1.5) 4
Injury, poisoning and procedural complications	0 (0.0)	1 (0.7) 1	0 (0.0)	0 (0.0)	1 (0.4) 1
Metabolism and nutrition disorders	0 (0.0)	1 (0.7) 1	1 (4.2) 1	0 (0.0)	2 (0.7) 2

System Organ Class	Group A Placebo Only N=63 n (%) events	Group B Blinded RBX2660 N=139 n (%) events	Group C Placebo/OL RBX2660 N=24 n (%) events	Group D Blinded RBX2660/OL RBX2660 N=41 n (%) events	Total N=267 n (%) events
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4) 1	1 (0.4) 1
Neoplasms benign, malignant and unspecified	0 (0.0)	1 (0.7) 1	0 (0.0)	0 (0.0)	1 (0.4) 1
Psychiatric disorders	0 (0.0)	1 (0.7) 2	1 (4.2) 2	0 (0.0)	2 (0.7) 4

Source: Study 2017-01 CSR, Table 14.3.1.7.4

Reviewer Comment: The proportions of subjects with SAEs are generally comparable between the placebo and RBX-2660 treatment groups. After review of the non-fatal SAEs, this reviewer agrees with the investigator and the Applicant that none of the SAEs are related to RBX2660. Some select SAEs of interest are described in more detail as follows. There were three cases of recurrent CDI in subjects who had a history of recurrent CDI prior to enrollment in the study. One subject had an SAE of abdominal abscess on Day 22, which was a complication of chronic sigmoid diverticulitis; it was regarded as unrelated to the enema and this reviewer agrees with the investigator and the Applicant. One subject on dialysis had an SAE of sepsis (methicillin-sensitive Staphylococcus aureus*) secondary to presumed central line-associated blood stream infection on Day 139, treated with intravenous vancomycin after dialysis. One subject who received 2 doses of RBX2660 reported a non-serious adverse event of urinary tract infection (UTI) due to* Escherichia coli *on Day 23 after the last dose of RBX2660, which was treated with nitrofurantoin. The subject also experienced an SAE of* Providencia *bacteremia (blood cultures positive for* Providencia rustigianii*) on Day 19 post last dose of RBX2660 and was treated with tobramycin and ceftriaxone, after which the event resolved. Peer-reviewed literature suggests that the most frequent clinical manifestation of* Providencia spp *is UTI. Given the delayed time of onset (>2 weeks) post receipt of RBX2660, UTI being very common in postmenopausal women and the significant association between older age females and bacteremic UTI, this reviewer considers the SAE of Providencia bacteremia to be not related to RBX2660 and more likely related to UTI.*

6.2.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) were not prespecified in the protocols. In an advice letter to the Applicant on September 11, 2020, CBER requested that the Applicant perform standardized MedDRA query (SMQ) analyses using the following terms to facilitate safety signal detection and monitoring:

- Gastrointestinal and nonspecific inflammation and dysfunctional conditions
- Gastrointestinal perforation, ulceration, hemorrhage or obstruction
- Hyperglycemia/new onset diabetes mellitus
- Noninfectious diarrhea
- Medication errors
- Sepsis
- Shock

- Systemic lupus erythematous
- Vasculitis
- Immune mediated/autoimmune disorders

The Applicant chose to categorize PTs identified in the following two SMQs as AESIs:

- Hyperglycemia/new onset diabetes mellitus
- Immune-mediated/autoimmune disorders

A total of six subjects reported AESIs following study treatment, including five reported after RBX2660 and one reported after placebo:

- A 59-year-old white female with a medical history of multiple sclerosis was reported to have a nonserious adverse event of worsening of multiple sclerosis on Day 9 post RBX2660. The investigator considered the event to be unrelated to RBX2660, and this reviewer agrees with the assessment.
- An 85-year-old white female with a 30-year history of rheumatoid arthritis (RA) and 29 year history of systemic lupus erythematous (SLE) was reported to have a nonserious adverse event of worsening RA of mild severity on day 67 post RBX2660 and nonserious event of worsening SLE on day 86 post RBX2660. The investigator considered the event of worsening RA and SLE to be possibly related to RBX2660, and possibly related to *C. difficile* disease. This reviewer agrees with the investigator's assessment; however, the relatedness of the events to RBX2660 appears less likely because of lack of a temporal relationship between the events and RBX2660 and the presence of the pre-existing condition.
- A 33-year-old white female with history of migraine, peptic ulcer disease, gastroesophageal reflux disease, endometriosis, epilepsy, renal impairment, idiopathic intracranial hypertension, pernicious anemia and Lyme disease was diagnosed with new onset Sjogren's syndrome on day 49 post RBX2660. The event was reported to be moderate in severity and treated with hydroxychloroquine. The investigator considered the Sjogren's syndrome to be unrelated to RBX2660, and this reviewer agrees with the assessment.
- A 61-year-old white female with history of depression, gastroesophageal reflux disease, diverticulitis, anxiety, obesity and hyperglycemia at baseline (fasting serum glucose of 11.2 mmol/L; reference range 3.3 to 6.4 mmol/L) was newly diagnosed with Type II diabetes mellitus on day 59 post RBX2660. The event was reported to be improved in the 6 months (day 176 post RBX2660) assessment but not recovered or resolved. The investigator considered the Type II diabetes mellitus to be unrelated to RBX2660 and this reviewer agrees with the assessment based on the presence of baseline hyperglycemia and other risk factors for Type II diabetes mellitus.
- A 44 year-old white male with history of granulomatous dermatitis, polycythemia, and anxiety was reported to have a nonserious adverse event of worsening of granulomatous dermatitis on day 19 after open label RBX22660. The investigator considered the event of worsening of granulomatous dermatitis to be moderate in severity, unrelated to RBX2660, and this reviewer agrees with the assessment based on the presence of pre-existing disease.
- A 59 year-old white female with history of gastroparesis, Type II (insulin dependent) diabetes mellitus, migraines, depression and generalized anxiety. The subject had a slightly elevated serum fasting glucose of 6.7 mmol/L at screening; reference range 3.3 to 6.4 mmol/L). A nonserious event of worsening of pre-existing diabetes mellitus was reported on day 59 post placebo and noted

to be improved on day 176. The investigator considered the worsening of diabetes mellitus unrelated to placebo.

Reviewer Comment: All seven AESIs reported by the six subjects were mild or moderate in severity, and the majority were due to worsening of pre-existing conditions (multiple sclerosis, rheumatoid arthritis, systemic lupus erythematous, diabetes mellitus, impaired fasting glucose and granulomatous dermatitis). There was a new onset diagnosis of Sjogren's syndrome and Type II diabetes mellitus in one subject each. No patterns or clusters were observed to support a specific risk among recipients of RBX2660 compared to placebo.

In Study 2017-01, there were two major complications of CDI events related to new CDI reported in two subjects randomized to blinded RBX2660 enema. One subject experienced septic shock and emergency colectomy as major complications of new CDI, and these complications required ICU admission. The second subject was admitted to the ICU for a new, severe CDI. Hospitalizations due to rCDI occurred in 4 subjects (1.5%) treated with RBX2660 within 8-week follow-up of blinded treatment. Three subjects required hospitalization due to rCDI within the 8-week follow-up period of open-label treatment, and none resulted in ICU admission. None of the subjects in the placebo group with rCDI required hospitalization.

Reviewer Comment: One study conducted in a hospital in Canada suggested that a hospital admission was necessary for approximately one-third of CDI recurrences; the study also noted CDI related ICU admission in 4.5% and 3.1% and colectomy in 0.6% and 1.6% of first and second recurrences of CDI, respectively.[23] Thus, these events reported in Study 2017-01 did not raise a safety concern.

6.2.12.6 Clinical Test Results

No clinical laboratory tests were drawn for safety monitoring during the follow-up period as part of the study protocols. However, if a subject had a suspected recurrence of CDI, stool samples were submitted for analysis. The results of the stool tests were listed in CDI History and New CDI Events.

6.2.12.7 Dropouts and/or Discontinuations

Study discontinuation due to death occurred in 2 subjects ((b) (6)). Please see Section 6.1.12.3 for further details on these 2 subjects. The deaths were not related to the IP or the enema procedure.

6.2.13 Study Summary and Conclusions

The primary efficacy analysis for study 2017-01 resulted in an estimated success rate of 0.71 in the RBX2660 group and 0.57 in the placebo group for the mITT population; the difference in treatment success rates was 13.1% (95% credible interval: 2.3%, 24.0%). The posterior probability that RBX2660 was superior to placebo was 0.991, which met the second (less stringent) success threshold of 0.9750338, equivalent to a frequentist one-sided Type 1 error rate <0.025 but did not meet the first (more stringent) success threshold of 0.9993275, equivalent to a frequentist one-sided Type 1 error rate

23 Sheitoyan-Pesant C, Chakra C, Pépin J, Marcil-HéguyA , et al, Clinical and Healthcare Burden of Multiple Recurrences of *Clostridium difficile* Infection, *Clinical Infectious Diseases*, Volume 62, Issue 5, 1 March 2016, Pages 574–580, https://doi.org/10.1093/cid/civ958

<0.00125. The primary efficacy endpoint analysis using the ITT and the PP populations led to the same conclusion.

The proportions of subjects reporting solicited events in the RBX2660 group were generally comparable to or lower than the placebo group.

TEAEs were most commonly reported in the MedDRA SOC *Gastrointestinal disorders* and were mostly mild to moderate in severity. There were 54 serious TEAEs, including two deaths, none of which were considered related to the RBX2660 or the enema procedure by this reviewer.

The most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to RBX2660 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 events declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse drug reactions were mild to moderate in severity.

6.3 Trial #3, Study 2019-01

Study 2019-01 is an ongoing Phase 3, prospective, multi-center, open-label study to demonstrate the safety, tolerability and effectiveness of RBX2660 for single and repeat administration in a broader population to include subjects with irritable bowel disease (IBD).

Protocol ID: 2019-01
ClinicalTrials.gov ID: NCT03931941
Date First Subject Enrolled: July 30, 2019
Ad-hoc data cutoff: April 20, 2021
Completion date: Study is ongoing

6.3.1 Objectives

- Primary objective:
  - To evaluate safety and tolerability of RBX2660 in subjects with rCDI
- Secondary objectives:
  - To evaluate the efficacy of RBX2660 in preventing recurrent episodes of CDI through 8 weeks after treatment
  - To evaluate the sustained clinical responses rate of RBX2660 after treatment
- Other objectives:
  - To evaluate health-related quality of life in subjects with CDI as measured by the Cdiff32 questionnaire
    - The Cdiff32 health-related quality of life instrument comprises 32 self-administered questions about the impact of CDI in 3 broad domains pertaining to the health of CDI patients (physical, mental and social). Some of the questions are scored ‘1 (best) to 5 (worst)’ and others are score ‘1 (worst) – 5 (best).’ For calculation of an overall Cdiff32 score, each of the raw scores for the 32

questions are standardized to '1 (worst) to 5 (best)', converted from '1 to 5' to '0 (worst score) to 100 (best score)' and then average. Changes from screening were summarized using descriptive statistics at 1 and 8 weeks, and 4 and 6 months after study treatment using the safety population.

- To identify baseline characteristics predictive of efficacy outcomes
- To characterize the changes from baseline fecal microbial composition at each timepoint
- To evaluate the efficacy of a second dose of RBX2660 in preventing CDI recurrence
- To assess the clearance rate of vancomycin-resistant enterococcus (VRE) in subjects who are carriers at baseline
- To assess the clearance of *C. difficile* following enema treatment at 1, 4, 8 weeks, and 6 months after study treatment in subjects receiving RBX2660.

Reviewer Comment: The review of efficacy data in this memo is limited to the primary and secondary objectives that CBER considered most pertinent to the indication and prescribing information to be approved.

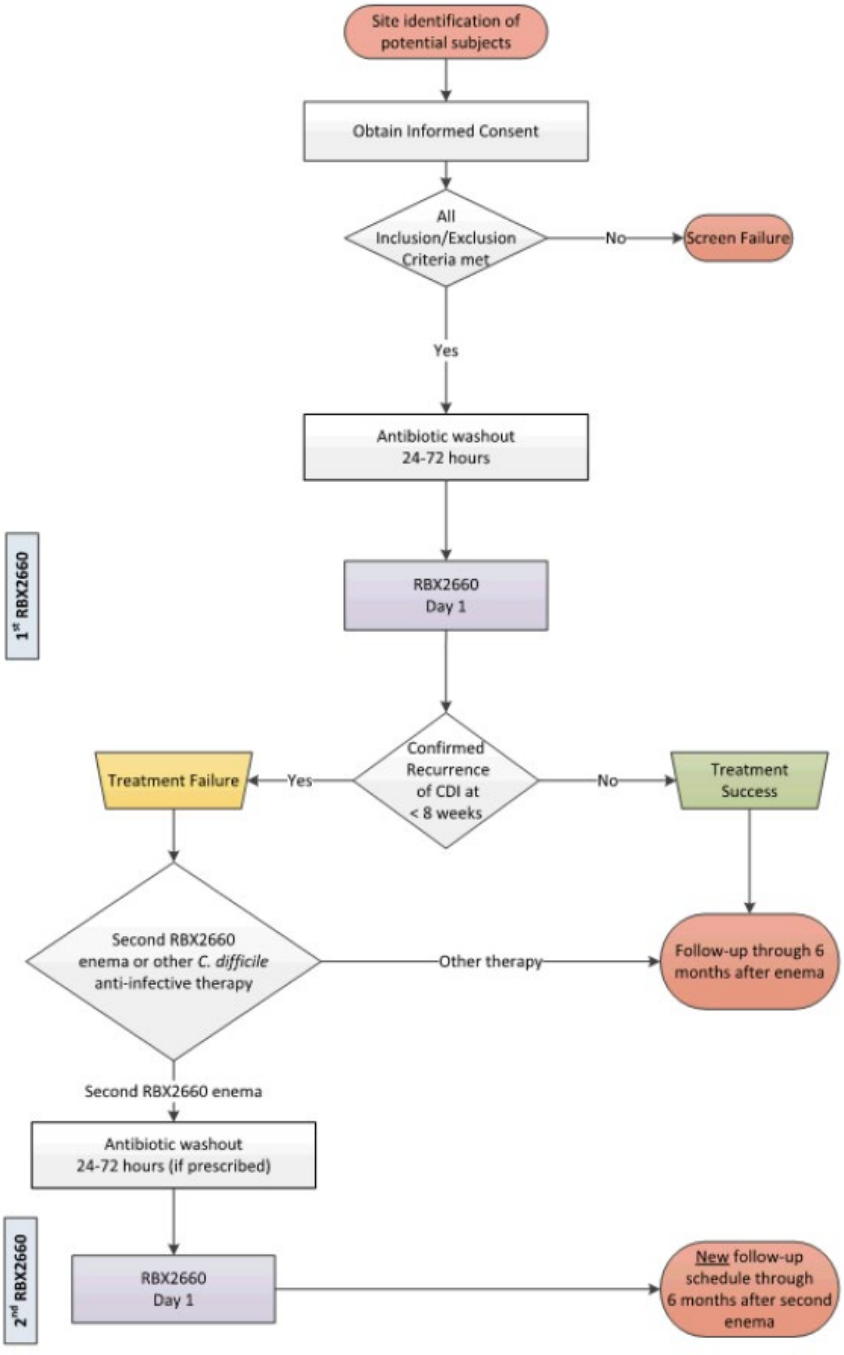
6.3.2 Design Overview

Study 2019-01 was a prospective, multi-center, open-label, Phase 3 study to evaluate the safety and tolerability of RBX2660 for the prevention of rCDI in subjects with prior rCDI that resolved with antibiotic treatment.

Study treatment was completed within 21 days following screening and within 24 to 72 hours of completion of antibiotic treatment (i.e., antibiotic washout). All subjects received open-label RBX266.

