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

NCT03244644

Sponsor: Rebiotix Inc.
2660 Patton Road
Roseville, MN 55113 USA
P: 1-651-705-8770

Study Product: RBX2660 (microbiota suspension)

Protocol #: 2017-01
Version #: 7.0; 06 August 2019

Table of Contents

List of Abbreviations and Acronyms

AE – adverse event
AIDS – Acquired Immunodeficiency Syndrome
ALT – alanine aminotransferase
AST – aspartate transaminase
BUN – blood urea nitrogen
CBC – complete blood count
CDAD – *Clostridium difficile*-associated diarrhea
CDI – *Clostridium difficile* infection
CFR – Code of Federal Regulations
CMP – comprehensive metabolic panel
CRP – C-reactive protein
DSMB – Data and Safety Monitoring Board
EAC – Endpoint Adjudication Committee
eCRF – electronic case report form
EIA – enzyme immunoassay
EVA – ethylene vinyl acetate
FDA – Food and Drug Administration
FT – fecal transplant
GCPs – Good Clinical Practices
GDH – glutamate dehydrogenase
HIV – human immunodeficiency virus
IBD – inflammatory bowel disease
IBS – irritable bowel syndrome
ICF – informed consent form
ICH – International Council on Harmonisation
ICU – intensive care unit
IgG – Immunoglobulin
IP – Investigational product
IRB – Investigational Review Board
ISF – Investigator Site File
ITT – Intent-to-Treat
IV – intravenous
IVIG – intravenous immunoglobulin
MDRO – multi-drug resistant organism
mL – milliliter
NA – not applicable
PAL – Product Accountability Log
PCR – Polymerase chain reaction
PP – Per Protocol
REB – Research Ethics Board
SAE – serious adverse event
SAP – Statistical Analysis Plan
SAR – suspected adverse reaction
VRE – vancomycin-resistant *enterococci*

Study Synopsis

Title	A Phase 3 Prospective, Randomized, Double-blinded, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of Rebiotix RBX2660 (microbiota suspension) for the Prevention of Recurrent *Clostridium difficile* Infection.
Investigational Product and Indication for Use	RBX2660 (microbiota suspension). RBX2660 is being studied for the prevention of recurrent *Clostridium difficile* infection (CDI) in individuals with prior recurrent *Clostridium difficile* infection resolved following antibiotic treatment.
Control Product	Placebo (enema) of normal saline.
Study Purpose	The purpose of this study is to confirm the efficacy and safety of RBX2660 for the prevention of recurrent CDI in subjects who have had prior recurrent *Clostridium difficile* infection that was resolved with antibiotic treatment.
Definition of Recurrent CDI for Study Entry	The definition of recurrent CDI for study entry is a documented diagnosis of: 1. CDI diarrhea; the passage of three or more unformed/loose stools in 24 or fewer consecutive hours for at least two consecutive days, that began within 8 weeks after completion of previous CDI treatment; 2. *and* at least one positive stool test for the presence of toxigenic *C. difficile*, which must be within 30 days prior to or on the date of enrollment (informed consent). To be considered for enrollment, a subject must have medical record documentation of recurrent CDI per the above study definition that includes either: a) at least one recurrence after a primary episode and has completed at least one round of standard-of-care oral antibiotic therapy or; b) had at least two episodes of severe CDI resulting in hospitalization within the last year.
Definition of CDI Diarrhea	The definition of CDI diarrhea for use in enrolled subjects throughout the study includes: 1. The passage of three or more unformed/loose stools (i.e. Bristol Stool Scale type 6-7) in 24 or fewer consecutive hours for at least two consecutive days; 2. *and* a positive stool test for the presence of *C. difficile* toxin; documented at the time of the diarrhea.

Objectives	Primary Objective: To confirm the efficacy of RBX2660 as compared to a 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.
Endpoints	Primary Efficacy Endpoint: Recurrence of CDI within 8 weeks of blinded treatment. Secondary Efficacy Endpoint: Loss of sustained clinical response through 6 months after blinded treatment. Safety Endpoints: 1. Number of adverse events per subject 2. Timing of attributable adverse event post-treatment exposure (treatment emergent adverse event TEAE) 3. Duration of TEAE 4. Relatedness of TEAE 5. Severity of TEAE 6. Causality of TEAE to IP, enema, *C difficile* or prior condition 7. Number of each of the following through 8 weeks post blinded treatment: death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, and ICU admission. 8. Onset of new chronic conditions relative to blinded treatment administration
Study Design	This is a prospective, multicenter, randomized, double-blinded, placebo-controlled Phase 3 study to confirm the efficacy and safety of RBX2660 for the prevention of recurrent CDI. Up to 270 subjects may be randomized and treated in this study. Randomization will be at a 2:1 ratio (RBX2660:Placebo); approximately 180 subjects will be randomized to RBX2660 treatment and 90 subjects randomized to Placebo. Consented subjects who meet all eligibility criteria (inclusion and exclusion) will be randomized. Consented subjects who do not meet the eligibility criteria will be considered screen failures and will not count towards the total randomized. Subjects who are randomized but exit prior to the administration of the first blinded enema may be replaced with additional subjects which could cause overall number of subjects randomized to be greater than the 270 anticipated, however no more than 270 subjects will be treated with a blinded enema. Any replacement subjects will be randomized to ensure maintenance of proper blinding. Potential subjects are expected to already be taking or have just been prescribed antibiotics to control recurrent CDI symptoms at the time of enrollment per the investigator's standard of care. This means patients who have already completed their prescribed course of antibiotics to treat