Enrollment of up to 500 subjects is planned. The study design schematic for Study 2019-01 is presented in Figure 5.

Figure 5. Study Design for Study 2019-01



Source: STN 125739/0, Clinical Study Report 2019-01, page 21/78

At the time of enrollment, subjects were already taking or had been prescribed antibiotics to control rCDI symptoms. Safety and efficacy were assessed at the 1 and 8 week in-office follow-up visits. Scheduled assessments included discussions with the subject on CDI symptoms and review of the subject diary. Subject symptoms were reviewed during phone assessments at week 4 and at 4 and 6 months. The last phone call occurred 6 months after the last RBX2660 administration, including 6 months after a second RBX2660 study treatment, if applicable. An unscheduled in-office visit to assess

possible treatment failure occurred in cases of possible recurrence, where new stool samples were collected from subjects to test for the presence of *C. difficile,* if a CDI recurrence was suspected any time within 8 weeks of the last study enema. Subjects were offered a second RBX2660 enema if they were deemed failures following treatment per the protocol-specified Treatment Failure definition.

6.3.3 Population

Inclusion Criteria

Key inclusion criteria included:

- Adults ≥18 years old.
- Medical record documentation of either a) a current diagnosis or history of rCDI as determined by the treating physician, or b) has had at least 2 episodes of severe CDI resulting in hospitalization.
- Currently taking or had just been prescribed antibiotics to control CDI-related diarrhea at the time of enrollment. Note: Subject's CDI diarrhea had to be controlled (<3 unformed/loose, i.e., Bristol Stool Scale type 6 to 7, stools/day for 2 consecutive days prior to completion of the antibiotic treatment.)
- Willing and able to have an enema(s) and complete the stool and blood testing required for the study.
- Agreed not to take non-dietary probiotics from Screening through 8 weeks after receiving the last study enema (including OTC and prescription).
- Agreed not to take any oral vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide, bezlotoxumab, or intravenous immunoglobulin (IVIG) through the 8-week follow-up assessment, unless newly prescribed by a treating investigator during the course of the study as a result of rCDI diagnosis. Note: Use of IVIG for treatment of a non-CDI indication was allowed.

Exclusion criteria

Key exclusion criteria included:

- A known history of refractory CDI.
- Continued CDI diarrhea despite being on a course of antibiotics prescribed for CDI treatment.
- Required systemic antibiotic therapy for a condition other than CDI.
- Prior participation in a Rebiotix clinical study receiving RBX2660.
- FMT within the past 6 months.
- Receipt of bezlotoxumab (CDI monoclonal antibodies) within the last year, prior to study enrollment.
- FMT with an associated SAE related to the FMT product or procedure.
- Disease symptoms (diarrhea) caused by a confirmed intestinal pathogen other than *C. difficile*.
- Currently had a colostomy.
- Intraabdominal surgery within the last 60 days. Note: laparoscopic procedures that did not involve the gastrointestinal tract were permitted.
- Planned surgery requiring perioperative antibiotics through the 8-week follow-up
- assessment.
- Life expectancy of <6 months.
- CD4 count <200/mm^3 during screening.
- An absolute neutrophil count of <1000 cells/µL during screening.

Reviewer Comment: The eligibility criteria were less restrictive than previous RBX2660 studies, to allow for safety evaluation in a broader rCDI population intended to be more representative of standard clinical practice (e.g., laboratory diagnosis of toxigenic C. difficile infection was not required, and IBD, IBS and immunocompromising diseases were not excluded).

6.3.4 Study Treatments or Agents Mandated by the Protocol

Study treatment included RBX2660 (see Section 4.1 for a description of study drug product) administered via enema.

6.3.5 Directions for Use

See Section 6.1.5.

RBX2660 was administered by an authorized RBX2660 administrator qualified and trained in administration, instructions for use, and standard site procedures. Subjects remained at the site under supervision for at least 1-hour post-enema administration for vital sign assessment (temperature, heart rate, blood pressure, respiratory rate) and observation.

6.3.6 Sites and Centers

Subjects were enrolled at 29 sites (24 in the United States and 5 in Canada).

6.3.7 Surveillance/Monitoring

The schedule of study procedures is shown in Table 33.

Table 33. Study 2019-01 Schedule of Events

Activity	Screening (Enrollment)	Baseline / Enema Administration (≤ 21 days from Screening)	Follow-up Visits: 1- and 8-Week (± 3 days) Assessments[a]	Follow-up Phone Assessment: Week 4 (± 3 days)	Follow-up Phone Assessment: 4 and 6 months (± 14 days)	Unscheduled Possible Recurrence Visit	Second Enema Administration (≤ 21 calendar days post Tx Failure)	Second Enema Follow- up Phone Assessment: 1-, 4-, and 8-weeks (± 3 days), and 6 months (± 14 days)
Informed consent obtained	X							
Demographics, medical history	X							
Prescribe/continue antibiotics for CDI symptom control	X							
Physical exam	X							
Stool sent to Rebiotix by subjects for testing and archiving (optional)	X		X	X	X	X		X
Central Lab CBC w/differential testing[c]	X[c]	X						
Central Lab CD4 testing	X[c]							
Central Lab CMP & CRP testing	X							
C. difficile testing[d]						X[d]		
Central Lab stool and blood testing		X						
Urine pregnancy testing performed at site (if applicable)	X	X					X	
Cdiff32 Questionnaire	X		X		X	X		
Inclusion/exclusion criteria confirmed	X	X						
24-72hr washout		X					X[g]	

Activity	Screening (Enrollment)	Baseline / Enema Administration (≤ 21 days from Screening)	Follow-up Visits: 1- and 8-Week (± 3 days) Assessments[a]	Follow-up Phone Assessment: Week 4 (± 3 days)	Follow-up Phone Assessment: 4 and 6 months (± 14 days)	Unscheduled Possible Recurrence Visit	Second Enema Administration (≤ 21 calendar days post Tx Failure)	Second Enema Follow- up Phone Assessment: 1-, 4-, and 8-weeks (± 3 days), and 6 months (± 14 days)
period confirmed								
Enema administered		X					X	
Product complaint (if applicable)		X					X	
CDI symptoms assessed		X	X	X	X	X	X	X
Vital signs assessed	X	X				X	X	
Weight	X		X	X	X			X
Subject Diary discussed/reviewed	X	X	X[e]					
Employment status assessed	X		X[f]		X			
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events assessed		X	X	X	X	X	X	X
Solicited events assessed[b]		X	X[b]					

Source: STN 125739/0, Clinical Study Report for Study 2019-01, page 27/78
CBC=complete blood count; CDI=*C. difficile* infection; CMP=comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, albumin, AST, ALT, alkaline phosphatase, bilirubin [direct, indirect and total], and glucose); CRP=C-reactive protein, Tx=treatment.
a. Documented Treatment Failures may receive a second RBX2660 enema.
b. Study enema until the day prior to the 1-week Follow-up visit. The Subject Diary is reviewed at the 1- at increase in severity from Screening should be assessed for a possible adverse
c. Exclusion criteria for absolute neutrophil count and CD4 should be assessed based on the blood samples collected at the Screening visit.
d. Tested at the central laboratory.
e. Subject Diary is reviewed only at the 1-week Follow-up visit.
f. Collected at the 8-week follow-up visit only.
g. If ant biotics were administered to manage CDI recurrence.

Safety assessments included:

1. Solicited events were collected from the day of enrollment through Day 7 after treatment and from the day of second enema (if applicable) through 1-week visit. Solicited events included gas (flatulence), abdominal distension or bloating, abdominal pain or cramping, rectal irritation or pain, rectal bleeding, chills/severe shivering, increased diarrhea, constipation, nausea, vomiting and fever ≥37.8° C (100.0°F). A solicited event became an AE after the data entry had been reviewed by the site investigator to determine if the severity grade entered matched the severity definition provided in the diaries. Solicited AEs with increased severity from pre- to post-enema were captured as an AE or SAE as determined by the site's investigator.
2. All AEs, including SAEs, were collected at the in-person site visits, which included a discussion of symptoms with the subjects at weeks 1 and 8, and during phone calls at week 4 and months 4 and 6, with a review of the subject diary at baseline and at the 1-week follow-up visit. An AE was considered serious if it was life threatening, resulted in death, in-patient hospitalization ≥24 hours or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or was a congenital anomaly/birth defect.
3. Frequency of major complications of CDAD including death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, or intensive care unit (ICU) admission

Adverse events were graded by the site investigators for severity with the adapted Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events and Addendum 3: Rectal Grading Table for Use in Microbicide Studies (May 2012).
The DSMB reviewed AEs reported during the study to look for trends and unanticipated events, either in severity, seriousness or incidence, and to assess if a study stopping rule was triggered.

An independent DSMB, consisting of two physicians specializing in infectious diseases or gastroenterology who have experience managing subjects with rCDI and were not investigators in the study, reviewed safety data for trends for the final analysis and determined if the study should be paused, terminated, or other actions taken based on their assessment of:

- Probable cause that IP or the enema procedure contributed to a pathogenic intestinal infection in the stool of any subject or
- Any events of major significance such as death or other serious outcome for which a causal connection with the IP is plausible and represented an excess of the important adverse events(s).

6.3.8 Endpoints and Criteria for Study Success

Safety

- Primary safety endpoint:
    - Number of subjects with RBX2660 and/or enema-related treatment emergent adverse events (TEAEs).
- Other safety endpoints:
    - Number of adverse events per subject
    - Timing of attributable TEAEs
    - Duration of TEAEs

- Relatedness of TEAEs
- Severity of TEAEs
- Causality of TEAEs to RBX2660, enema, *C. difficile*, or prior condition
- Number of each of the following CDI-related TEAEs through 8 weeks post-treatment: death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, and intensive care unit (ICU) admission
- Major complications of CDI and onset of new chronic conditions relative to treatment administration

Efficacy

Secondary efficacy endpoints included:

- Recurrence of CDI through 8 weeks after treatment
- Loss of sustained clinical response through 6 months after treatment

Definitions for the efficacy analysis included the following:

- Treatment success: Defined as absence of CDI diarrhea through 8 weeks after completing a study treatment
- Treatment failure: Defined as presence of CDI diarrhea within 8 weeks of administration of a study enema, which includes a positive stool test for *C. difficile* as determined by the central laboratory
- Sustained clinical response: Defined as treatment success of the presenting CDI recurrence and no new CDI episodes through 6 months after completing a study treatment

Initial determination of treatment success and treatment failure was determined by the site investigator followed by independent EAC adjudication.

Subjects who exited prior to the 8-week efficacy assessment due to CDI-related symptoms were considered Indeterminate and analyzed as Treatment Failures. The ITT analysis considered all subjects who exited prior to the 8-week efficacy assessment as Treatment Failures regardless of Treatment Failure documentation.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The planned enrollment is up to 500 subjects.

The efficacy analyses were performed ad hoc, with a data cut-off of April 20, 2021.

All statistical tests were two-sided with a significance level of $\alpha=0.05$ and confidence intervals were constructed at the level of 95%, unless otherwise specified. Descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, interquartile range [IQR], minimum, and maximum) were generated for continuous variables. The number and percentage of non-missing subjects were generated for discrete/categorical variables. Descriptive statistics were provided for all subjects.

Table 34. Subjects with Protocol Deviations in ITT, Study 2019-01

Deviation Type	Total (N=264) n (%)
Subjects with at least one protocol deviation	26 (9.8%)
Reason for protocol deviation	--
Laboratory not done per protocol	10 (3.8)
Inclusion or exclusion criteria not met	9 (3.4)
Medications not done per protocol	5 (1.9)
Informed consent	4 (1.5)
Study procedures not performed per protocol	2 (0.8)
Diary was not returned by the subject	1 (0.4)

Source: STN 125739/0 Clinical Study Report for Study 2019-01, page 47/78, Table 14.1.1.8
Percentage calculated using the N' number of subjects in the specified site as the denominator
Note: some subjects had protocol deviations in multiple categories

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Study 2019-01 include four analysis populations:

- Safety population: subjects who had any treatment attempted or completed. This population was used in the analysis of all safety endpoints, including the primary endpoint.
- The intent to treat population (ITT): defined as all enrolled subjects. This population was used in the analysis of the secondary and other endpoints.
- The modified intent to treat population (mITT): defined as all enrolled subjects who successfully received treatment but excluded subjects in whom treatment was attempted but not completed.
    - Exclusions include the following:
        - Subjects who discontinued from the study prior to evaluation of treatment failure/success for the 8-week efficacy endpoint if the reason for exit was not related to CDI symptoms.
        - Subjects who withdrew consent
        - Death of subjects unrelated to CDI
    - Subjects who exited prior to the 8-week efficacy assessment due to CDI-related symptoms were considered indeterminate and counted as treatment failures, even if documentation as required per protocol was not on file for treatment failure.
    - The mITT was the primary analysis population for efficacy.
- Per-Protocol population (PP): defined as all subjects who successfully received treatment, and analyzed according to the treatment received, excluding subjects who have documented deviations to inclusion/exclusion criteria and/or subjects who exited prior to the 8-week efficacy evaluation if the reason for the exit was not related to CDI symptoms in the same manner as the mITT population. The secondary and other endpoints were evaluated using the PP population.

6.3.10.1.1 Demographics

The demographics and baseline characteristics of subjects in study 2019-01 is below.

Table 35. Demographics and Baseline Characteristics, Study 2019-01

Characteristic	Total N=254 n (%)
Age	--
Mean years [range]	58.8 [18 – 94]
<65, n (%)	154 (60.6)
≥65, n (%)	100 (39.4)
Sex, n (%)	--
Male	84 (33.1)
Female	170 (66.9)
Ethnicity, n (%)	--
Hispanic or Latino	7 (2.8)
Not Hispanic or Latino	246 (96.9)
Not Reported	1 (0.4)
Race, n (%)	--
Black/African American	8 (3.1)
White	237 (93.3)
Other	4 (1.6)
Asian	2 (0.48
Multiple	3 (1.2)

Source: Adapted from STN 125739/0, Clinical Study Report 2017-01, Table 8 and 14.1.2.4

Reviewer Comment: Most of the subjects in study 2017-01 were White, not-Hispanic or Latino, and female, which was similar to the demographics of subjects seen in study 2014-01 and 2017-01.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The baseline disease characteristics of subjects in study 2019-01 is below.

Table 36. Baseline Disease Characteristics, Study 2019-01

Category	Total N=54 n (%)
Total number of CDI episodes before blinded treatment	--
≤1	13 (5.1)
2	76 (29.9)
≥3	165 (65.0)
Episode duration (days)	--
Mean	45.2
Minimum - Maximum	10 - 396

Source: STN 125739, Adapted from Clinical Study Report 2019-01, Table 9 and Table 14.1.2.4

In the safety population, 94/254 (37.0%) of the subjects had 3 CDI episodes before the first dose of RBX2660 and 76/254 (29.9%) of the subjects had 2 CDI episodes before the first dose of RBX2660, with a mean duration of 45.2 days of qualifying CDI episodes.

Among the most frequent conditions listed in medical history were hypertension (41.7% of subjects), depression (29.5% of subjects) and Crohn's disease (4.7% of subjects). In total, 27 subjects (10.6%) reported a history of irritable bowel syndrome (IBS) and 19 subjects (7.5%) reported a history of inflammatory bowel disease (IBD).

6.3.10.1.3 Subject Disposition

A total of 293 subjects were screened, 29 of whom were screen failures. Of the 264 subjects enrolled (ITT population), 10 (3.8%) were never treated. Thus, the safety population included 254 subjects who received at least one RBX2660 enema. Of these, 43 subjects received a second RBX2660 enema for CDI recurrence.

Of the 254 subjects in the safety population, 23 (9.1%) discontinued from the study, including 3 subjects with fatal adverse events that led to discontinuation, none of which were assessed as being related to RBX2660 or the enema procedure (see Section 8.4.1 for more details). The majority of subjects discontinued from the study due to withdrawal by subject.