	recurrent CDI, are not eligible for enrollment unless they have another recurrence that is treated with antibiotics. Once enrolled (informed consent obtained), in order to be randomized and treated: 1. Subject must meet all the inclusion and none of the exclusion criteria; 2. Antibiotics will have been administered for a minimum of 10 consecutive days prior to the washout period; 3. CDI symptoms must be under control leading into the antibiotic washout period. Control of CDI symptoms is defined as no longer meeting the symptomatic criteria for CDI diarrhea which is 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 while taking antibiotics. Thus, at minimum the Subject Diary (completed from time of enrollment until day of treatment) must show that symptoms are under control the two days prior to the washout period in order for the subject to be treated. Once screening is completed and all inclusion and exclusion verified, the subject can be randomized. The assigned study treatment will be scheduled to consist of a single, blinded study enema according to the randomization assignment. Study treatment is to be completed as soon as possible, but no more than 14 calendar days following randomization. Ultimately, the study treatment needs to be administered within 21 days of the Screening visit. A minimum of 24hr to maximum of 72hr antibiotic washout period is required prior to administration of the assigned study treatment. In-office study follow-up visits occur at weeks 1, 4 and 8 after completing the blinded study treatment. Telephone assessments for adverse events occur during weeks 2, 3 and 6 after the study enema and at months 3 and 6. Subjects are required to keep a detailed diary to assess for solicited events from the date of enrollment (informed consent) to the 1-week follow-up visit. The diary will be collected and reviewed at the baseline visit prior to blinded enema administration. The subject will continue to complete the diary following enema administration and it will be collected and reviewed at the 1-week follow-up visit. Subjects who are deemed failures following the blinded treatment per the pre-specified treatment failure definition may elect to receive an unblinded RBX2660 enema. This unblinded enema is to be administered within 21 calendar days of failure determination. If a subject receives an

	unblinded RBX2660 enema, the follow-up requirements will restart from the day of the unblinded RBX2660 enema received according to the same schedule as required for the blinded portion of the study. A primary efficacy and safety analysis will be conducted when all the randomized subjects have completed their 8-week follow-up assessment after receiving the blinded treatment. One or more interim analyses will be conducted to evaluate the primary efficacy endpoint for possible early study stopping for success or futility. The first interim analysis will occur after a minimum of 160 subjects have been treated and evaluated for efficacy. A second interim analysis could occur when 220 subjects have been treated and evaluated for efficacy if success is not achieved at the first interim analysis. The details of the planned interim analyses are included in the statistical analysis plan. A final analysis and report will be completed once the last subject has completed the 6-month follow-up visit for their study treatment. This includes 6-month follow-up after an unblinded RBX2660 study treatment. At that time the study will be considered complete.
Randomized Study Dosing	Placebo Arm – Group A • Placebo dosing consists of one enema of Placebo given in a blinded manner. RBX2660 Arm – Group B • Active treatment consists of one enema of RBX2660 given in a blinded manner.
Definition of Treatment Success	Treatment success is defined as: • The absence of CDI diarrhea for 8 weeks after completing a study treatment.
Definition of Sustained Clinical Response	Sustained Clinical Response is defined as: • Treatment success of the presenting CDI recurrence and no new CDI episodes for greater than 8 weeks through 6 months after completing a study treatment.
Definition of Treatment Failure (CDI recurrence)	Treatment failure (CDI recurrence) is 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 using the study required *C. difficile* testing algorithm. If a recurrence is suspected, an in-office visit is required and the subject must provide a fresh stool sample. The stool sample is to be sent to the central laboratory for analysis. In the case of suspected treatment failure where there is an immediate concern for subject safety, including the

	potential for serious adverse events, an additional C. DIFF QUIK CHEK COMPLETE® Test will be permitted to be conducted at the site or other laboratory known to the site **in addition to** sending a sample to the central laboratory for testing.
Management of Treatment Failures	Following blinded treatment, subjects meeting the protocol definition of treatment failure may be scheduled for administration of an unblinded RBX2660 enema within 21 calendar days of failure determination. In order to receive the unblinded RBX2660 enema, the site must provide documentation of meeting all treatment failure criteria as defined by the protocol. If antibiotics are given to control symptoms, a 24-72hr washout period prior to administration of an unblinded RBX2660 enema is required. If elected, the unblinded enema is to be administered within 21 calendar days of failure determination. The use of antibiotics prior to an unblinded RBX2660 enema is at the discretion of the investigator. If a subject receives an unblinded RBX2660 enema, the follow-up requirements will restart from the day of administration of the unblinded RBX2660 enema according to the same schedule as required for the blinded portion of the study. This results in completion of a new Subject Diary for up to 7 days after treatment; in-office visits at 1-, 4- and 8-weeks as well as telephone calls at 2, 3 and 6 weeks and at 3-and 6 months after the unblinded RBX2660 treatment. Treatment failures who do not receive an unblinded RBX2660 enema will continue to follow their original schedule of assessments for the duration of the study based on the blinded study enema.
Concomitant Therapy	The subject must agree not to take any oral vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide, and 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 recurrent CDI diagnosis.
Determination of Success/Failure: (Investigator and EAC)	The site investigator makes the initial determination of success or failure based on the pre-defined study definitions. The site investigator's assessment will then be provided to the Endpoint Adjudication Committee (EAC) for independent, blinded adjudication of treatment success or failure that will be utilized for study analysis and reporting purposes.

Medical Monitor	The Medical Monitor provides blinded review of serious adverse events to assess accuracy of the reporting as related to seriousness and causality, and periodic review of adverse events for trends. The Medical Monitor's review will be provided to the Data and Safety Monitoring Board (DSMB) for analysis purposes and as applicable for the proper adjudication of potential study stopping rules.
Data and Safety Monitoring Board (DSMB)	The DSMB will review safety data for trends and may be unblinded to adjudicate certain adverse events and for review of both the primary efficacy and safety analysis and the final analysis. Details regarding DSMB responsibilities related to analysis oversight and data reporting will be provided in the DSMB Charter.
Blinding	Subjects, site personnel, the DSMB, EAC and the Medical Monitor are blinded to the randomization assignment. Blinding will be maintained through the data cutoff for the primary efficacy analysis after which the blind may be lifted for the DSMB. The DSMB may be unblinded to individual assignments earlier as needed to adjudicate certain adverse events. Individual randomization assignments will not be revealed to the subjects, site personnel, EAC or the Medical Monitor until the study is completed. Subjects will be randomized to receive either RBX2660 or placebo through an Interactive Response Technology (IRT) System prior to the blinded study treatment. Randomization assignment is provided to the Rebiotix Operations Department personnel for product preparation and shipment. The Rebiotix Kit is shipped to the site in a sealed carton that is only opened by the site IP administrator at the time of administration, out of view of the subject and other site personnel. While the site IP administrator will not have access to the actual randomization assignment, it may be possible to guess through visualization at the time of enema preparation and administration. Additionally, subjects will be instructed to disregard any product characteristics that may become evident during or after administration such as the presence or absence of color or odor. To limit study bias, the IP administrator is not allowed to perform any of the subject study assessments from completion of the enema administration visit through the subject's final study visit.
Sample Size	To demonstrate a 69% success with one dose of the RBX2660 treatment group vs. 47% success in the Placebo control group, 240 subjects are required (power 90%). Up to an additional 30 subjects will be enrolled to allow for a 10% lost-to-follow up rate, for a total of up to 270 subjects randomized and treated with a blinded enema. Considering the 2:1

	randomization, this results in approximately 180 subjects in the RBX2660 arm and 90 subjects in the Placebo arm. Potential subjects who have signed consent but do not meet all inclusion and/or exclusion criteria will be considered screen failures. Randomized subjects who withdraw for any reason prior to administration of the blinded enema will be replaced without counting toward the sample size cap which may result in more than 270 subjects being randomized, however no more than 270 subjects will be treated with a blinded enema. Replacement subjects will be randomized in the same manner as other subjects.
Statistical Considerations	The primary efficacy analysis will be performed on all pre-defined analysis populations comparing the RBX2660 arm to the Placebo arm, Intent-to-Treat (ITT), modified Intent-to-Treat (mITT) and Per-Protocol (PP). However, the determination of meeting the pre-defined primary efficacy endpoint will utilize the mITT population results. The primary endpoint analysis will be based on Pearson's chi-square test with a 0.05 alpha level for this comparison. Secondary efficacy endpoints will also be completed on all analysis populations. Finally, all safety analyses will be performed on the Safety population (SP) which includes all subjects in whom a blinded enema was at least opened and attempted. A primary efficacy and safety analysis will be conducted when all subjects have completed their 8-week follow-up assessment after receiving the blinded treatment. Safety analysis will be completed for safety endpoints defined at or prior to 8 weeks following blinded treatment along with any longer term safety data available at the time of analysis. One or more interim analyses will be conducted to evaluate the primary efficacy endpoint for possible early study stopping for success or futility. The first interim analysis will occur after a minimum of 160 subjects have been treated and evaluated for efficacy. A second interim analysis could occur when 220 subjects have been treated and evaluated for efficacy if success is not achieved at the first interim analysis. The details of the planned interim analyses are included in the statistical analysis plan. Final long-term safety results as well as unblinded RBX2660 efficacy data will be analyzed and reported in a final report after the last subject has completed the 6-month follow-up visit for their study treatment. This includes 6-month follow-up after an unblinded RBX2660 study treatment. At that time the study will be considered complete.

Study Stopping Rules	The DSMB will determine whether enrollment will be paused, the study terminated, or other action taken based on their assessment that: 1. There is probable cause that the IP or enema procedure (e.g., due to transfer from an RBX2660 donor) contributed to a new pathogenic intestinal infection in the stool of any subject, or 2. Any series of events of major significance such as death or other serious outcome for which a causal connection with the IP is plausible represents an excess of the important adverse event(s) in one of the study arms. In the event that one of the preceding rules appears to be met based on site reported data and/or medical monitor review, the Rebiotix Operations Department will review the donor history and batch processing/release records for the product unit(s) administered in these cases. A report of the review will be forwarded to the DSMB Chair for blinded review. If probable cause is suspected, the DSMB Chair will convene the entire DSMB for event review. Upon the DSMB's determination of action, the Chair will notify the Rebiotix Clinical Department, who will notify the study sites. If enrollment is stopped, Rebiotix and the study sites will assess for the occurrence of similar events, and evaluate IP and study records for possible root cause(s). Enrollment may be re-started upon further review and approval from the DSMB. As appropriate, the DSMB may recommend study termination or measures short of termination with the objective of reducing the risk of adverse events. Details regarding DSMB responsibilities will be provided in the DSMB Charter.
Key Inclusion Criteria	1. ≥ 18 years old. 2. Medical record documentation of recurrent CDI per the study definition, that includes either: a) at least one recurrence after a primary episode and has completed at least one round of standard-of-care oral antibiotic therapy or b) has had at least two episodes of severe CDI resulting in hospitalization within the last year. 3. A positive stool test for the presence of toxigenic *C. difficile* within 30 days prior to or on the date of enrollment. 4. Is currently taking or was just prescribed antibiotics to control CDI related diarrhea at the time of enrollment. *Note: Subject's CDI diarrhea must be controlled (<3 unformed/loose stools/day, i.e. Bristol Stool Scale type 6-7, for two consecutive days) while taking antibiotics during screening* 5. Willing and able to have an enema(s). 6. Willing and able to complete the stool and serum testing required for the study. 7. Agrees not to take non-dietary probiotics through 8 weeks after receiving the last study enema (including OTC and prescription).