Protocol deviations
A total of 31 protocol deviations were reported for 26 subjects (9.8%). Protocol deviations included: not performed per protocol (labs, medications, study procedures; n=17), eligibility criteria not met (n=9), informed consent (n=4), and dairy not returned (n=1).

Based on a detailed review of the protocol deviations, the Applicant concluded that none of these protocol deviations had a significant impact on subject safety or study outcomes.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Not applicable.

6.3.11.2 Analyses of Secondary Endpoints

Results of the descriptive ad hoc efficacy analyses for Study 2019-01 are presented in Table 37.

Table 37. Interim Efficacy Analyses, Study 2019-01

Category/Statistics	mITT (N=248) n (%)	ITT (N=264) n (%)	PP (N=236) n (%)
Adjudicated, N'	154	158	143
Treatment success[a], n (%)[a]	113 (73.4)	113 (71.5)	104 (72.7)
Treatment failure, n (%)	37 (24.0)	37 (23.4)	36 (25.2)
Indeterminate, n (%)	4 (2.6)	8 (5.1)	3 (2.1)
Unadjudicated	94	106	93
Adjudicated subjects who completed or discontinued from the study, N'	100	104	91
Sustained clinical response, n (%)[b]	82 (53.2)	82 (51.9)	75 (52.4)

Source: STN 125739/0, Adapted from Clinical Study Report for Study 2019-01, page 54-55/78
Note: Percentage calculated using N', the number of adjudicated subjects as the denominator.
a. Treatment Success - absence of CDI diarrhea through 8 weeks after completing first enema treatment.
b. Sustained Clinical Response - Treatment Success of the presenting CDI recurrence and no new CDI episodes for greater than 8 weeks after completing the first enema treatment during the 6 months of follow-up.
Unadjudicated subjects: treatment outcome not adjudicated by Endpoint Adjudication Committee at the time of data cutoff.

In the primary efficacy (mITT) population, 154/248 (62.1%) of the subjects had adjudicated treatment outcomes. There were 94/248 (37.9%) subjects whose treatment outcome had not been adjudicated by the EAC at the time of the data cutoff.
Six months of follow-up after RBX2660 enema was completed in 100/154 (64.9%) of the adjudicated subjects.

Subjects who exited prior to the 8-week efficacy assessment due to CDI-related symptoms were considered indeterminates and analyzed as treatment failures.

Reviewer Comment: Treatment success rates of ~70% were observed across analysis population, with sustained clinical response rates of 75-82%. Limitations in interpretation of efficacy data from this study include that the results were based on interim, descriptive analyses from an open-label study with no comparator, which was not designed to draw conclusions about product efficacy.

6.3.11.3 Subpopulation Analyses

Subgroup analyses by age (<65 years, ≥65 years), sex (Female, Male), race group (White, Nonwhite), ethnicity (Hispanic-Latino, not Hispanic-Latino), site geography (outside the US, Eastern US, Southern US, Northern US, and Western US), and number of previous episodes of CDI recurrence at baseline were planned for the efficacy endpoint recurrence of CDI within 8-week follow-up, provided a sufficient sample size (of at least 20 subjects) existed for each subgroup. None of the subgroups showed notable differences in their results.

6.3.11.4 Dropouts and/or Discontinuations

In the ITT population, 23/264 (8.7%) of subjects discontinued from the study. The most frequently reported reason for subject discontinuation from study was due to subject withdrawal (11/254; 4.2%). Fatal adverse events that led to study discontinuation were reported in 3/254 (1.2%) of subjects; none of these events were assessed as being related to RBX2660 or the enema procedure (see Section 8.4.1 for more details). Of the 23 subjects that discontinued from the study, 12/264 (4.5%) subjects were treated and withdrew prior to the 8-week primary endpoint evaluation.

Please see Section 6.3.8 for a description of how subjects who discontinued from the study were handled in the primary efficacy analysis.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety was assessed based on the safety population of 254 subjects.

Adverse events were categorized by severity, seriousness, and relatedness by site investigator.

Adverse events were independently reviewed by a medical monitor with additional oversight by a DSMB for evaluation of safety trends and stopping rules.

AEs were coded using MedDRA version 20.0.

6.3.12.2 Overview of Adverse Events

Solicited events

A subject diary was used to solicit the incidence and severity of anticipated events for the first 7 days after the first treatment. The solicited events included gas or flatulence, abdominal distension or bloating, rectal irritation or pain, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, rectal bleeding, nausea, vomiting, and fever ≥38.0°C (100.4°F).

Compliance with returning the subject diary was 89.4% (227/254 subjects). Completed diary compliance was assessed with a cutpoint of <80% and ≥80%, where completed was defined as having responses for all 11 daily questions for at least 80% of the expected number of diaries; 229/254 (90.2%) subjects completed at least 80% of the daily questions.

Solicited events were reported by 225/254 (88.6%) of the subjects. The most commonly reported solicited events (≥30% of subjects) from Day 1 through Day 7 following first enema were gas or flatulence, abdominal pain or cramping, abdominal distention or bloating, increased diarrhea, and nausea. The majority of solicited events were reported as mild or moderate in severity. Severe solicited events included abdominal pain or cramping (11% of subjects), abdominal distension or bloating (7.1% of subjects), diarrhea (6.7% of subjects), constipation (3.9% of subjects), rectal irritation or pain in (2.8% of subjects), chills/severe shivering (2.0% of subjects), and rectal bleeding (0.8% of subjects).

Treatment emergent adverse events (TEAEs)

TEAEs, including all non-solicited AEs and solicited events that were categorized as AEs (see Section 6.3.7), were reported in 150/254 (59.1%) of the subjects in Study 2019-01, most of which were mild or moderate in severity. Severe TEAEs were reported by 13.0% of subjects (n=33).

An overall summary of TEAEs reported during the overall study period through the data cut-off date of April 20, 2021, is presented in Table 38.

Table 38. Overview of Treatment Emergent Adverse Events, Study 2019-01, Safety Population, duration of study

TEAE Category	Total N=254 n (%)
Subjects with TEAEs	150 (59.1)
Severe TEAEs	33 (13.0)
TEAEs leading to discontinuation	4 (1.6)
TEAEs leading to death	3 (1.2)
Related to RBX2660	44 (17.3)
Serious TEAEs	22 (8.7)
Related to RBX2660	0

Source: STN 125739/0, Clinical Study Report 2019-01, page 60/78, Table 14.3.1.1.1, and JMP Reviewer ADAM Dataset Analysis

No serious TEAEs were reported to be related to RBX2660.

Table 39 lists the most common frequently occurring TEAEs within and after the 8-week follow-up of the first treatment.

Table 39. Treatment Emergent Adverse Events Within and After 8 Weeks of First RBX2660 Dose, by System Organ Class and Preferred Term, Study 2019-01, Safety Population

System Organ Class Preferred Term	Within 8-Week Follow-Up N=254 n (%)	After 8-Week Follow-Up N=254 n (%)
Subjects with TEAEs, n (%)	130 (51.2)	40 (15.7)
Gastrointestinal disorders	87 (34.3)	17 (6.7)
Diarrhea	40 (15.7)	5 (2.0)
Abdominal pain	25 (9.8)	3 (1.2)
Nausea	23 (9.1)	0
Flatulence	14 (5.5)	2 (0.8)
Abdominal distension	13 (5.1)	0
Constipation	9 (3.5)	0
Abdominal discomfort	6 (2.4)	0
General disorders and administration site conditions	18 (7.1)	0
Chills	8 (3.1)	0
Fatigue	5 (2.0)	0
Infections and infestations	33 (13.0)	11 (4.3)
Urinary tract infection	6 (2.4)	4 (1.6)
Nervous system disorders	20 (7.9)	3 (1.2)
Headache	9 (3.5)	2 (0.8)
Dizziness	6 (2.4)	0
Vascular disorders	6 (2.4)	2 (0.8)
Hypotension	5 (2.0)	0

Source: STN 125739/0, Clinical study report for Study 2019-01, page 61/78, Table 14.13.1.2.2/Table 14.3.1.2.5 and JMP Reviewer ADAM Dataset Analysis

Reviewer Comment: The majority of events were reported in the first 8 weeks after treatment and were most commonly reported in the MedDRA SOC Gastrointestinal disorders. An assessment of safety data following the second dose of RBX2660 in this study showed that TEAEs were not more frequent following a second administration of RBX2660 as compared to the first administration (data not shown).

6.3.12.3 Deaths

A total of 3 subjects (1.2%) experienced fatal adverse events, none of which were considered related to RBX2660 or the enema procedure. All deaths had plausible alternate etiologies compounding a pre-existing condition (one fatal event each of COVID-19 pneumonia in a subject at high baseline risk of severe COVID-19, spina bifida complication, and cardiac arrest). See Section 8.4.1 for details on fatal AEs.

Reviewer Comment: This reviewer agrees with the investigator assessments of the 3 deaths in Study 2019-01 as being due to alternative etiologies compounding pre-existing conditions and not related to RBX2660 or the enema procedure.

6.3.12.4 All Serious Adverse Events

A total of 22 (8.7%) subjects reported SAEs. The majority of SAEs were assessed by the investigator as related to *C. difficile* disease and pre-existing conditions, and none were considered related to RBX2660 or the enema procedure.

Within 8 weeks of either the first or second treatment, a total of 14 subjects reported SAEs, most of which were reported in the MedDRA SOC I*nfections and infestations*. The only SAE reported by more than one subject was CDI (n=2).

Reviewer Comment: There were no new safety issues identified in the evaluation of SAEs in this study. This reviewer agrees with the investigator's assessment that the deaths and SAEs were not plausibly related to RBX2660.

6.3.12.5 Adverse Events of Special Interest (AESI)

No subject reported AESIs.

6.3.12.6 Clinical Test Results

No safety monitoring labs were drawn as part of the study protocol. Stool samples were analyzed at the central laboratories if a subject had a suspected recurrence of CDI.

6.3.12.7 Dropouts and/or Discontinuations

A total of four subjects (1.2%) reported TEAEs that led to study discontinuation, including the three fatal events discussed in Sections 6.3.12.3 and 8.4.1. An additional event of non-fatal diarrhea and flatulence in a 73-year old subject resulted in study discontinuation and was not considered related to RBX2660.

6.3.13 Study Summary and Conclusions

Study 2019-01 was designed with less restrictive eligibility criteria than previous RBX2660 studies (e.g., laboratory diagnosis of toxigenic *C. difficile* not required, no exclusion for immunocompromising diseases, etc.) to allow evaluation of safety and tolerability of RBX2660 in a more comprehensive rCDI population, including subjects with comorbidities such as IBS and IBD.

In the primary efficacy analysis population (mITT), treatment success at 8 weeks post first RBX2660 enema was achieved in 73.4% of the subjects who had adjudicated outcomes. Interpretation of this result is limited by lack of a comparator group and the open-label study design.

Based on the available interim data, the safety findings in Study 2019-01 are consistent with prior studies in the RBX2660 clinical development program (e.g., Study 2014-01 and Study 2017-01).

7. INTEGRATED OVERVIEW OF EFFICACY

Study 2017-01 provided the primary efficacy for this BLA submission, while Study 2014-01 provided supplemental efficacy evidence through integration of the studies in a Bayesian framework model. Therefore, no traditional integration of efficacy data was conducted, and no integrated summary of efficacy was provided in the Application. Please see Sections 6.1 and 6.2 for the full clinical reviews of Study 2014-01 and Study 2017-01, respectively, including efficacy data and analyses.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated summary of safety (ISS) included pooled safety data from all subjects who were exposed to at least one dose of RBX2660 in five prospective studies (three Phase 2 studies: 2013-001, 2014-01, 2015-01, and two Phase 3 studies: 2017-01 and 2019-01). The following subjects were excluded from the ISS: (1) subjects who were enrolled but not treated; (2) 110 subjects who enrolled into the antibiotic-treated historical control arm of Study 2015-01 were excluded from the ISS, as they did not receive a protocol-defined treatment; and (3) 78 subjects from the retrospective Study 2019-02. The ISS was organized by study groupings as follows:

- The Full ISS group included any subject who was exposed to at least one dose of RBX2660 (blinded or open-label) or placebo from the five prospective studies. See Table 5 and Table 6 in Section 5.3 for summaries of studies included in the ISS. This population included 749 subjects exposed to at least one dose of RBX2660 and 83 subjects exposed only to placebo. The safety review specifically focused on the 429 subjects who received one dose of RBX2660 (dosing regimen proposed for licensure). Of the 429 subjects who received one dose of RBX2660, most were enrolled in the open-label Phase 3 Study 2019-01 (n=211; 49.2%) and the placebo-controlled Phase 3 Study 2017-01 (n=163; 38.0%). The majority of the placebo recipients (n=63; 75.9%) were enrolled in 2017-01.

  A safety update was submitted in an amendment to the BLA in May 2022 that added 229 subjects exposed to open-label RBX2660 in Study 2019-01, bringing the total pre-licensure clinical trial safety database to 978 subjects. A review of adverse events reported by these additional subjects did not reveal any new safety signals, so CBER review of the Full ISS remained limited to the 749 subjects included in the initial BLA submission. Section 9.2 includes a review of safety data from the additional 229 subjects.

- The Blinded ISS group included any subject who was exposed to RBX2660 or placebo in the randomized, double-blind, placebo-controlled studies 2014-01 and 2017-01. Subjects in the placebo group who experienced a CDI recurrence and received open-label RBX2660 were removed from the placebo group and counted as being exposed to RBX2660 in the safety analyses.

For each ISS group, the safety data are analyzed by group (administration, blinding, and sequence) and by number of exposures (1-4 doses of RBX2660).

All studies included at least 6 months of safety follow-up from the last dose. Two studies (2014-01 and 2015-01) included follow up through 24 months; data from 6 months through 24 months of follow up were analyzed separately.

Additional analyses were conducted on different subgroups to identity trends that might not have been apparent in the overall pooled analysis.

Review of safety data in the ISS focused on treatment emergent adverse events (TEAEs) assessed through the 6-month phone call.

- Solicited events were collected daily via subject diary through seven days after a treatment with the assigned study enema (blinded portion) or after a treatment with RBX2660 (open-label portion) for each of the prospective studies. Solicited events included gas (flatulence), abdominal distension or bloating, rectal irritation or pain, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, rectal bleeding, nausea, vomiting, and fever ≥38.0°C (in Studies 2013-001, 2014-01, and 2015-01) or 37.8°C (in Studies 2017-01 and 2019-01). Solicited events were analyzed as adverse events according to criteria described for the study in which the solicited event was reported.
- AEs were serious if they were life-threatening and/or resulted in death, inpatient hospitalization ≥24 hours or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or congenital anomaly/birth defect.
- AESIs were retrospectively identified based on analyses of Standardized MedDRA Queries (SMQs) with broad search terms that were performed in accordance with CBER's recommendation's as follows:
    - Gastrointestinal and nonspecific inflammation and dysfunctional conditions
    - Gastrointestinal perforation, ulceration, hemorrhage or obstruction
    - Hyperglycemia/new onset diabetes mellitus
    - Noninfectious diarrhea
    - Immune-mediated/autoimmune disorders
    - Shock
    - Systemic lupus erythematosus
    - Sepsis
    - Vasculitis
    - Medication errors

Specific Preferred Terms were not pre-specified as AESIs in the protocols. However, the Applicant designated events identified by two of the pre-specified SMQs (Hyperglycemia/new onset diabetes mellitus and Immune-mediated/autoimmune disorders) as AESIs to enhance detection of any potential safety signals.

Definitions of solicited events, AEs, and TEAEs were the same across studies. Criteria for grading the severity and relatedness of AEs were also the same across all studies. Adverse events were categorized by severity, seriousness, and relatedness by the site investigator.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 5 and Table 6 (Section 5.3) provides the features of the study designs of all studies included in the ISS.