	8. Agrees not to take any oral vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide and 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 recurrent CDI diagnosis. 9. Agrees to practice a form of effective contraception during study participation, does not apply to persons with documented non-child bearing potential. 10. Has a negative urine pregnancy test at the time of enrollment and on the day of each enema prior to administration (persons of child-bearing potential only). 11. Willing and able to provide informed consent and local privacy authorization as applicable. 12. Willing and able to complete the required Subject Diary. 13. Willing and able to meet all study requirements, including attending all assessment visits and telephone calls.
Key Exclusion Criteria	1. A known history of refractory CDI. 2. Currently has continued CDI diarrhea despite being on antibiotics prescribed for CDI treatment. 3. Requires antibiotic therapy for a condition other than CDI. 4. Previous fecal transplant, RBX2660 treatment, receipt of CDI vaccine or treatment with CDI monoclonal antibodies prior to study enrollment. 5. History of inflammatory bowel disease (IBD), e.g., ulcerative colitis, Crohn's disease, or microscopic colitis. 6. Diagnosis of irritable bowel syndrome (IBS) as determined by Rome III criteria. 7. History of chronic diarrhea. 8. History of celiac disease. 9. Disease symptoms (diarrhea) caused by a confirmed intestinal pathogen other than *C. difficile*. 10. Have a current colostomy. 11. Intraabdominal surgery within the last 60 days. 12. Evidence of active, severe colitis. 13. History of short gut syndrome or motility disorders. 14. Requires the regular use of medications to manage bowel hypermotility. 15. Planned therapy in the next 3 months that may cause diarrhea (e.g., chemotherapy). 16. Planned surgery requiring perioperative antibiotics within 6 months of study enrollment. 17. Life expectancy of < 6 months. 18. Compromised immune system (e.g., HIV infection with CD4 count <200/mm^3; inherited/primary immune disorders; immunodeficient or immunosuppressed due to a medical condition or medication). *Note: Eligible HIV patients who have a CD4 count >200/mm^3 who are on stable, highly active anti-retroviral therapy may be considered for enrollment.*

	19. Taking systemic steroids > 20 mg a day or prednisone-equivalent, or is expected to be on steroids (> 20 mg 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 be enrolled only after consultation with the Medical Monitor, and only if the doses have been stable (except for drug therapeutic monitoring adjustments for calcineurin inhibitors) for 90 days and have not been associated with diarrhea prior to the current episode of CDI.* 20. An absolute neutrophil count of <1000 cells/µL during screening. 21. Known or suspected current (< 90 days) illicit drug use. *Note: marijuana use is allowed.* 22. Participant is unable to discontinue opioids (unless on a stable dose with no increase in dose planned for the duration of the study). *Note: Opioids are permitted as needed as long as participants are on a stable dose at the time of randomization and expect to maintain the same dose until the 8 week follow-up visit OR if the participant has been on short-term (i.e., ≤ 14 days) opioid treatment and there is anticipation of a dose decrease or cessation of use during the course of the study. Participants who only receive a few doses at the time of presentation of CDI may be considered for participation. Investigator should consult on any clarification of the opioid doses/treatment with the Medical Monitor.* 23. Pregnant, breastfeeding, or intends to become pregnant during study participation. 24. Participating in a clinical trial of another investigational product (drug, device or other) and has not completed the required follow-up period. 25. Subject, in the opinion of the investigator, for whatever reason, should be excluded from the study.
Study Sites	Approximately 80 US and Canadian sites will participate in this study.
Study Sponsor	Rebiotix Inc. 2660 Patton Road Roseville MN 55113 USA www.rebiotix.com 651-705-8770
Contract Research Organization	Medpace, Inc. [redacted]

Central Laboratory	Medpace Central Labs LLC [redacted]

1. Introduction

1.1. Background

RBX2660 (microbiota suspension) is an intestinal microbial suspension prepared from human stool obtained from carefully and thoroughly screened healthy human donors. It is being studied for the treatment of recurrent *Clostridium difficile* infection (CDI). RBX2660 is prepared from a standardized amount of stool mixed with saline and a cryoprotectant. It is stored at the manufacturer in a frozen state and is shipped frozen to the clinical site for administration via enema.

The donor selection process is multifaceted in its original screening of candidate donors as well as the ongoing assessment of donated samples prior to release for use in a clinical study. Some of these measures include the following:

1. Donor qualification screening includes questions that specifically address risk factors for colonization with multi-drug resistant organisms (MDROs), and individuals at higher risk of colonization with MDROs are excluded from donation. Examples of persons at higher risk for colonization with MDROs include:
    a. Health care workers
    b. Persons who have recently been hospitalized or discharged from long term care facilities
    c. Persons who regularly attend outpatient medical or surgical clinics
    d. Persons who have recently engaged in medical tourism
2. Donor stool testing includes MDRO testing to exclude use of stool that tests positive for MDRO. The MDRO tests include at minimum extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, vancomycin-resistant *enterococci* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).
3. All drug product currently in storage has undergone screening and stool testing for MDROs as described above.
4. The informed consent process for subjects being treated with RBX2660 product as part of this study describes the risks of MDRO transmission and invasive infection as well as the measures implemented for donor screening and stool testing.

Rebiotix has concluded the first clinical study of RBX2660 (n=34) in an open-label, non-controlled Phase 2 study demonstrating the safety of the product. Additionally, Rebiotix has completed enrollment and interim reports of two Phase 2 clinical studies. Protocol 2014-01 is a prospective, multicenter, randomized, double-blinded, placebo-controlled, 3-arm Phase 2B study (n=127 treated) designed to demonstrate the efficacy and safety of RBX2660 for the treatment of recurrent CDI. Primarily, the Phase 2B

study compared the efficacy of RBX2660 to placebo, and secondarily compared the efficacy of two planned enemas of RBX2660 to one planned enema of RBX2660 with one enema of placebo. The study has completed enrollment and primary efficacy analysis and continues in long term follow-up. Protocol 2015-01 is an open label study comparing the efficacy and safety of two planned RBX2660 enemas (n=136 treated) to a historical control (n=110) is in long-term follow-up.

Finally, to complete the RBX2660 clinical development program, Rebiotix is initiating a Phase 3 study. The purpose of this Phase 3 study is to confirm the efficacy and safety of RBX2660 for the prevention of recurrent CDI in subjects who have had prior recurrent *Clostridium difficile* infection that was resolved with antibiotic treatment.

The study will be conducted in compliance with this protocol as approved by the federal Food and Drug Administration and each site's governing Institutional Review Board or Research Ethics Board (Canada); in accordance to relevant regulations in 21 CFR Part 11, 50, 54, 56 and 312; and the ICH E6 Good Clinical Practice: Consolidated Guidance.