The safety population included any subject who was administered an RBX2660 enema from the five prospective studies (2013-001, 2014-01, 2015-01, 2017-01, and 2019-01). The safety population comprised 749 subjects in the Any RBX2660 group, of which 429 subjects received one dose of RBX2660 and 83 subjects received placebo. The focus of this review is the 429 subjects who received one dose of RBX2660 compared to the 83 subjects who received placebo only.

Reviewer Comment: Integration and analysis of the safety data across multiple studies in the clinical development program provided more complete data to facilitate a benefit/risk assessment for RBX2660, increased the precision to detect safety signals compared with placebo for all events, and increased the potential to identify less frequent events.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The number of subjects contributing to the ISS by exposure and study are described in Table 40.

Table 40. Treatment Exposure, Full ISS Group, ISS Population

Study Number	Placebo Only 1-2 Doses (N=83)	RBX2660 1 Dose (N=429)	RBX2660 2 Doses (N=294)	RBX2660 3 Doses (N=14)	RBX2660 4 Doses (N=12)	Total (N=832)
2013-001	0	19 (4.4)	15 (5.1)	0	0	31 (4.1)
2014-01	20 (24.1)	30 (7.0)	52 (17.7)	14 (100.0)	12 (100.0)	128 (15.4)
2015-01	0	6 (1.4)	143 (48.6)	0	0	149 (17.9)
2017-01	63 (75.9)	163 (38.0)	41 (13.9)	0	0	267 (32.1)
2019-01	0	211 (49.2)	43 (14.6)	0	0	254 (30.5)

Source: STN 125739/0, Integrated summary of safety, page 51/260, adapted from Table15 and 14.1.1.6 and JMP ADAM datasets review

Studies 2017-01, 2019-01, and 2013-001 used a dosing regimen in which a complete course consisted of one enema, while in studies 2014-01 and 2015-01, a course was defined as two enemas administered one week apart. All studies except 2015-01 offered an open-label course of RBX2660 to subjects who experienced a recurrence of their CDI within 8 weeks of administration. Comparing the rates of AEs by the number of enema administrations was not treated as a dose-dependent assessment, because the number of doses a subject received depended on the study in which the subject participated and whether a subject experienced a recurrence of CDI.

Subjects were counted as receiving two enemas if they either received two enemas as a single course (for example, blinded RBX2660 followed by blinded RBX2660 in Study 2014-01) or received two courses of one enema (for example, blinded RBX2660 followed by open-label RBX2660 in Study 2017-01). Subjects who received more than two doses of RBX2660 (i.e., three or four doses) would have been enrolled in Study 2014-01 and experienced a recurrence of CDI prior to the administration of the 3rd and 4th RBX2660 doses.

Demographics
The demographics and baseline characteristics of subjects included in the ISS are presented in Table 41.

Table 41. Demographic and Baseline Characteristics by Treatment Exposure, Blinded ISS and Full ISS Population

Characteristic	Placebo Only 1-2 Doses N=83 n (%)	Blinded RBX2660 1-2 Doses N=193 n (%)	RBX2660 1 Dose N=429 n (%)	Any RBX2660 1-4 Doses N=749 n (%)
Age (years)	--	--	--	--
Mean	58.1	61.1	59.5	61.3
Minimum-maximum	19.0 – 90.0	18.0 – 91.0	18.0 – 94.0	18.0 – 103.0
Age group (years), n (%)	--	--	--	--
<65	52 (62.7)	99 (51.3)	245 (57.1)	390 (52.1)
≥65	31 (37.3)	94 (48.7)	184 (42.9)	359 (47.9)
≥75	12 (14.5)	48 (24.9)	86 (20.0)	193 (25.8)
Sex, n (%)	--	--	--	--
Male	23 (27.7)	71 (36.8)	143 (33.3)	259 (34.6)
Female	60 (72.3)	122 (63.2)	286 (66.7)	490 (65.4)
Race, n (%)	--		--	--
American Indian or Alaska Native	0	2 (1.0)	3 (0.7)	4 (0.5)
Asian	0	1 (0.5)	3 (0.7)	6 (0.8)
Black or African American	6 (7.2)	8 (4.1)	13 (3.0)	27 (3.6)
White	75 (90.4)	180 (93.3)	401 (93.5)	701 (9.36)
Other	2 (2.4)	0	5 (1.2)	8 (1.1)
Multiple	0	1 (0.5)	4 (0.9)	4 (0.5)
Ethnicity		--		
Hispanic or Latino	3 (3.6)	3 (1.6)	12 (2.8)	19 (2.5)
Not Hispanic or Latino	79 (95.2)	183 (94.8)	407 (94.9)	719 (95.1)
Not reported	0	5 (2.6)	6 (1.4)	10 (1.3)
Unknown	1 (1.2)	2 (1.0)	4 (0.9)	8 (1.1)
Number of CDAD/CDI episodes before first enema n (%)	--	--	--	--
1	0 (0.0)	0 (0.0)	7 (1.6)	7 (0.9)
2	26 (31.3)	46 (23.8)	113 (26.3)	138 (18.4)
≥3	57 (68.7)	147 (76.2)	304 (70.9)	598 (79.8)
Number of CDAD/CDI episodes before first enema, n (%)	--	--	--	--
1	0	0	7 (1.6)	7 (0.9)
2	26 (31.3)	46 (23.8)	113 (26.3)	138 (18.4)
3	34 (41.0)	69 (35.8)	161 (37.5)	275 (36.7)
4	16 (9.3)	47 (24.4)	87 (20.3)	167 (22.3)
5	5 (6.0)	17 (8.8)	30 (7.0)	77 (10.3)
6	2 (2.4)	10 (5.2)	15 (3.5)	42 (5.6)
7	0	2 (1.0)	5 (1.2)	16 (2.1)
8	0	1 (0.5)	2 (0.5)	10 (1.3)
9	0	0	2 (0.5)	6 (0.8)
10	0	0	1 (0.2)	2 (0.3)
12	0	0	0	1 (0.1)
14	0	1 (0.5)	1 (0.2)	1 (0.1)
25	0	0	0	1 (0.1)

Source: STN 125739/0, Adapted from Clinical Study Report for the ISS, Tables 19 and 23
CDAD=*C. difficile* associated diarrhea; CDI=*C. difficile* infection

By exposure, subjects who received three or four doses of RBX2660 were older than those who received one or two doses of RBX2660. The most common medical conditions at baseline were hypertension (45.9%), gastroesophageal reflux disease (33.8%), anxiety (29.0%), depression (28.7%), and hyperlipidemia (23.7%).

Reviewer Comment: The mean age of subjects was comparable between the 1-dose RBX2660 group (59.5 years) and the placebo only group (58.1 years), as well as comparable between the blinded RBX2660 group (61.1 years) and Any RBX2660 group (61.3 years). A higher percentage of older subjects (≥65 years old and ≥75 years old) received more RBX2660 doses than the younger subjects. Given that age ≥65 years is a risk factor for CDI recurrence, the exposure to more than one RBX2660 dose is consistent with more CDI recurrences in these older subjects. The remaining demographic characteristics were generally comparable between the placebo only group and each of the RBX2660 groups. The proportion of subjects with a history of ≥3 previous events of CDI increased as the number of treatment exposures increased, which likely reflects prior rCDI as a risk factor for a subsequent recurrence.

8.2.3 Categorization of Adverse Events

For all studies in the ISS, AEs were coded using MedDRA version 20.0.

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

While some features were similar across the studies included in the ISS, caveats in pooling data include differences in:

- Number of doses
- Study design (two double-blind placebo-controlled, three open-label, and one-historical controlled)
- Blinding (blinded and open label)
- Phase of development (Phase 2 and 3)
- Case definitions for rCDI: In studies 2013-001, 2014-01, 2015-01 and 2017-01, rCDI was defined as having diarrhea (passage of three or more loose bowel movements within a 24-hour period for two consecutive days) and a positive stool test for *C. difficile*, or at least two episodes of severe CDI resulting in hospitalization. For study 2019-01, the diagnosis of rCDI at study entry relied on the opinion of the investigator, instead of requiring a positive stool test or strict definitions of time from the previous CDI episode
- Study population (less stringent eligibility criteria for 2019-01)

Additional considerations in the interpretation of comparisons between the placebo and pooled treatment groups in the ISS include:

- The open-label nature of many of the RBX2660 doses in the ISS population
- 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;
- The Placebo Only group does not include the subjects who experienced a CDI recurrence and received an open-label dose of RBX2660. Because this likely selects out the subjects at highest risk for recurrence (which includes co-morbidities that increase the risk for AEs) AE rates may be underestimated in this group, resulting in an overestimation of the difference in AE rates between the RBX2660 groups and the Placebo Only group.
- 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.

- 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.
- Due to the limited number of placebo recipients, differences between the two groups should be interpreted carefully.

8.4 Safety Results

Table 42 provides an overview of safety outcomes in the Full ISS Population.

Table 42. Overall Safety Outcomes, Full ISS Population

TEAE Category	Placebo Only (1-2 Doses) N=83 n (%)	RBX2660 1 Dose N=429 n (%)	RBX2660 2 Doses N=294 n (%)	RBX2660 3 Doses N=14 n (%)	RBX2660 4 Doses N=12 n (%)	Any[a] RBX2660 N=749 n (%)
TEAEs	--	--	--	--	--	--
Subjects with TEAEs	50 (60.2)	265 (61.8)	234 (79.6)	11 (78.6)	11 (91.7)	521 (69.6)
Subjects with severe TEAEs	7 (8.4)	40 (9.3)	48 (16.3)	1 (7.1)	6 (50.0)	95 (12.7)
Subjects with potentially life threatening (maximum severity) TEAEs	1 (1.2)	9 (2.1)	10 (3.4)	1 (7.1)	2 (16.7)	22 (2.9)
TEAEs leading to withdrawal from study	0	4 (0.9)	3 (1.0)	0	0	7 (0.9)
TEAEs leading to death	0	5 (1.2)	10 (3.4)	1 (7.1)	2 (16.7)	18 (2.4)
TEAE relatedness	--	--	--	--	--	--
Related to RBX2660	16 (19.3)	97 (22.6)	72 (24.5)	4 (28.6)	5 (41.7)	178 (23.8)
Related to Enema procedure	17 (20.5)	65 (15.2)	54 (18.4)	3 (21.4)	3 (25.0)	125 (16.7)
Related to *C. difficile* infection	17 (20.5)	90 (21.0)	109 (37.1)	7 (50.0)	7 (58.3)	213 (28.4)
Related to a pre-existing condition	29 (34.9)	155 (36.1)	145 (49.3)	5 (35.7)	10 (83.3)	315 (42.1)
Serious TEAEs	6 (7.2)	36 (8.4)	56 (19.0)	4 (28.6)	10 (83.3)	106 (14.2)
Serious TEAE relatedness	--	--	--	--	--	--
Related to RBX2660	0	1 (0.2)	2 (0.7)	0	2 (16.7)	5 (0.7)
Related to Enema procedure	0	0	1 (0.3)	0	0	1 (0.1)
Related to *C. difficile* infection	1 (1.2)	15 (3.5)	17 (5.8)	3 (21.4)	4 (33.3)	39 (5.2)
Related to a pre-existing condition	3 (3.6)	29 (6.8)	40 (13.6)	3 (21.4)	8 (66.7)	80 (10.7)
Serious TEAEs leading to withdrawal from study	0	3 (0.7)	2 (0.7)	0	0	5 (0.7)
Serious TEAEs leading to death	0	5 (1.5)	10 (3.4)	1 (7.1)	2 (16.7)	18 (2.4)

Source: STN 125739/0, Adapted from Integrated Summary of Safety, Table 33 and 34

Table 43 summarizes safety outcomes in the Blinded ISS population, including only blinded data.

Table 43. Safety Outcomes, Blinded ISS Population

TEAE Category	Blinded Placebo Only N=83 n (%)	Blinded RBX2660 Only N=193 n (%)
TEAEs	--	--
Subjects with TEAEs	50 (60.2)	135 (69.9)
Subjects with severe TEAEs	7 (8.4)	19 (9.8)
Subjects with potentially life threatening (maximum severity) TEAEs	1 (1.2)	6 (3.1)
TEAEs leading to withdrawal from study	0	1 (0.5)
TEAEs leading to death	0	5 (2.6)
TEAE relatedness	--	--
Related to RBX2660	16 (19.3)	51 (26.4)
Related to Enema procedure	17 (20.5)	37 (19.2)
Related to *C. difficile* infection	17 (20.5)	45 (23.3)
Related to a pre-existing condition	29 (34.9)	83 (43.0)
Serious TEAEs	6 (7.2)	20 (10.4)
Serious TEAE relatedness	--	--
Related to RBX2660	0	1 (0.5)
Related to Enema procedure	0	0
Related to *C. difficile* infection	1 (1.2)	3 (1.6)
Related to a pre-existing condition	3 (3.6)	19 (9.8)
Serious TEAEs leading to withdrawal from study	0	1 (0.5)
Serious TEAEs leading to death	0	5 (2.6)

Source: STN 125739/0, Adapted from Integrated Summary of Safety, Table 31

8.4.1 Deaths

Across studies, and across exposure groups, a total of 2.4% of subjects (18/749) in the Full ISS Any RBX2660 group experienced fatal TEAEs through 6 months post study enema administration compared to zero in the placebo only group. This imbalance was also observed when comparing the proportion of subjects with fatal TEAEs in the Blinded ISS blinded RBX2660 group (5/193; 2.6%) and the Full ISS one RBX2660 dose group (5/429; 1.2%) to the placebo only group (0%).

The proportion of subjects reporting any fatal TEAEs increased as the number of exposures increased, ranging from five deaths (5/429; 1.2%) in subjects who received one dose of RBX2660, to eleven deaths (11/294; 3.7%) in subjects who received two doses of RBX2660, to two deaths (2/12; 16.7%) in subjects who received 4 doses of RBX2660, reflecting that subjects requiring multiple RBX2660 doses were generally sicker than those whose rCDI was controlled with fewer RBX2660 doses.

Reviewer Comment: Of the 18 fatal TEAEs observed in the RBX2660 clinical program, 17 were adjudicated as being unrelated to RBX2660. This reviewer agrees with the assessment of causality for these cases. One death due to relapsed CDI on Day 21 (Study 2015-01) was considered possibly related to RBX2660 and the enema procedure and definitely related to CDI by the investigator. Following review of the narratives and

case report form by this reviewer, the event was considered not to be causally related to RBX2660 but was considered definitely related to CDI.

Four subjects had onset of the fatal TEAEs within 30 days of the last RBX2660 dose as follows:

- A 94-year-old white female with history of chronic kidney disease stage IV, hypertension, hyperglycemia, gastroesophageal reflux disease, depression with anxiety, anemia in chronic disease and rCDI (5 CDI recurrences) received 2 doses of RBX2660 and reported serious adverse events of ileus, leukocytosis, CDI (reported as relapsed severe CDI), and pyrexia (fever of 102.5°F) on Day 14 post-2nd RBX2660 dose. Her clinical course was complicated by serious unrelated adverse events of atrial fibrillation, acute myocardial infarction, and malnutrition. She underwent additional fecal transplant to manage the CDI non-invasively. Due to a decline in clinical status, surgical intervention was not attempted. The subject died on Day 24 post-2nd RBX2660 dose due to the serious event of CDI and other comorbidities. The investigator considered the events of ileus, leukocytosis, CDI, and pyrexia to be possibly related to RBX2660 and the enema procedure and definitely related to CDI disease and pre-existing conditions. As noted above, this reviewer's assessment is that the death was not causally related to RBX2660 but was attributable to the recurrent CDI.
- A 76-year-old white male with history of prostate and lung cancer and left thoracotomy with lobectomy and rCDI (6 episodes) who received two doses of RBX2660 was reported to have a serious adverse event of acute respiratory failure on Day 24 post-2nd RBX2660 dose (Day 31 from 1st dose), when he had respiratory distress, tachycardia, and shortness of breath following a cystoscopy procedure to replace a ureteral stent for right-sided hydronephrosis secondary to history of hormone refractory metastatic prostate cancer. He was diagnosed with acute hypoxic respiratory failure secondary to acute exacerbation of chronic obstructive pulmonary disease and left lower lobe pneumonia. On Day 56 post-RBX2660, the subject was reported to have worsening of acute respiratory failure and died on Day 68 due to acute respiratory failure, with contributing factors listed as pneumonia and lung cancer. The investigator reported the serious event of acute respiratory failure as unrelated to RBX2660, and this reviewer concurs with this assessment.
- A 63-year-old white male with history of end stage renal disease, diabetes mellitus and rCDI (4 episodes) who received three doses of RBX2660 and one dose of placebo and was reported to have serious adverse events of sepsis, bacteremia, respiratory failure and staphylococcal infection on Day 24 post last RBX2660 exposure. The subject died on day 28 post RBX2660 due to sepsis that was noted to be secondary to methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and possibly related to healthcare acquired associated pneumonia. The investigator reported the serious event of sepsis and bacteremia as unrelated to RBX2660, and this reviewer concurs with this assessment.
- An 84-year-old white female with history of renal insufficiency and rCDI (3 episodes) who received RBX2660 while admitted to the hospital for treatment of rCDI. The subject remained well without recurrent diarrhea with planned discharge; however, she was reported to have a serious event of renal impairment on Day 19 post-RBX2660 and was treated with intravenous fluids and interruption of antihypertensive medications. She was reported to have

recurrent *C. difficile* diarrhea on Day 23 post-RBX2660, and *Escherichia coli* urinary tract infection with worsening renal function on Day 26 post-RBX2660. The *C. difficile* diarrhea reportedly ended on Day 34 post-RBX2660, and two additional doses of RBX2660 were administered on Days 35 and 41. Nine days after the 4th RBX2660 dose, the subject was diagnosed with anuria and renal failure. Hemodialysis was initiated on Day 51. An additional diagnosis of rCDI was reported on Day 50. The subject was unable to tolerate oral or rectal antibiotic treatment and continued to have ongoing watery bowel movements. Dialysis was discontinued on Day 69 and the subject died on Day 74 (34 days after the most recent dose of RBX2660) due to renal failure. The investigator reported the SAEs of renal impairment, anuria, and sepsis as unrelated to RBX2660 the enema, or CDI. This reviewer considered the death unrelated to RBX2660 and likely related to the rCDI, intercurrent urinary tract infection, and history of renal impairment.

Details of all fatal cases are presented in Table 44.

Table 44. Summary of Fatal Adverse Events

Age/Sex Study	Number of RBX2660 Doses	Adverse Events	Time to TEAE From Last RBX2660 Dose (Days)	Time to Death from Last RBX2660 Dose (Days)	Relatedness to RBX2660 or CDI[a]
88/M 2014-01	1	General physical health deterioration	56	57	Unrelated: poor pre-treatment health status, multiple co-morbidities including anemia and BKA secondary to gangrene
83/M 2014-01	1	General physical health deterioration	88	100	Unrelated: poor pre-treatment health status, multiple co-morbidities including osteomyelitis and decubitus ulcers
75/M 2017-01	1	Cardio-respiratory arrest	37	37	Unrelated: history of coronary artery bypass x 4
94/M 2019-01	1	Pulmonary sepsis	153	153	Unrelated: co-morbidities including end stage CHF
44/F 2017-01	1	Spina bifida with osteomyelitis of coccyx, *C. difficile* infection contributing	35	36	Probably related to CDI
83/F 2013-01	2	Pelvic fracture, respiratory failure	19 33	36 36	Unrelated: chronic respiratory failure exacerbation following pelvic fracture
73/F 2014-01	2	Intestinal ischemia	Onset unknown	564	Unrelated
76/M 2014-01	2	Acute respiratory failure	49	68	Unrelated: history of upper lobectomy, respiratory failure worsened post-ureteral stent placement on Study Day 31
77/M 2015-01	2	Death (due to unknown reasons)	175	175	Unrelated: death certificate noted lung cancer, COPD and colitis
94/F 2015-01	2	*C. difficile* infection	14	24	Definitely related to CDI
67/M 2015-01	2	Cardiac failure COPD	111	253	Unrelated: Significant prior respiratory disease x 6 years prior to study entry
68/F 2015-01	2	Sepsis	147	178	Unrelated: multiple co-morbidities and multi-organism infections
91/F 2015-01	2	Nephropathy	85	613	Unrelated: cardiovascular and renal co-morbidities
79/F 2017-01	2	Multimorbidity (COPD, decubitus ulcer, cardiac failure and *C. difficile* infection)	151	151	Unrelated: multiple system co-morbidities

Age/Sex Study	Number of RBX2660 Doses	Adverse Events	Time to TEAE From Last RBX2660 Dose (Days)	Time to Death from Last RBX2660 Dose (Days)	Relatedness to RBX2660 or CDI[a]
62/M 2019-01	2	Cardiac arrest	168	168	Unrelated: multiple co-morbidities including quadriparesis, CHF
63/M 2014-01	2	Bacteremia/sepsis Staphylococcal infection Respiratory failure	25 25 25	29 29 29	Unrelated: subject with multiple co-morbidities including decubitus ulcers, PICC line, +MRSA blood culture
87/F 2014-01	4	Respiratory failure	157	157	Unrelated, subject reported respiratory failure following colectomy for adenocarcinoma of colon
84/F 2014-01	4	Renal failure	9	34	Possibly related to CDI: history of renal insufficiency that worsened after CDI recurrence

Source: STN 125739/4, Module 5, Adapted from study narratives and case report forms of deaths.
Note: AE start and death date is relative to the day of first enema dose
a Assessment after CBER review
Glossary: BKA=below the knee amputation, COPD=chronic obstructive pulmonary disease, CHF=congestive heart failure, MRSA=methicillin-resistant staphylococcus aureus, PICC=peripherally inserted central catheter, M=male, F=female

Reviewer Comment: Although the frequency of deaths in the RBX2660 group was higher than in the placebo group, the overall low numbers of subjects in the placebo group limits the comparison of the results, given that only 2 studies (Study 2014-01 and 2017-01) contributed the 83 subjects in the placebo group to the safety population, compared to the 749 subjects in the Any RBX2660 group from 5 studies. This reviewer did not find any basis to conclude a causal relationship between the fatal events and RBX2660 when the events were considered individually, and no concerning pattern of events was identified, although the imbalance in fatal events is notable and is observed in the Any RBX2660 group, the 1-dose RBX2660 group and the blinded RBX2660 group when compared to the placebo only group. The increased death rate with increasing number of RBX2660 doses may reflect both imprecision associated with the small sample size of the four-dose RBX2660 group and the severity of the underlying CDI and comorbidities in those subjects requiring multiple doses of RBX2660. Most subjects with fatal TEAEs had underlying medical conditions and most died at least 30 days after the last dose was received. This reviewer agreed with the investigator's and the Applicant's assessments that the deaths were not related to RBX2660.

8.4.2 All Serious Adverse Events

Table 45 below summarizes the serious TEAEs across exposure groups by MedDRA SOC.

Table 45. Serious Treatment Emergent Adverse Events Through 6 Months After Last RBX2660 Dose, by MedDRA SOC and Exposure Group, ISS Population

MedDRA System SOC	Blinded Placebo 1-2 Doses N=83 n (%)	Blinded RBX2660 1-2 Doses N=193 n (%)	RBX2660 1 Dose N=429 n (%)	Any RBX2660 1-4 Doses N=749 n (%)
Any SOC	6 (7.2)	20 (10.4)	36 (8.4)	106 (14.2)
Blood and lymphatic system disorder	0	1 (0.5)	2 (0.5)	4 (0.5)
Cardiac disorders	0	2 (1.0)	5 (1.2)	14 (1.9)
Congenital, familial and genetic disorders	1 (2.1)	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	1 (1.2)	6 (3.1)	6 (1.4)	25 (3.3)
General disorders and administration site conditions	0	4 (2.1)	4 (0.9)	10 (1.3)
Hepatobiliary conditions	0	0	1 (0.2)	2 (0.3)
Infections and infestations	4 (4.8)	7 (3.6)	18 (4.2)	41 (5.5)
Injury, poisoning and procedural complications	0	2 (1.0)	4 (0.9)	13 (1.7)
Investigations	0	0	0	4 (0.5)
Metabolism and nutrition disorders	1 (1.2)	1 (0.5)	4 (0.9)	9 (1.2)
Musculoskeletal and connective tissue disorders	0	0	2 (0.5)	8 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5)	2 (0.5)	6 (0.8)
Nervous system disorders	0	2 (1.0)	5 (1.2)	8 (1.1)
Psychiatric disorders	0	2 (1.0)	2 (0.5)	5 (0.7)
Renal and urinary disorders	1 (1.2)	2 (1.0)	1 (0.2)	8 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (2.1)	3 (1.6)	7 (1.6)	19 (2.5)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.1)
Social circumstances	0	0	0	1 (0.1)
Surgical and medical procedures	0	0	0	1 (0.1)
Vascular disorders	0	0	0	2 (0.3)

Source: Adapted from STN 125739/0, Module 5, ISS Table 79, 80 and 81, Table 14.3.3.10, and Reviewer's JMP Dataset Analysis
SOC=system organ class

Blinded ISS

In the Blinded ISS, the proportion of subjects reporting serious TEAEs was higher in the blinded RBX2660 group (10.4%) compared to the blinded placebo group (7.2%). Serious TEAEs were most commonly reported in the SOCs of *Gastrointestinal disorders* and *Infections and infestations*. Numerical imbalances (higher proportion of participants in the blinded RBX2660 group and reported by more than one subject) were noted for the following events: abdominal pain, general physical health deterioration, CDI, and chronic obstructive pulmonary disease (all 1.0% blinded RBX2660 [n=2/193] vs. 0% placebo). The remaining serious TEAEs were reported by one subject each (0.5%).

The following events were reported in the blinded placebo group: Arnold-Chiari malformation, colitis, sepsis, gastroenteritis, dehydration, acute kidney injury, acute respiratory failure (n=1 each, 1.2%), and cellulitis (n=2, 2.4%).

Full ISS

1-dose RBX2660 group

In the Full ISS, the proportion of subjects reporting serious TEAEs was comparable between the 1-dose RBX2660 group (8.4%) and the placebo only group (7.2%). In the 1-dose RBX2660 group, serious events were most commonly reported in the SOCs of *Infections and infestations* (CDI, *C. difficile* colitis, urinary tract infection, pneumonia, and sepsis), *Gastrointestinal disorders* (abdominal pain, diarrhea, ileus, colitis), and *Respiratory, thoracic and mediastinal disorders* (chronic obstructive pulmonary disease, acute respiratory failure, and dyspnea). The most commonly reported serious TEAEs included CDI (reported by 9/429 subjects; 2.1%) and *C. difficile* colitis (reported by 3/429 subjects; 0.7%).

Numerical imbalances (higher proportion of participants in the 1-dose RBX2660 group and reported by more than one subject) were noted for the following events: CDI (2.1% 1-dose RBX2660 vs. 0% placebo*)*; *C. difficile* colitis, and chronic obstructive pulmonary disease (each 0.7% 1-dose RBX2660 vs. 0% placebo); bacteremia, pneumonia, urinary tract infection, general physical health deterioration, vomiting, ileus, diarrhea, abdominal pain, and cardiac failure congestive each (0.5% 1-dose RBX2660 vs. 0% placebo). The remaining serious events were reported by one subject each (0.2%).

Any RBX2660 group

Including all RBX2660 recipients, the imbalance in serious TEAEs was larger, with 14.2% of the subjects in the Any RBX2660 group reporting events compared to 7.2% of subjects in the placebo only group. This larger imbalance is attributable to the high rate of serious TEAEs in the multiple dose populations (19%, 28.6%, and 83.3% of subjects in the 2-, 3-, and 4-dose RBX2660 groups, respectively). Serious events were most commonly reported in the SOCs of *Gastrointestinal disorders* (reported by 25/749 subjects; 3.3%) and *Infections and infestations* (reported by 41/749 subjects; 5.5*%)*. The most commonly reported serious TEAEs included CDI (reported by 16/749 subjects; 2.1%) and urinary tract infection (reported by 8/749 subjects; 1.1%).

Numerical imbalances (higher proportion of participants in the Any RBX2660 group and reported by more than one subject) were noted for the following events: CDI (2.1% Any RBX2660 vs. 0% placebo); urinary tract infection (1.1% Any RBX2660 vs. 0% placebo); chronic obstructive pulmonary disease, cardiac failure congestive (each 0.9% Any RBX2660 vs. 0% placebo); *C. difficile* colitis, pneumonia (each 0.8% Any RBX2660 vs. 0% placebo); abdominal pain, diarrhea, (each 0.7% Any RBX2660 vs. 0% placebo); ileus, bacteremia (each 0.5% Any RBX2660 vs. 0% placebo); gastrointestinal hemorrhage, respiratory failure (each 0.4% Any RBX2660 vs. 0% placebo); nephrolithiasis, upper abdominal pain, colitis, constipation, intestinal obstruction, nausea, esophagitis, vomiting, pyrexia, acute myocardial infarction, transient ischemic attack, alcohol withdrawal syndrome, atrial fibrillation, leukocytosis, hyperkalemia, dyspnea, and alcohol poisoning (each 0.3% Any RBX2660 vs. 0% placebo).

Events reported by a higher proportion of the placebo only group compared to the Any RBX660 group included: sepsis (0.7% Any RBX2660 vs. 1.2% placebo), colitis and

acute respiratory failure (each 0.3% Any RBX2660 vs. 1.2% placebo), and acute kidney injury (0.4% Any RBX2660 vs. 1.2% placebo).

All remaining serious TEAEs in the Any RBX2660 group were reported by one subject each (0.1%).

Through 8 weeks
For the time period from baseline to 8 weeks after administration of the first RBX2660 exposure, serious TEAEs were reported in 3.6% (3/83) of subjects in the placebo only compared to 6.1% (26/429) subjects in the 1-dose RBX2660 group, and 8.9% (67/749) subjects in the Any RBX2660 group.

Although the overall imbalances in serious TEAEs between the blinded and Any RBX2660 groups when compared to the placebo group are notable, a review of the events did not identify apparent trends in serious TEAEs by MedDRA SOC or PT that would suggest a causal association. Following review of individual case narratives, this reviewer did not identify any serious TEAEs that were considered causally related to RBX2660.

Related Serious TEAEs
Five subjects had serious TEAEs considered related to RBX2660 by the investigator, all of which were considered by this reviewer to be plausibly related to other pre-existing conditions or recurrent CDI.

Three serious TEAEs were reported in the context of rCDI following RBX2660 administration, including one fatal case described in Section 8.4.1. In these cases, this reviewer considers the serious events to be plausibly related to rCDI and not to RBX2660. Details of the two non-fatal cases are as follows:

- A 44-year-old white female with history of Marfan syndrome, interstitial cystitis, hypertension, angina, fibromyalgia, depression, morbid obesity, and rCDI (4 episodes) received 2 doses of RBX2660 and reported an SAE of abdominal pain on day 10 post RBX2660 exposure. The subject reported nausea, vomiting and eight bowel movements with abdominal pain worse after eating and was diagnosed with rCDI. The investigator reported the serious event of abdominal pain as related to RBX2660 and CDI. The investigator reported the rCDI as unrelated to RBX2660.
- A 58-year-old white male with history of diabetes and atrial fibrillation received one of two doses of RBX2660 and reported two serious adverse events of rCDI on day 4 and recurrent CDI and diarrhea on day 22 post-RBX2660. The subject did not receive the second dose because of a serious adverse event of rCDI that was diagnosed on day 4 and considered resolved on day 17. Diarrhea requiring hospitalization was reported as a serious adverse event on day 24 and considered resolved on day 27 post-RBX2660. Recurrent CDI was reported as a serious adverse event on days 31 and 64 post-RBX2660 and considered resolved on days 41 and 69 post-RBX2660 respectively. The investigator reported the three rCDI episodes as possibly related to RBX2660 and related to CDI, and the diarrhea was reported as being possibly related to RBX2660 and CDI.