1.2. Investigational Agent

RBX2660 (microbiota suspension) 50g/150mL in an enema bag within a brown opaque sleeve, which is to remain in place over the bag and tubing during administration and disposal. Each bag contains one dose. Each dose contains minimum 10^7 microbes/mL of suspension in a saline/polyethylene glycol 3350 vehicle.

Note: *For this protocol, the term "Investigational Product (IP)" refers to both RBX2660 and the Placebo.*

1.3. Placebo

The Placebo consists of 150 mL of normal saline, but without the polyethylene glycol 3350 or drug substance, human stool. It is supplied in an enema bag within a brown opaque sleeve, which is to remain in place over the bag and tubing during administration and disposal. Each bag contains one dose.

1.4. Preclinical Data

Fecal transplantation is being used today in many highly respected hospitals throughout the world with no significant reports of adverse events or other safety-related complications. Rebiotix has conducted an extensive literature review from the first published cases in 1958 (Eiseman et al., 1958) to the present. The literature presents significant evidence of the safe and effective use of FT for over 500 cases of recurrent *Clostridium difficile* infection (CDI) with no product-related adverse events reported to

date and only a few procedure-related events, none of which have occurred in subjects receiving FT via enema (Bakken, 2015). Based on the significant human clinical experience documented in the literature, it has been determined that preclinical studies are not warranted.

1.5. Clinical Data to Date

1.5.1. Phase 2 Study Protocol 2013-001 Final Data

On July 12, 2013, Rebiotix received permission from FDA to proceed with the Phase 2 clinical study entitled "A Phase 2 Open-label Clinical Trial Demonstrating the Safety of RBX2660 Microbiota Suspension for the Treatment of Recurrent *Clostridium difficile*-associated Diarrhea." This study ended with the last subject's 6-month assessment in July 2014.

It was a prospective, multi-center, open-label, non-controlled Phase 2 study designed to demonstrate the safety of RBX2660 (50 g/150 mL) for the treatment of recurrent CDI. The target population was adults (≥ 18 years old) with recurrent CDI who had either a) at least two recurrences after a primary episode (primary episode + ≥ two recurrences, i.e., at least three episodes) and had completed at least two rounds of standard-of-care oral antibiotic therapy or b) had at least two episodes of severe CDI resulting in hospitalization. The Rebiotix Phase 2 study was the first study assessing the safety of RBX2660, although similar fecal transplant products have been used in humans for many years, as discussed in the literature. The study's primary objective was to assess the safety of RBX2660 but additional information was gathered on efficacy and the therapy's impact on quality of life. Eligible subjects who proceeded to treatment received one treatment with RBX2660. If their CDAD returned before Day 56 after receiving one treatment, they were eligible to receive a second treatment if the re-treatment occurred within ten days of recurrence.

Follow-up visits occurred at Days 7, 30 and 60, and subjects remained in the study for telephone assessments for adverse events at 3 and 6 months. If a subject received a second treatment, the follow-up schedule was re-set, so that they came in for visits at 7, 30 and 60 days after the second treatment and receive 3- and 6-month telephone assessments. Subjects also kept a written diary for the first 60 days after each treatment with RBX2660, including the collection of detailed information on solicited adverse events for the first eight days after receiving an RBX2660 enema.

Rebiotix performed a final analysis of the Phase 2 data for the generation of the Final Clinical Study Report. As of the report's data lock on July 28, 2014, 40 subjects were enrolled. Of these, six did not proceed to receive a treatment with RBX2660 (screen failures). Of the 34 treated subjects, two subjects terminated their participation in the study around their respective 7-day visit. One subject, 02-RBX01-007, died 35 days

after receiving her second treatment with RBX2660 from respiratory failure, which was not related to RBX2660 or the administration procedure. As of July 28, 2014, 31 subjects remained in active follow-up and all completed the study (6-month telephone assessment after their last treatment with RBX2660). Here are the clinical study data and conclusions as presented in the Final Report.

Efficacy Results

The primary efficacy parameter of this study was treatment success, defined as the absence of CDAD (passage of three or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days) at 56 days after the last treatment with RBX2660. Of the 34 subjects who received at least one treatment with RBX2660, 31 of them were presented in this efficacy analysis (31 had efficacy data available). Twenty-seven (27) out of 31 subjects, or 87.1%, were considered a treatment success. Sixteen (16) subjects or 50.0% (N=16/32) were considered a treatment success after their first treatment with RBX2660. Of the 16 subjects who failed their first treatment, 15 subjects proceeded to receive a second enema of RBX2660. Of those, 11 subjects or 78.6% (N=11/14) were considered a treatment success (one subject was not counted because she did not reach the 56-day endpoint). The reasons for the increased rate of success after the second enema were not fully understood. It may be due to a number of factors, including changes in the subject's microbiome after one treatment, complete elimination of vancomycin from the subject's stool over time, or other reasons not yet determined.

Safety Results

The subjects enrolled in the Rebiotix Phase 2 study had significant pre-existing comorbidities. Even with their recurrent CDI symptoms temporarily controlled by standard-of-care antibiotic therapy, they remained very sick people. The incidence, severity, and seriousness of the adverse events observed in this study represented the first attempt to systematically and rigorously collect, and consistently analyze and characterize them in a subject group suffering from recurrent CDI who were treated with an intestinal microbiota fecal transplant product. There were 188 adverse events reported by 28 subjects, which were gathered through the very rigorous solicitation of events. The adverse events reported were mostly mild-to-moderate in severity and were primarily related to gastrointestinal disorders as was expected in this population. Most resolved within the 7-day interval after RBX2660 administration. This was true whether the subject received one or two treatments with RBX2660.