Details of the remaining two events are as follows:

- A 53-year-old white male with history of acute myeloid leukemia (AML) in remission following stem cell transplant received 2 doses of RBX2660 and was diagnosed with a serious adverse event of recurrent acute myeloid leukemia on day 69 post RBX2660 exposure. The investigator reported the recurrent AML as related to RBX2660 and pre-existing condition. The subject received multiple chemotherapy regimens and the event was noted to be resolved on day 253 post RBX2660. However, subject was diagnosed with relapsed AML on day 357 post RBX2660 and subsequently died. The death was considered unrelated to RBX2660 by the investigator.
- A 59-year-old white female with history of Parkinson's disease and chronic constipation received two doses of RBX2660 and reported a serious adverse event of worsening chronic constipation on day 45 post RBX2660. The investigator reported worsening chronic constipation as related to RBX2660.

  Reviewer Comment: This reviewer does not consider this event as related to RBX2660 due to a lack of temporal relationship (onset 45 days post RBX2660 exposure).

  Reviewer Comment: Although the overall imbalances in serious TEAEs between the blinded and Any RBX2660 groups were notable when compared to the placebo group, a review of the individual case reports and narratives did not identify any apparent trends in serious TEAEs that would suggest a causal association. None of the serious TEAEs were considered to be causally related to RBX2660 administration by this reviewer. The majority of the serious TEAEs were related to a pre-existing condition or recurrent CDI.

8.4.3 Study Dropouts/Discontinuations

Across all the studies included in the ISS, seven subjects experienced TEAEs leading to study discontinuation. Five of the seven subjects received one dose of RBX2660, and the other two subjects received two doses of RBX2660.

Of the seven events, four resulted in discontinuation because the events were fatal (complications of spina bifida, cardiorespiratory arrest, COVID-19 pneumonia). Please see Section 8.4.1 for additional information on these fatal events. The remaining three TEAEs that led to discontinuation were due to diarrhea, two of which were mild or moderate and reported as probably related to a pre-existing condition (reported 3 and 25 days after the most recent dose of RBX2660, respectively) and one of which was severe (reported on day 1) and considered definitely related to CDI.

In the long-term follow up period (6 months to 24 months follow-up), two additional subjects discontinued from the study due to fatal TEAEs of cardiac arrest (Day 168 after the most recent dose of RBX2660) and cerebrovascular accident (Day 718 after the most recent dose of RBX2660), both of whom received two doses of RBX2660.

Reviewer Comment: None of the TEAEs leading to discontinuation were considered related to the RBX2660 or to the enema procedure.

8.4.4 Common Adverse Events

Solicited events

After the first RBX2660 enema administration, the most frequently reported solicited events from Days 1 through 7 were gas (flatulence), abdominal distension/bloating, and abdominal pain/cramping in the blinded placebo group, blinded RBX2660 group, 1-dose RBX2660 group, and Any RBX2660 group.

Most of the solicited events were mild or moderate in severity. Abdominal pain/cramping, increased diarrhea, and abdominal distension/bloating were the most frequently reported severe solicited AEs, all of which were more common in the placebo group compared to the RBX2660 group. Life threatening solicited AEs were reported in two subjects with nausea, one subject with increased diarrhea, and three subjects with abdominal pain/cramping.

Treatment emergent adverse events (TEAEs)

The frequency of subjects experiencing a TEAE ranged from 60.2% in the placebo only group to 91.7% in the 4 RBX2660 enema group. The rates of TEAEs in subjects exposed to placebo only (60.2%) were similar to the rates of TEAEs in subjects exposed to 1 RBX2660 enema only (61.8%). Subjects in the Any RBX2660 group who received 4 doses of RBX2660 had the highest percentage of TEAEs (91.7%), mostly related to CDI recurrence requiring retreatment (data not shown).

The most commonly reported TEAEs (>4% of subjects) are summarized in Table 46 below.

Table 46. Treatment Emergent Adverse Events Reported in >4% of Subjects Through 6 Months by Treatment and Exposure after Last RBX2660 Dose, Safety Population

System Organ Class Preferred Term	Placebo Only (1-2 Doses) N=83 n (%)	Blinded RBX2660 (1-2 Doses) N=193 n (%)	RBX2660 1 Dose (N=429) n (%)	Any RBX2660 (1-4 Doses) N=749 n (%)
Subjects with any TEAE	50 (60.2)	135 (69.9)	265 (61.8)	521 (69.6)
Gastrointestinal disorders	33 (39.8)	89 (46.1)	180 (42.0)	352 (47.0)
Diarrhea	15 (18.1)	41 (21.2)	77 (17.9)	173 (23.1)
Abdominal pain	7 (8.4)	38 (19.7)	64 (14.9)	123 (16.4)
Nausea	3 (3.6)	21 (10.9)	43 (10.0)	70 (9.3)
Flatulence	1 (1.2)	14 (7.3)	36 (8.4)	60 (8.0)
Abdominal distension	3 (3.6)	11 (5.7)	24 (5.6)	54 (7.2)
Constipation	5 (6.0)	11 (5.7)	16 (3.7)	51 (6.8)
Infections and Infestations	27 (32.5)	50 (25.9)	89 (20.7)	191 (25.5)
Urinary tract infection	4 (4.8)	10 (5.2)	17 (4.0)	50 (6.7)
General disorders and administration site conditions	10 (12.0)	32 (16.6)	43 (10.0)	102 (13.6)
Chills	4 (4.8)	6 (3.1)	12 (2.8)	34 (4.5)
Pyrexia	4 (4.8)	6 (3.1)	8 (1.9)	31 (4.1)
Nervous system disorders	8 (9.6)	17 (8.8)	34 (7.9)	74 (9.9)
Headache	4 (4.8)	9 (4.7)	18 (4.2)	37 (4.9)

Source: STN 125739/0, Adapted from ISS Table 48, Table 14.3.2.2 and Reviewer's JMP Dataset Analysis
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities
PT=preferred term; SOC=System organ class
TEAE=Treatment emergent adverse event
Coding was based on MedDRA, version 20.0

Percentages calculated based on number of subjects exposed to enema in the column heading as the denominator
A subject with multiple events coded to the same PT within a primary SOC was counted only once for the PT within the primary SOC. A subject with multiple events coded to the same SOC was counted only once within the SOC.

Blinded ISS

In the Blinded ISS, the proportion of subjects reporting TEAEs was higher in the blinded RBX2660 group (69.9%) compared to the blinded placebo group (60.2%). The most commonly reported TEAEs were gastrointestinal, including diarrhea, abdominal pain and distention, nausea, flatulence, constipation, and vomiting. Numerical imbalances (higher proportion of participants in the RBX2660 group) were noted for the following events: abdominal pain (19.7% blinded RBX2660 vs. 8.4% blinded placebo), nausea (10.9% vs. 3.6%), flatulence (7.3% vs. 1.2%), abdominal distention (5.7% vs. 3.6%), anxiety (3.6% vs. 1.2%), depression (3.1% vs. 0%), chronic obstructive pulmonary disease (3.1% vs. 0%), decreased diastolic blood pressure (2.6% vs. 0%), cough (2.6% vs. 0%), and asthenia (2.1% vs. 0%).

Related events were reported by a higher proportion of subjects after blinded RBX2660 (26.4%) compared to blinded placebo (19.3%). The most commonly reported related TEAEs included gastrointestinal events (diarrhea, abdominal pain and distention, nausea, flatulence, constipation, and anorectal discomfort), all of which were reported by a higher proportion of subjects in the blinded RBX2660 group.

The proportions of subjects reporting severe and life threatening unsolicited TEAEs were higher in the blinded RBX2660 group (9.8% and 3.1%, respectively) compared to the blinded placebo group (8.4% and 1.2%, respectively). No life-threatening events were considered related by the investigator.

Full ISS

1-dose RBX2660 group

In the Full ISS, the proportion of subjects reporting unsolicited TEAEs was comparable between the placebo only (50/83; 60.2%) and 1-dose RBX2660 (265/429; 61.8%) groups, with higher rates reported in subjects who received two doses (234/294; 79.6%), three doses (11/14; 78.6%), and four doses of RBX2660 (11/12; 91.7%). The most commonly reported TEAEs were gastrointestinal, including diarrhea, abdominal pain and distention, nausea, flatulence, constipation, and vomiting. Numerical imbalances (higher proportion of participants in the 1-dose RBX2660 group) were noted for the following events: abdominal pain (14.9% 1-dose RBX2660 vs. 8.4% placebo), nausea (10.0% vs. 3.6%), flatulence (8.4% vs. 1.2%), abdominal distention (5.6% vs. 3.6%), CDI (2.1% vs. 0%), decreased diastolic blood pressure (1.9% vs. 0%), and depression (2.3% vs. 0%).

The incidence rates of reported diarrhea were similar between subjects in the 1-dose RBX2660 group (17.9%) and subjects in placebo groups (18.1%), while abdominal pain was reported in a higher percentage of subjects in the one to four doses of RBX2660 group (16.4%) than in subjects in the placebo only group (8.4%).

Related events were reported by a similar proportion of subjects in the 1-dose RBX2660 group (22.6%) compared to the placebo group (19.3%). The most commonly reported related TEAEs included gastrointestinal events (diarrhea, abdominal pain and distention, nausea, flatulence, constipation, and anorectal discomfort), all of which (other than constipation) were reported by a higher proportion of subjects in the blinded RBX2660 group.

Any RBX2660 group
The proportions of subjects reporting TEAEs, severe TEAEs, and potentially life threatening TEAEs was higher in the Any RBX2660 group (n=749; 69.6%, 12.7%, and 2.9%, respectively) compared to the placebo group (60.2%, 8.4%, and 1.2%, respectively). In general, the pattern of the most commonly reported TEAEs in the Any RBX2660 group was consistent with the other analyzed RBX2660 groups. Related events were reported by a similar proportion of subjects in the Any RBX2660 group (23.8%) compared to the placebo group (19.3%).

TEAEs by Severity

Table 47. Treatment Emergent Adverse Events by Severity, Safety Population

Category	Blinded Placebo 1-2 Doses N=83 n (%)	Blinded RBX2660 1-2 Doses N=193 (%)	RBX2660 1 Dose N=429 n (%)	Any RBX2660 1-4 Doses N=749 n (%)
Subjects with any TEAE	50 (60.2)	135 (69.9)	265 (61.8)	521 (69.6)
Mild	13 (15.7)	56 (29.0)	91 (21.2)	182 (24.3)
Moderate	29 (34.9)	54 (28.0)	125 (29.1)	222 (29.6)
Severe	7 (8.4)	19 (9.8)	40 (9.3)	95 (12.7)
Potentially life threatening	1 (1.2)	6 (3.1)	9 (2.1)	22 (2.9)

STN 125739/0, Adapted from Clinical study report ISS page 115/260, Table 14.3.2.2

The majority of the TEAEs were mild or moderate in severity, with a few TEAEs reported as potentially life threatening.

The proportions of subjects reporting severe and potentially life threatening TEAEs was higher in the Any RBX2660 group (12.7%, and 2.9%, respectively) compared to the placebo group (8.4%, and 1.2%, respectively).

The proportions of subjects reporting severe and potentially life threatening TEAEs was generally comparable between the 1-dose RBX2660 group (9.3%, and 2.1%, respectively), the Blinded RBX2660 group (9.8% and 3.1%, respectively), and the placebo group (8.4%, and 1.2%, respectively). The incidence of severe TEAEs was higher in subjects exposed to two doses of RBX2660 (16.3%) and four doses of RBX2660 (50.0%).

Most of the severe TEAEs were reported in the SOC *Gastrointestinal disorders*, with PTs of abdominal pain (25/749; 3.3%) and diarrhea (17/749; 2.3%) occurring most frequently in the Any RBX2660 group.

MedDRA SMQs
The following SMQs were performed to detect safety signals: Gastrointestinal and nonspecific inflammation and dysfunctional conditions; Gastrointestinal perforation, ulceration, hemorrhage or obstruction; Hyperglycemia/new onset diabetes mellitus; Noninfectious diarrhea; Medication errors; Sepsis; Shock; Systemic lupus erythematosus; Vasculitis; and Immune mediated/autoimmune disorders.

Analyses of the results of these SMQs did not identify any safety concerns.

8.4.5 Clinical Test Results

Blood samples were collected at screening and baseline. Specifically, all studies required a complete blood count, and Study 2019-01 also required a cluster of differentiation 4 (CD4) count to assess immune status before the first enema administration. Receipt of the first enema was not dependent on the result of the baseline blood and stool tests. No clinical laboratory tests were drawn for safety monitoring during the follow-up period as part of the study protocols; however, stool samples were submitted for analysis if a subject had a suspected CDI recurrence.

The blood and stool tests collected prior to the first enema administration at baseline were used to establish baseline values for each subject.

Vital signs including temperature, blood pressure, and respiratory rates were measured on days 1 and 8 and weight measured on days 1, 8, 15, 36, 57, 64, 91, 121, and 181. Vital signs were analyzed relative to the first enema of the first course. Vital signs data were available for evaluation of AEs.

8.4.6 Adverse Events of Special Interest

Specific preferred terms (PTs) were not pre-specified as adverse events of special interest (AESI) in the protocols. The Hyperglycemia/new onset diabetes mellitus SMQ and Immune-mediated/autoimmune disorders SMQ were retrospectively identified as relevant to potential AESIs. Across all the studies included in the ISS, PTs in the SMQ Hyperglycemia/new onset diabetes mellitus were reported in 10/749 subjects (1.3%) in the Any RBX2660 group compared to 2/83 subjects (2.4%) in the placebo only group, and PTs in the SMQ Immune-mediated/autoimmune disorders were reported in 10/749 subjects (1.3%) in the Any RBX2660 group compared to 1/83 subjects (1.2%) in the placebo only group.

Reviewer Comment: The overall rates of AESIs in the ISS were low across study groups. No patterns or clusters were observed to support causality. No safety signals were identified.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Subjects who received four doses of RBX2660 reported more TEAEs and serious TEAEs compared to subjects who received one dose of RBX2660, potentially reflecting that the subjects in the 4-dose RBX2660 group had more risk factors for CDI recurrences that required re-treatment (e.g., associated co-morbidities that confer a higher risk for TEAEs).

8.5.2 Time Dependency for Adverse Events

Adverse events by time interval in the Any RBX2660 group

- From baseline to 8 weeks after enema administration:
  - From baseline to 8 weeks after first enema administration, 62.1% of subjects (465/749) reported a TEAE. Most of the TEAEs were mild or moderate in severity, with similar rates of severe TEAEs, with the exception of the 4-dose

RBX2660 group, which had the highest rate of severe TEAEs (50% of subjects). The remaining groups had a similar percentage of subjects with severe TEAEs. Events in the SOC *Gastrointestinal disorders* were the most frequently reported (34.8% of subjects), and diarrhea was the most commonly reported PT (15.4% of subjects). TEAEs were most frequently related to the subject's pre-existing conditions. Eleven subjects (1.3%) had potentially life threatening TEAEs. Nine subjects (1.2%) had TEAEs leading to death.

- From 8 weeks to 6 months after enema administration:
  - From 8 weeks to 6 months after first enema administration, 30.7% of subjects (230/749) reported a TEAE, with the highest reported rates in the 4-dose RBX2660 group. Three subjects (0.4%) had a TEAE leading to death and nine subjects (1.1%) had TEAEs leading to death. Events in the SOC *Gastrointestinal disorders* were the most frequently reported (17.8% of subjects) and diarrhea was the most commonly reported PT (9.3% of subjects). A smaller percentage of subjects had TEAEs in the 8 weeks to 6 months after the first dose, compared to the first 8 weeks. The frequency of gastrointestinal TEAEs decreased from 30.7% in the first 8 weeks after first enema administration to 17.8% in the time interval from 8 weeks to 6 months. There was a similar reduction of CDI-related TEAEs from the first 8 weeks after enema administration (26.1%) to the time interval from 8 weeks to 6 months (4.0%).
  - No safety trends were noted in the TEAEs that occurred on or before 6 months after the last enema administration.

8.5.3 Product-Demographic Interactions

TEAEs in the safety population was summarized by age group, sex, number of previous CDI episodes, ethnicity and race groups.

No notable differences were observed across groups in the pre-defined subgroup categories of sex, prior CDI episodes, ethnicity, and race. However, severe TEAEs increased slightly with older age, and TEAEs leading to death increased with older age.

Subpopulation of TEAEs by Age group
Of the 749 subjects treated with RBX2660, 52.1% were <65 years of age, 47.9% were ≥65 years of age, and 25.8% were ≥75 years of age.

TEAEs by pre-specified age subgroups is presented in the table below.

Table 48. TEAEs by Pre-specified Age Subgroups, Safety Population

TEAE Category	<65 Years of Age N=390 n (%)	≥65 Years of Age N=359 n (%)	≥75 Years of Age N=193 n (%)
TEAEs	268 (68.7)	253 (70.5)	150 (77.7)
Severe TEAEs	45 (11.5)	50 (13.9)	27 (14.0)
Potentially life threatening TEAEs	6 (1.5)	16 (14.5)	13 (6.7)
Serious TEAEs	41 (10.5)	65 (18.1)	47 (24.4)
Deaths	3 (0.8)	15 (4.2)	12 (6.2)

Source: Adapted from STN 125739/0, Module 5, ISS Table 97

Of the subjects exposed to RBX2660, severe and potentially life threatening TEAEs were more frequent in subjects ≥65 years old (13.9% and 4.5%, respectively) compared to subjects <65 years old (11.5% and 1.5%, respectively). Potentially life threatening TEAEs occurred more frequently in subjects in the ≥75 years of age group (6.7%), all of which occurred in the RBX2660 group. In general, the observed TEAEs in the older age group were related to pre-existing conditions and recurrent CDI and unrelated to RBX2660.

In the Any RBX2660 group, serious TEAEs were reported by a higher proportion of subjects ≥75 years of age (24.4%), compared to subjects ≥65 years of age (18.1%) and subjects <65 years of age (10.5%). Serious TEAEs leading to death were reported more frequently in subjects ≥75 years of age (12/18) compared to subjects <65 years of age (3/18).

The proportions of subjects reporting TEAEs and serious TEAEs assessed by the investigator as related to the RBX2660 were similar across age groups: 97/390 (24.9%) for subjects <65 years, 81/359 (22.6%) for subjects ≥65 years and 44/193 (22.8%) for subjects ≥75 years. The proportions of subjects reporting TEAEs assessed by the investigator to be related to RBX2660 were 4/390 (1.0%) for subjects <65 years, 1/359 (0.3%) in subjects ≥65 years, and 1/193 (0.5%) in subjects ≥75 years.

Reviewer Comment: The majority of the severe, potentially life threatening and serious TEAEs were observed in the older age groups and unrelated to study drug, which likely reflects co-morbid conditions of that age cohort and is consistent with age >65 years being an independent risk factor for rCDI.

8.6 Safety Conclusions

The frequency of TEAEs in the 1-dose RBX2660 group was similar to the placebo only group (61.8% vs. 60.2% respectively). The majority of the TEAEs were mild or moderate, and the rates of severe TEAEs were similar between the 1-dose RBX2660 group and placebo only group (9.3 vs. 8.4% respectively). Rates of TEAEs leading to study discontinuation were low, with rates of 0.9% and 0.0% in the 1-dose RBX2660 group and the placebo only group, respectively.

Rates of all TEAEs, serious TEAEs, and fatal TEAEs increased with increasing number of RBX2660 doses and reflected an imbalance when compared to the placebo only group. Review of individual serious/fatal TEAEs did not identify any events thought to be causally related to RBX2660 or patterns of events suggestive of a specific safety concern. These imbalances may be related to the underlying conditions of subjects who had more recurrences of CDI resulting in more exposures to RBX2660, and interpretation of these differences is confounded by loss of a placebo comparator group for additional doses given in the open label portions of studies. Despite these differences, there were no patterns of AEs raising a concern for a safety signal in the safety population analyzed through the integrated summary of safety.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No subject in the ISS population had a positive pregnancy test through 6 months after the last enema. In the long term follow-up period (between 6 months and 24 months after the last enema), there were 3 pregnancies reported (one in Study 2014-01 and two in Study 2015-01) as described below:

- A subject who received 2 doses of placebo experienced a ruptured ectopic pregnancy 222 days after the last enema. The subject was hospitalized and underwent laparoscopic surgery. The event was reported as serious, unrelated to RBX2660 and definitely related to pre-existing condition (i.e., endometriosis and ovarian cysts). The subject completed the study and exited following completion of the final 24-month phone assessment.
- A subject who received two doses of RBX2660 informed the site that she was 8 months pregnant at the time of the final 24-month follow-up phone assessment, 720 days after the last RBX2660 dose. The subject exited the study with no reported adverse events. The subject contacted the site to report the delivery of a healthy baby one month after exiting the study.
- A subject who received two doses of RBX2660 informed the site that she was approximately 3 months pregnant 576 days after the last RBX2660 dose. The subject was considered high risk due to maternal age of 35 years old at delivery and group B streptococcus positivity. She delivered a healthy baby via scheduled caesarean section at 39 weeks 6 days, without complications. The subject exited the study one month postpartum, following completion of the final 24-month phone assessment.

Reviewer Comment: Only three subjects reported pregnancies, and none were reported in the immediate post-procedure timeframe. Two of the three pregnancies resulted in healthy, live births, with the third being a nonviable ectopic pregnancy not temporally or causally related to RBX2660 administration. No clinical trial data exist to inform the safety of RBX2660 administration just prior to or during pregnancy; however, RBX2660 is not systemically absorbed and, therefore, is not expected to directly impact pregnancy.

9.1.2 Use During Lactation

RBX2660 enema was not evaluated in lactating females; however, RBX2660 is not systemically absorbed and, therefore, is not expected to be associated with safety concerns related to use during lactation.

9.1.3 Pediatric Use and PREA Considerations

RBX2660 received orphan designation (Designation No. DRU-2013-4210) for use of fecal microbiota (RBX2660) for the “prevention of recurrent *C. difficile* infection (CDI) in individuals with prior recurrent *C. difficile* infection resolved following antibiotic treatment.” As an orphan designated product, RBX2660 is exempt from PREA requirements.

9.1.4 Immunocompromised Patients

RBX2660 was evaluated in a limited number of immunocompromised patients (mainly patients with IBD in Study 2019-01), and CBER considered the available data insufficient to determine whether safety or effectiveness in immunocompromised populations are different than in the general population.

9.1.5 Geriatric Use

Of the 978 adults who received RBX2660, 48.8% were 65 years of age and over (n=477), and 25.7% were 75 years of age and over (n=251). Data from clinical studies of RBX2660 are not sufficient to determine if adults 65 years of age and older respond differently than younger adults.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

9.2.1 2013-001: Open-label Study

Protocol ID: 2013-001
ClinicalTrials.gov ID: NCT01925417
Date First Subject Enrolled: July 12, 2013
Date Last Subject Completed: July 11, 2014
Date of Final Study Report: October 20, 2014

Study 2013-001 was a Phase 2, multicenter, prospective, non-controlled, open-label study to assess the safety of RBX2660 for the treatment of rCDI.

Subjects received one dose of RBX2660 and were eligible to receive a second administration if their CDAD recurred before day 56 after receiving the first administration, if the second administration could be performed within 10 days of recurrence.

The study enrolled 40 subjects, though 6 subjects did not receive RBX2660: 4 subjects failed to meet inclusion/exclusion criteria after giving informed consent, 1 subject refused administration with RBX2660 (wanted a known donor), and 1 subject failed to return for required laboratory tests and scheduled study administration.

A total of 34 subjects received at least one dose of RBX2660 enema. Of the 34 subjects that received RBX2660, 2 subjects withdrew consent after receiving 1 dose of RBX2660 enema, and 1 subject died from causes unrelated to the study drug. A total of 31 subjects were followed for 6 months after completing RBX2660.

No formal statistical analysis was planned for study 2013-001 to demonstrate efficacy, therefore, treatment success was assessed based on descriptive statistics. Treatment success was defined as the absence of CDAD at 56 days after the last RBX2660 enema. Of the 34 subjects who received at least one RBX2660 enema, 32 subjects had efficacy data for the 8-week follow-up period after the first dose of RBX2660, and 16 (50%) were considered a treatment success.

The safety population included all 34 subjects who received RBX2660. Of the 34 subjects, 33 subjects reported solicited events. The most common solicited events that worsened from baseline included flatulence (30.3%) and abdominal pain (21.3%).

TEAEs were reported by 28/34 (82.3%) subjects, most of which were mild to moderate in severity and primarily related to events in the SOC *Gastrointestinal disorders*. The most commonly reported PTs were diarrhea, flatulence, abdominal pain and constipation. Serious TEAEs were reported by 20.6% of subjects through six months from the last RBX2660 dose and none were considered related to RBX2660. One death was reported in an 83 year-old wheel-chair bound female with history of severe chronic obstructive pulmonary disease dependent on 2L of oxygen at baseline, hypertension, hyperlipidemia and recurrent CDAD. The subject received two doses of RBX2660 and died 36 days after receiving the second dose from respiratory failure following pelvic fracture. The death was not considered to be related to RBX2660. Please see Section 8.4.1 for details of this fatal event. The results of study 2013-001 informed the study design of Study 2014-01.

9.2.2 2015-01: Open-label, Historical-Controlled Study

Protocol ID: 2015-01
ClinicalTrials.gov ID: NCT02589847
Date First Subject Enrolled: October 01, 2015
Date Last Subject Completed: March 25, 2019
Date of Final Study Report: September 10, 2020

2015-01 was a Phase 2, multicenter, prospective, open-label, historical-controlled study to assess the efficacy and safety of RBX2660 for the prevention of rCDI. A total of 272 subjects were included in Study 2015-01, with 162 subjects enrolled in the RBX2660 group and matched to a historical control group of 110 subjects.

Of the 162 enrolled subjects, 149 received RBX2660, including 143 who received two doses of RBX2660 administered 7±2 days apart, and 6 who received one dose of RBX2660. A second course was not offered to subjects who experienced a recurrence of CDI.

The primary efficacy analysis was based on the proportion of subjects meeting the treatment success criterion. Treatment success was defined as the absence of CDAD without the need for retreatment with *C. difficile* anti-infective therapy or fecal transplant at 56 days after completion of study administration.

The statistical analysis in study 2015-01 was performed using Pearson's chi-square test, with no formal hypothesis testing done and no adjustment for multiplicity made for the study.

The treatment success rate was higher in the RBX2660 group (78.9%) compared to the historical group (30.7%).

Follow-up continued through 24 months after completing RBX2660, with AEs collected through 12 months and SAEs collected through 24 months. TEAEs were reported in 123/124 subjects (82.6%) in the RBX2660 group and 67/104 subjects (64.4%) in the historical group. The TEAEs were mostly mild or moderate in severity. Overall, events in the SOC *Gastrointestinal disorders* were the most common, and diarrhea, and abdominal pain, the most commonly reported PTs. A total of 52/208 subjects (34.9%) in the RBX2660 group reported serious TEAEs compared to 30/104 subjects (28.8%) in the historical control group. A total of 15/149 (10.1%) subjects in the RBX2660 group

reported a fatal AE, one of which was considered possibly related to RBX2660 or the enema procedure and definitely related to *C. difficile* disease and pre-existing conditions by the investigator. Please see Section 8.4.1 for additional information on the deaths in Study 2015-01. Fatal events were reported for 5/104 subjects (4.8%) in the historical control arm.

9.2.3 2019-02: Retrospective Study

Protocol ID: 2019-02
First Date of First Eligible Study Data: November 11, 2015
Last Date of Study Data: March 01, 2020
Initiation of First Site: May 28, 2020
Date of Database Lock: November 16, 2020

2019-02 was a retrospective, multicenter, safety and tolerability study of RBX2660 for the prevention of recurrent *C. difficile* infection. The study was intended to obtain safety data from up to 200 subjects who received RBX2660 under enforcement discretion during a defined period. The primary endpoint was the number of subjects with RBX2660- and/or enema- related TEAEs. The secondary objectives included evaluating efficacy of RBX2660 in the prevention of recurrent episodes of CDI through 8 weeks after administration and loss of sustained clinical response rate of RBX2660 through 6 months after administration.

In the primary safety set population, 53 (82.8%) subjects achieved success through 8 weeks after the last dose of RBX2660 and 47 (88.7%) subjects had a sustained clinical response through 6 months after the last dose of RBX2660.

A total of 11 (17.2%) subjects reported TEAEs considered related to RBX2660 and three subjects reported TEAEs considered related to the enema procedure. Two deaths were reported, neither of which was considered to be related to RBX2660 or the enema procedure.

9.2.4 2019-01: Open-Label Study Safety Update

On May 13, 2022 (6 months after BLA submission), the Applicant submitted safety data from the ongoing Study 2019-01 as an amendment to the BLA. The safety update report included data from April 20, 2021, through March 25, 2022, for the ongoing open-label Study 2019-01.

Number of subjects
An additional 229 subjects were enrolled and exposed to at least one dose of RBX2660 in Study 2019-01 and included in the safety update, which increased the overall RBX2660 exposure from 749 subjects to 978 subjects. A total of 483 subjects have now received RBX2660 in Study 2019-01, 414 of whom have completed week 8 of follow up and 319 subjects of whom have completed month 6 of follow-up.

Disposition
Disposition of subjects in the safety population (483 subjects) for Study 2019-01 is provided in Table 49.

Table 49. Study Disposition of Safety Update, Study 2019-01

Category	Total N=483 n (%)
Subjects who completed the study	302 (62.5)
Subjects who discontinued the study	37 (7.7)
Adverse event	1 (0.2)
Death	3 (0.6)
Failure to comply to study requirements	2 (0.4)
Investigator withdrawal	1 (0.2)
Lost to follow-up	13 (2.7)
Withdrawal by sponsor	16 (3.3)
Other	1 (0.2)

Source: STN 125739/0, Table 14.1.2.1 and Reviewer's Analysis of JMP ADAM datasets

Demographic and Baseline Characteristics

Table 50 is a comparison of the demographic and baseline characteristics of the subjects in Study 2019-01 before and after the safety update.

Table 50. Demographics, Study 2019-01 Safety Update

Category	Total Before Update N=254 n (%)	Total After Update N=483 n (%)
Female	170 (66.9)	337 (69.8)
White, not Hispanic or Latino	237 (93.3)	453 (93.8)
<65 years	154 (60.6)	265 (54.9)
≥65 years	100 (39.4)	218 (45.1)
Median age	62.0 years	63.0 years

Source: STN 125739/0, Table 14.1.2.4 and Reviewer's Analysis of JMP ADAM datasets

Reviewer Comment: The population before and after the safety update appears similar, with the majority of subjects in the safety population being female, White, <65 years old and not Hispanic or Latino. The median age was slightly higher at 63.0 years and slightly more subjects (45.1% vs. 39.4%) were ≥65 years of age.

Updated Efficacy Evaluation

The secondary efficacy endpoint of treatment success appeared to be unchanged from the interim analyses, with 74.6% of subjects achieving treatment success in this open-label safety study.