Of the reported solicited events, which were collected during the 8-day period inclusive of the day of dosing and the subsequent 7-day follow-up period, the incidence and severity of these events declined over the 8-day period. The proportion of subjects reporting solicited AEs was lower on Day 7 in subjects who received two treatments (41.7%; N=5/12) with RBX2660 than in subjects who received one treatment (51.5%; N=17/33), yet the efficacy rate after two treatments rose to 78.6% from 50% after one

treatment. There were seven subjects who experienced a total of 20 SAEs, only one of which had a possible relationship to RBX2660; most were probably or definitely related to a pre-existing condition, including CDI. Overall, adverse events declined over time; 66.5% of AEs occurred from baseline through the 7-day visit. This was the first known study to prospectively, systematically, consistently and aggressively solicit, record, and classify adverse events in subjects who received an intestinal microbiota fecal transplant product. It was therefore expected that the incidence rate of reported AEs might be higher than that reported in the literature, but it represented the true rate and types of events experienced by this population after treatment with an intestinal microbiota fecal transplant product.

Figure 1-1 shows the decline in the proportion of subjects reporting solicited adverse events over the 8 days from the day of dosing (Day 0) to the seventh day after dosing (Day 7).

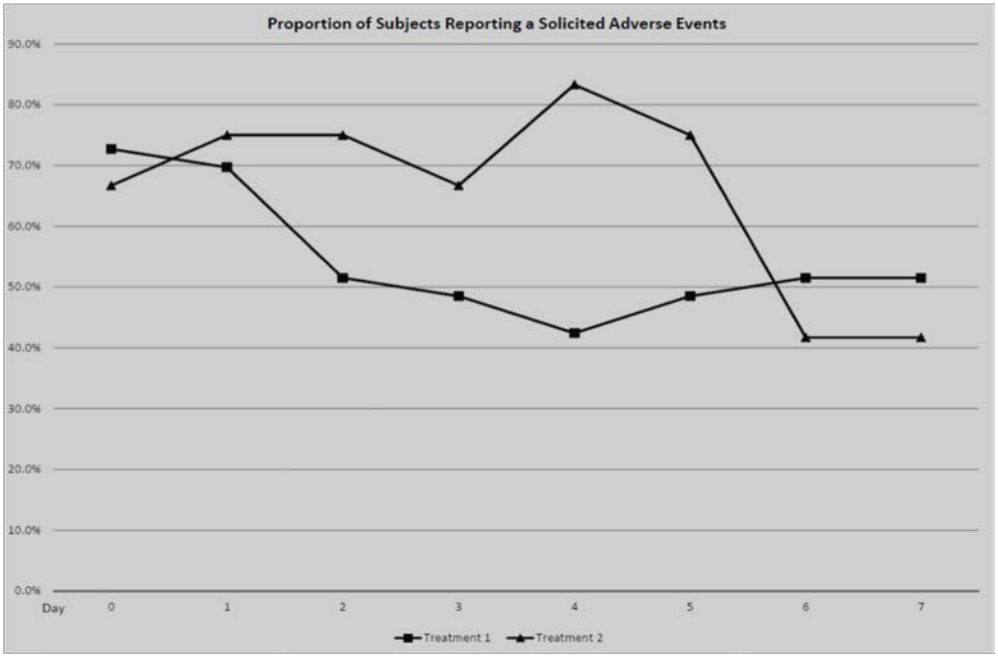


Figure 1-1: Proportion of Subjects Reporting Solicited AEs from Day 0-Day 7

Conclusions

The RBX2660 efficacy rate of 87.1% represented a significant improvement over reported success rates for oral antibiotics and was within the range of results reported in the literature for similar fecal microbiota products. This was the first known study to prospectively, systematically, consistently and aggressively solicit, record, and classify adverse events in subjects who received an intestinal microbiota fecal transplant product. It was therefore expected that the incidence rate of reported AEs (188 events in 28 subjects) might be higher than that reported in the literature but it represented the true

rate and types of events experienced by this population receiving this therapy. The incidence rate and type of adverse events were not unexpected, given the high number of comorbidities that existed in this very sick, primarily elderly population. None of the SAEs were determined to be probably or definitely related to RBX2660 and most were related to a pre-existing condition, primarily *C. difficile* infection. Efficacy rose after two treatments with RBX2660 yet the proportion of subjects reporting solicited AEs was lower on Day 7 in subjects who received two treatments than in subjects who received one treatment. The efficacy benefit of RBX2660 outweighed the incidence and type of adverse events, especially the risk of recurrent CDI, thus providing a satisfactory benefit: risk ratio.

1.5.2. Phase 2B Study Protocol 2014-01 Interim Study Data

EFFICACY RESULTS: The efficacy objectives of the study were analyzed using the n=127 treated subjects (n=41 Group A, n=44 Group B, n=42 Group C) in the ITT population. In particular the assessment of RBX2660 as compared to placebo for subjects with a history of recurrent CDI and the assessment of further treatment on subjects who are confirmed treatment failures.

While the anticipated primary efficacy endpoint of two (2) enemas of RBX2660 administered 7 ±2 days apart (61.0%) as compared to placebo (45.5%) in the blinded phase was not met, the key secondary efficacy endpoint of one (1) enema of RBX2660 (66.7%) as compared to the placebo group (45.5%) was met with a p-value of *0.048*. All other secondary objectives for the study were also met. The active RBX2660 treatment groups A and C in the were compared to each other with a p-value of 0.589 indicating no difference between one RBX2660 enema and two (2) administered 7 ±2 days apart. As such, an analysis using the combined RBX2660 treatment groups A and C with a success rate of 63.9% (53/83) was compared to the placebo (45.5%) also with a significant p-value of *0.046* by Pearson's chi-square.

Additionally, analysis of the ITT population was done to establish the overall efficacy rate for RBX2660 which took into consideration both blinded and open label treatments. The resulting overall efficacy for all subjects treated with RBX2660 (n=107) was 88.8% which compared to the placebo rate of 45.5% was also significant with a p-value of *<0.0001*.

Finally, an analysis of the ITT placebo group subjects using them as their own control by comparing blinded treatment success (placebo treatment) to open label success (after RBX2660 treatment) showed a significant increase in success rate from 45.5% (20/44) in the blinded phase to 87.5% (21/24) after treatment with RBX2660 with a resulting p-value of *<0.0001*.