Treatment Emergent Adverse Events

In the safety update, 67.9% of subjects reported TEAEs. The majority of the TEAEs were related to pre-existing conditions and C. *difficile* disease. TEAEs were similar before and after the safety update, as shown in Table 51.

Table 51. Overview of TEAEs From the Safety Update, Study 2019-01, Safety Population

TEAE Category	Before Update Total N=254 n (%)	After Update Total N=483 n (%)
TEAEs	150 (59.1)	328 (67.9)
Severe TEAEs	33 (13.0)	65 (13.5)
Potentially life threatening (maximum severity)	4 (1.6)	8 (1.7)
TEAEs leading to discontinuation	4 (1.6)	5 (1.0)
TEAEs leading to death	3 (1.2)	3 (0.6)
TEAEs relatedness	--	--
Related to RBX2660	44 (17.3)	81 (16.8)
Related to Enema procedure	27 (10.6)	38 (7.9)
Related to *C. difficile* disease	51 (20.1)	99 (20.5)
Related to a pre-existing condition	85 (33.5)	167 (34.6)
Serious TEAEs	22 (8.7)	51 (10.6)
Serious TEAEs relatedness	--	--
Related to RBX2660	0	2 (0.4)
Related to Enema procedure	0	1 (0.2)
Related to *C. difficile* disease	9 (3.5)	18 (3.7)
Related to a pre-existing condition	14 (5.5)	35 (7.2)

Source: STN 125739/0, Clinical study report for Study 2019-01, page 61/78, Table 14.13.1.2.2/Table 14.3.1.2.5/Table 14.3.1.1.1 (safety update) and JMP Reviewer ADAM Dataset Analysis

Serious TEAEs

Serious TEAEs were reported by 51/483 subjects (10.6%), most of which were related to pre-existing conditions and *C. difficile* disease. Two subjects experienced three serious TEAEs that were reported to be related to RBX2660 (CDI and ulcerative colitis in one subject and CDI in the second subject). One subject experienced 2 serious TEAEs of CDI that were reported to be related to the enema procedure.

Reviewer Comment: This reviewer considered the two serious TEAEs (CDI and ulcerative colitis and CDI) reported by the investigator to be possibly related to RBX2660 to have plausible alternative etiologies, including rCDI and pre-existing conditions.

Deaths

The safety update did not include any additional reports of deaths. Please see Section 8.4.1 for discussion of deaths reported in the initial interim analysis of Study 2019-01.

TEAEs leading to study discontinuation

The safety update included a subject with TEAE of belching/reflux that led to study discontinuation, and it was considered to be related to RBX2660.

Overall summary of the 2091-01 safety update

The safety update included an additional 229 subjects exposed to one RBX2660 enema; therefore, the overall number of subjects with one RBX2660 enema exposure increased from 429 subjects to 658 subjects, and the number of subjects with one or more RBX2660 exposures increased from 749 to 978.

Reviewer Comment: Similar rates of TEAEs were reported before and after the safety update. A slightly higher rate of serious TEAEs were reported in the updated dataset; however, these serious TEAEs were not considered plausibly related to RBX2660 or the enema procedure. No additional deaths were reported in the update, and only one

additional TEAE that led to study discontinuation was reported. The safety update submitted to Study 2019-01 did not reveal any new patterns of TEAEs or new safety signals.

10. CONCLUSIONS

This BLA includes data from six clinical studies: three Phase 2 trials (2013-001, 2014-01 and 2015-01), two Phase 3 trials (2017-01 and 2019-01), and one retrospective study (2019-02). Assessment of efficacy was based on a Bayesian analysis of data from a single pivotal trial, 2017-01, and one supportive trial, 2014-01. Studies 2013-001, 2014-01, 2015-01, 2015-01, and 2019-01 provided safety data for a period of at least 6 months after the last dose of RBX2660 or placebo enema, and studies 2013-001, 2015-01, and 2019-01 provided additional uncontrolled analyses of treatment success rates for RBX2660.

The primary efficacy endpoint analysis for the Phase 3 Study 2017-01 (mITT population), performed with a Bayesian analysis borrowing information from Phase 2 Study 2014-01, resulted in an estimated difference in success rates of RBX2660 as compared to placebo of 13.1% (95% credible interval: 2.3%, 24.0%). The posterior probability that RBX2660 was superior to placebo was 0.991. The efficacy results met the second, less stringent, success threshold (posterior probability of superiority 0.9750338, equivalent to a frequentist one-sided Type 1 error rate <0.025) but did not meet the first, more stringent, success threshold (posterior probability of superiority 0.9993275, equivalent to a frequentist one-sided Type 1 error rate <0.00125).

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.[16,17,18,19,20]

In the blinded and placebo-controlled Study 2017-01, the most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to RBX2660 by the investigator) reported by ≥3% of RBX2660 recipients within 8 weeks after receipt of RBX2660 or placebo, and at a rate greater than that reported by placebo recipients, included: abdominal pain, (8.9% vs. 6.9%), diarrhea (7.2% vs. 3.4%), abdominal distention (3.9% vs. 2.3%), flatulence (3.3% vs. 0%), and nausea (3.3% vs. 1%). Most adverse reactions occurred during the first 2 weeks after treatment. After this, the proportion of subjects with adverse events declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse drug reactions were mild to moderate in severity. No life-threatening adverse reaction was reported.

A safety evaluation was conducted using an ISS that was comprised of subjects enrolled in five prospective studies in the clinical development program for RBX2660. The majority of the subjects in the ISS were White, female, and not Hispanic or Latino. The subjects were predominantly older at baseline and with several comorbid conditions at baseline, age ranging from 18 to 103 years old, median age between 60-70 years old. All subjects had at least 2 CDI episodes with at least one recurrence prior to study entry, with almost 80% reporting a history of ≥3 CDI episodes. Subjects in the placebo only group were generally younger with a lower number of CDI episodes prior to study entry compared with subjects in the RBX2660 group.

The most frequently reported solicited events 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.

In the ISS, a total of 749 subjects were exposed to RBX2660 and included in the Any RBX2660 group and 83 subjects received only placebo. The proportion of subjects reporting TEAEs was 61.8% in the 1-dose RBX2660 group, 69.9% in the blinded RBX2660 group, and 69.6% in the Any RBX2660 group, compared to 60.2% in the placebo group. In all groups, the most commonly reported adverse events were gastrointestinal. For both the 1-dose and blinded RBX2660 groups compared to placebo, numerical imbalances in events of abdominal pain, nausea, flatulence, and abdominal distention were observed. The proportion of participants reporting severe and life threatening TEAEs was numerically higher in the RBX2660 groups compared to the placebo group; however, this difference was small, not statistically significant, and not likely clinically significant.

The proportion of subjects reporting serious TEAEs was 8.4% in the 1-dose RBX2660 group, 10.4% in the blinded RBX2660 group, and 14.2% 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 subjects in the 2-, 3-, and 4-dose RBX2660 groups, respectively). None of the serious TEAEs were considered plausibly related to RBX2660 by FDA.

The proportion of subjects reporting fatal TEAEs was 1.2% in the 1-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 subjects reporting any TEAEs leading to death increased as the number of exposures increased, ranging from 3.4% in subjects who received two doses of RBX2660 to 16.7% of subjects 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 narratives and case report form by FDA, the event was considered not to be causally related to RBX2660 but was considered definitely related to CDI.

A safety update submitted by the Applicant as an amendment to the BLA provided safety data for an additional 229 subjects exposed to RBX2660 in the open-label study, 2019-01. This update increased the total pre-licensure clinical trial safety database to 978 subjects, and review of the safety data did not reveal any new patterns of adverse events or safety signals.

Overall, the safety review demonstrated imbalances in gastrointestinal TEAEs and serious adverse events, 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 AESIs that would suggest a causal relationship to RBX2660, and these imbalances were assessed as being driven by underlying medical conditions among subjects who received additional doses of RBX2660.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 52. Risk-Benefit Analysis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Clostridioides difficile* (formerly *Clostridium difficile*), also known as *C. difficile*, is serious condition that results in significant morbidity and mortality. In the United States, CDI is associated with 15,000 to 30,000 deaths annually, with acute inpatient costs exceeding $4.8 billion • The most common signs and symptoms of *C. difficile* infection (CDI) are watery diarrhea >3 times a day for more than one day and mild abdominal cramping and tenderness. • Severe infection can be associated with significant colitis leading to colectomy and death. • CDI complications include dehydration, hypotension and kidney failure from significant loss of fluids and electrolytes due to severe diarrhea. Although rare, toxic megacolon can occur, resulting in colonic rupture, septicemia, and death. • Recurrent CDI (rCDI) is defined as an episode of CDI occurring within 8 weeks of a previous episode and associated with increased risks of mortality and significant morbidities. • Approximately 25% to 35% of patients develop recurrent CDI disease after the initial episode. • Approximately 40% to 60% of patients experience additional recurrent episodes after the first CDI recurrence, creating a subpopulation of subjects with an infection that does not respond to standard therapies. • Quality-of-life scores in patients with rCDI are lower compared to patients with a first episode of CDI, and consistently decrease with increasing number of CDI episodes.	• Recurrent CDI (rCDI) is a serious condition that is associated with significant healthcare costs and decreased quality of life for affected patients.
Unmet Medical Need	• Antibiotics are first line therapy, which are generally effective at curing the acute infection, but can further disrupt the gut bacteria and limit the recovery of the gut microbiome following CDI. • Bezlotoxumab, a human monoclonal antibody against CDI Toxin B was approved for the indication to reduce recurrence of *C. difficile* infection in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and at high risk for CDI recurrence. Bezlotoxumab must be administered with antibiotics and carries a warning related to heart failure.	• There is currently only one FDA-approved product indicated to reduce recurrence of CDI, and availability of additional safe and effective options would be beneficial. RBX2660 is intended to be used as a preventive agent against rCDI and would be an option with a different route of administration and presumed mechanism of action than bezlotoxumab.
Clinical Benefit	• All 6 studies of RBX2660 conducted in individuals 18 years of age and older, including the 5 prospective studies and 1 retrospective study, defined recurrence of CDI as any confirmed infection occurring within 8 weeks of completing treatment. This aligns with both CDC and clinical treatment guidelines. In the prospective studies, RBX2660 was administered 24-72 hours after completion of antibiotic therapy for a prior episode of rCDI. • The primary evidence of efficacy for RBX2660 was provided by Study 2017-01, which used a prespecified Bayesian hierarchical model that formally integrated data from the previous clinical Study 2014-01. In this analysis, the rate of treatment success in the mITT population in the RBX2660 arm (70.4%) was superior to the rate in the placebo arm (58.1%) through 8 weeks after completing blinded treatment. The 95% credible interval around the estimate of treatment effect (13.1%; 95% CrI: 2.3, 24.0) met the posterior probability threshold equivalent to a one-sided frequentist Type 1 error rate <0.025 but did not meet the more stringent posterior probability threshold equivalent to a one-sided frequentist Type 1 error rate <0.00125. • The prospective open-label studies of RBX2660, while lacking a control group which limits interpretation of efficacy results, provide supportive evidence for the benefit of RBX2660 in preventing rCDI.	• Considered together, the placebo-controlled and prospective open-label studies of RBX2660 provide evidence that RBX2660 is effective in preventing rCDI in individuals 18 years of age and older with prior rCDI. • Available data support the effectiveness of RBX2660 when administered 24-72 hours after completion of antibiotic therapy for the previous episode of rCDI.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• In the larger of the blinded, placebo-controlled studies, 2017-01, 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 events declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse drug reactions were mild to moderate in severity. No life-threatening adverse reaction was reported. • No safety signals were apparent in the safety population evaluated in the ISS (N=749 pooled across 5 studies) or in data provided in a safety update from an additional 229 subjects (total N=978). • Pathogen transmission from the RBX2660 enema to subjects was not observed in the safety population.	• Most adverse reactions associated with RBX2660 were gastrointestinal events that occurred soon after exposure to the product, and most reported adverse events, including all reported serious adverse events and deaths, were most likely associated with recurrent CDI or underlying comorbid illnesses or treatments. • While transmission of pathogens is a safety concern for FMT products, the risk of pathogen transmission appears to be low for RBX2660.
Risk Management	• Ongoing donor and stool screening and testing to mitigate the potential risk of transmission of pathogens through RBX2660.	• If RBX2660 were approved for use in individuals 18 years of age and older with recurrent *C. difficile* infection, the proposed measures of donor and stool screening and testing for pathogens, product labeling, and routine pharmacovigilance would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

Recurrent CDI (rCDI) is a serious condition that is associated with significant healthcare costs and decreased quality of life for affected patients. Bezlotoxumab is the only currently approved product for prevention of recurrent *C. difficile* infection, indicated for use in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at risk for CDI recurrence. Availability of additional safe and effective options for prevention of rCDI would be beneficial and meet an unmet need. RBX2660 is intended to be used as a preventive agent against rCDI and would be an option with a different route of administration and presumed mechanism of action than bezlotoxumab.

Data submitted to the BLA establish that RBX2660 is effective in preventing recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. Available data as summarized in Table 52 above, and in greater detail elsewhere in this review memorandum, support the effectiveness of RBX2660 when administered 24-72 hours after completion of antibiotic therapy for the previous episode of rCDI. The primary evidence of effectiveness (superiority to placebo) is provided by a Bayesian analysis of efficacy data from two placebo-controlled studies, with additional supportive effectiveness data provided by multiple uncontrolled studies. While the estimated treatment effect is modest (13.1%, with a 95% credible interval lower bound of 2.3% in the Bayesian analysis), it is clinically meaningful for the population of patients with rCDI, who have limited FDA approved options for prevention of further episodes of rCDI.

As summarized in in Table 52 above, and in greater detail elsewhere in this review memorandum, most adverse reactions associated with RBX2660 in clinical trials were gastrointestinal events that occurred soon after exposure to the product, and most reported adverse events, including all reported serious adverse events and deaths, were most likely associated with recurrent CDI or underlying comorbid illnesses or treatments. While transmission of pathogens is a safety concern for FMT products, the risk of pathogen transmission appears to be low for RBX2660. Rigorous screening and testing of stool donors and stool will be an ongoing part of risk mitigation and post-licensure product quality controls. If RBX2660 were approved for use in individuals 18 years of age and older with recurrent CDI, the proposed measures of donor and stool screening and testing for pathogens, product labeling, and routine pharmacovigilance would be adequate to manage the risks.

In summary, this reviewer concludes that the benefit-risk balance for RBX2660 is favorable for the intended use being requested by the Applicant.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval of RBX2660 to prevent recurrence of CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. As summarized above, available data support that RBX2660 is safe and effective for the intended indication, with favorable benefit-risk balance in the intended patient population that is experiencing a serious condition with limited FDA approved treatment options.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of RBX2660 for the reduction of the recurrence of CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

11.5 Labeling Review and Recommendations

The following major revisions to product labeling were recommended:

- The approved trade name for RBX2660, Rebyota, was added to the PI.
- CBER requested that the Applicant revise the proposed indication on the prescribing information to be consistent with the submitted data, the indication on the orphan designation status, and labeling regulations. The proposed indication was revised from “reduce the recurrence of *Clostridioides difficile* infection in adults following antibiotic treatment for first or more recurrences of CDI” as originally requested to “prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.” The revision was acceptable.
- CBER requested that the Applicant revise Section 6, Adverse Reactions, Clinical Trials Experience, to highlight the studies conducted to evaluate the safety of RBX2660, including the safety methods, demographics of the population assessed for safety, and the description of the most common adverse reactions.
- CBER requested that the Applicant revise Section 14 to detail the study populations, efficacy assessment and the outcomes that contributed to the efficacy conclusions.

11.6 Recommendations on Postmarketing Actions

Based on the absence of any clear safety signals in the pre-licensure safety database, CBER is not requiring any post-marketing safety studies. The Applicant is conducting 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).