Confirmation is provided by the Per Protocol (PP) population analysis in which the combined RBX2660 treatment groups A and C with a success rate of 75.0% (45/60) were compared to the placebo 52.9% (18/34) with a significant p-value of *0.029* by Pearson's chi-square during the blinded treatment phase. Further, overall RBX2660 efficacy rate in PP subjects who received at least 1 RBX2660 enema either blinded or in open label (n=76) was 93.4% (71/76). When compared to the PP Control Group B rate of 52.9%, a resulting p-value of *<0.0001* further substantiates that RBX2660 is an effective treatment for the prevention of recurrent CDI.

Overall the efficacy data confirms the following primary conclusions:

- Treatment with RBX2660 following a standard course of antibiotics significantly increases the success rate for prevention of recurrent *Clostridium difficile* infection in subjects with a history of multi-recurrent disease.
- Appropriate treatment with RBX2660 includes a single enema administered following completion of a standard course of antibiotics with another RBX2660 enema administered only if CDI symptoms return.

Not only do these results prevent a recurrence of CDI within the 56 day (8 week) timeline as established by the CDC, the results are maintained longer term. The long term CDI free rate at the time of this analysis was 95.8% (91/95) for subjects successfully treated with RBX2660 at an average follow-up of 8.2 months (range: 1.6 – 14.9).

Lastly, the donor screening and manufacturing process appears to properly ensure the quality of the RBX2660 product as consistent results in treatment success are shown regardless of donor.

These efficacy results also validate previous results from the Phase 2 study which reported an 87.1% treatment success with RBX2660.

SAFETY RESULTS: The Safety Population (SP) consists of any subject who had a study enema attempted (n=128) whether placebo or RBX2660. Adverse events were independently reviewed by a Medical Monitor with additional oversight by a DSMB for evaluation of safety trends and stopping rules. The DSMB completed an interim review of safety data as reported during the double-blind period. Following review, the DSMB recommends continuation of the study as no pre-defined study stopping rules have been met or other safety concerns identified.

Adverse events (n=580 in 94 subjects) were collected by the investigational sites and solicited via subject diary following administration of a study enema. The adverse

events reported were mostly mild-to-moderate in severity (90.8%) and were primarily related to gastrointestinal disorders (41.9%) as would be expected in this population.

Death has been reported in seven (7) subjects at the time of the analysis, none (0) of which were reported as related to the study enemas or procedure. Six (6) of the seven (7) were reported as related to a pre-existing condition. Further, one (1) of the seven (7) subjects died prior to receiving the assigned study treatment.
There were 45 (7.8%) serious adverse events (SAEs) in 26 subjects reported. Of the SAEs only three (3) were reported as possibly related to the study enema. Additionally, of the 345 enemas administered in the study, zero (0) had a report of SAE related to the enema procedure. While 31.1 % of SAEs were reported as related to CDI and 77.8% reported as related to a pre-existing condition. No differences in the rate of adverse events between treatment groups was identified in the number of subjects experiencing an adverse event. Additionally, only five (5) subjects were hospitalized for CDI recurrence during the blinded period, none (0) resulting in ICU admission.

A detailed review of subjects with adverse events relative to the number of exposures to RBX2660 (0-4 exposures) was completed which showed there was no significant increase in the number or rate of adverse events with increased exposure to RBX2660. There were 108 subjects (84.4%) in the safety population who were exposed to RBX2660 with a total of 223 exposures for an average of two (2) exposures per subject.

Analysis of the donor screening process indicated no adverse events subsequent to treatment with RBX2660 were linked to transfer of conditions to a subject from an RBX2660 enema or its constituents.

Overall the safety data indicates that treatment with an RBX2660 enema followed by an additional treatment with RBX2660 if needed due to recurrence of CDI symptoms can be safely administered as it does not increase the risk for adverse events or result in a transfer of donor conditions.

OVERALL RESULTS: These results conclude that a single enema of RBX2660 followed by an additional RBX2660 enema if needed due to a recurrence of CDI symptoms is a safe and effective treatment for the prevention of recurrent CDI following a standard course of antibiotics.

1.5.3. Phase 2B Study Protocol 2015-01 Interim Study Data

EFFICACY RESULTS: The efficacy objectives of the study were analyzed using the n=246 treated subjects (n=136 treated with at least one enema of RBX2660, and 110 historical controls) in the Full Analysis Set defined as all subjects who received any study treatment. In particular the assessment of RBX2660 as compared to historical

controls for subjects with a history of recurrent CDI and the assessment of further treatment on subjects who are confirmed treatment failures. Historical controls were subjects who received antibiotics for recurrent CDI, not RBX2660 or other enema treatment, and were identified through review of patient records.

The primary efficacy endpoint analysis of treatment success for the RBX2660 treatment administered 7 ±2 days apart (79.4%) as compared to historical controls (51.8%) reached statistical significance ($p < 0.0001$).

Further sensitivity analysis was completed in which the RBX2660 improvement in treatment success remained statistically significant versus the control group after adjusting for age ($p<0.0001$), race (p-value 0.0003), sex ($p<0.0001$), number of previous episodes of CDI at baseline (p-value 0.0002).

Overall the efficacy data confirms the following primary conclusions:

- Treatment with RBX2660 following a standard course of antibiotics significantly increases the success rate for prevention of recurrent *Clostridium difficile* infection in subjects with a history of multi-recurrent disease.

SAFETY RESULTS: The Safety Population (SP) consists of any subject who had a study enema attempted (n=136) of RBX2660. Adverse events were independently reviewed by a Medical Monitor. Following review, the Medical Monitor did not see an emergence of new adverse events or change in the occurrence rate.

A total of 482 adverse events were reported in 99 subjects (72.8% of subjects) in the RBX2660 treatment group. This was similar to the number and percentages of adverse events documented in the historical control group (n=691 events in 69 subjects; 62.7% of subjects).

There were 385 treatment emergent adverse events (TEAEs) in 94 subjects (69.1% of subjects) in the RBX2660 treated group. The TEAEs reported were mostly mild-to-moderate in severity (89.1%) and primarily related to gastrointestinal disorders (37.4%) as would be expected in this population

Three deaths were reported in RBX2660 treated subjects at the time of the interim analysis data cutoff date, 12 January 2017, one of which was reported as possibly related to the RBX2660 or procedure but definitely related to *C. difficile* disease and pre-existing condition(s). The other two recorded deaths were reported as definitely related to a pre-existing condition. Death was reported in eight of the 110 subjects in the historical control group (7.3%).

In the RBX2660 treated group, there were 82 Serious Adverse Events (SAEs) reported in 25 subjects. Two of these SAEs occurred prior to administration of the first enema, leaving 80 treatment emergent SAEs (20.8% of all TEAEs) in 23 subjects (16.9%). Of the treatment emergent SAEs, 11 (13.8%) were reported as possibly related to the

investigational product, and 5 (6.3%) were reported as possibly related to the enema procedure. Additionally, 23 (28.8%) of the treatment emergent SAEs were reported as related to CDI disease and 62 (77.5%) were reported as related to a pre-existing condition. No adverse events subsequent to treatment with RBX2660 were linked to transmission of disease to a subject from an RBX2660 enema or its constituents.

In the historical control group, there were 80 reported SAEs in 31 subjects (28.2% of subjects).

As of the interim analysis, none of the pre-identified study stopping rules were met as determined by the medical monitor and the study continues as planned.

OVERALL RESULTS: These results indicate that treatment with RBX2660 is a safe and effective treatment for the prevention of recurrent CDI following a standard of care course of antibiotics as compared to a historical control.

1.6. Treatment Rationale and Risk/Benefit

RBX2660 microbiota suspension was developed after careful, controlled component and process testing performed by Rebiotix using applicable scientific methods. RBX2660 (microbiota suspension) 50 g/150 mL is supplied in an ethylene vinyl acetate enema bag. Each bag of RBX2660 contains one enema; each enema of RBX2660 consists of a suspension of minimum 10^7 live organisms/mL in polyethylene glycol 3350/0.9% Sodium Chloride Irrigation, USP, solution to ensure a consistent product is delivered. This study is confirming the optimal dosing strategy of RBX2660 enemas (one enema followed by a second if needed due to a recurrence of CDI symptoms) as compared to a placebo enema. In an assessment of risk of recurrent CDI, which often results in severe and serious consequences, the benefit of preventing recurrent episodes by administering multiple enemas of RBX2660 outweigh the risk of the predominately mild to moderate AEs experienced by subjects in the Phase 2 and Phase 2B studies. The enema route was chosen over other potential routes of administration because the risk of procedural complications for the subject is low and the method is easy to perform and requires no special equipment. In addition, the enema route for fecal transplants is routinely used and has high efficacy rates reported in the literature with no reports of safety issues.

Based on the results of the Rebiotix Phase 2 and Phase 2B studies, and the known, documented, safe and highly effective use of fecal transplantation for recurrent CDI with other products administered either via enema, colonoscopy or nasogastric/duodenal tube, the rigor of Rebiotix's donor screening process, and implementation of quality assurance testing at all stages of manufacturing, the anticipated risks to subjects are acceptable in relation to the potential benefits of RBX2660.

2. Study Objectives and Endpoints

2.1. Primary Objective

To confirm the efficacy of RBX2660 as compared to a Placebo in preventing recurrent episodes of CDI through 8 weeks.

2.2. Secondary Objective

To evaluate the sustained clinical response rate of RBX2660 as compared to Placebo after blinded treatment.

2.3. 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.
6. To characterize the baseline severity of CDI in subjects with documented CDI recurrence.
7. Evaluate treatment success of RBX2660 in Placebo subjects who are documented study treatment failures then went on to receive RBX2660.
8. Assess the ability of more than one dose of RBX2660 to prevent CDI recurrence.
9. 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. Assess the clearance rate of vancomycin resistant enterococcus in subjects who are carriers at baseline.
11. 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.

2.4. Primary Efficacy Endpoint

Recurrence of CDI within 8 weeks of blinded treatment.

2.5. Secondary Efficacy Endpoint

Loss of sustained clinical response through 6 months after blinded treatment.

2.6. Safety Endpoints

1. Number of adverse events per subject
2. Timing of attributable adverse event post-treatment exposure (treatment emergent adverse event TEAE)
3. Duration of TEAE
4. Relatedness of TEAE
5. Severity of TEAE
6. Causality of TEAE to IP, enema, *C. difficile* or prior condition
7. Number of each of the following through 8 weeks post blinded treatment: death, septic shock, toxic megacolon, colonic perforation, emergency colectomy, and ICU admission
8. Onset of new chronic conditions relative to blinded treatment administration

2.7. Other Efficacy Endpoints

1. Baseline characteristics
2. Subject fecal microbial composition at Screening, and 4-weeks, 8-weeks, 3 months and 6 months after blinded study treatment.
3. Charlson Comorbidity Index at Screening, 8-week, 3-, and 6- month phone assessments.
4. Cdiff32 questionnaire at Screening, Week 1, 4, 8, month 3 and 6
5. ATLAS score for CDI severity of qualifying CDI event.
6. Recurrence of CDI within 8 weeks of unblinded (open-label) RBX2660 treatment in Placebo subjects who were documented blinded study treatment failures.
7. Recurrence of CDI within 8 weeks of unblinded (open-label) RBX2660 treatment in subjects who received a blinded dose of RBX2660.
8. Occurrence of CDI through 6 months in all subjects receiving a single dose of RBX2660.
9. Concentration of vancomycin resistant enterococcus in stool samples for subjects who were carriers at baseline.
10. Presence of *C. difficile* in stool samples at Screening, and 4-weeks, 8-weeks, 3 months and 6 months after study treatment.

3. Study Design

3.1. Study Purpose

The purpose of this study is to confirm the efficacy and safety of RBX2660 for the prevention of recurrent CDI in subjects who have had prior recurrent *Clostridium difficile* infection that was resolved with antibiotic treatment.

3.2. General Study Design

This is a prospective, multicenter, randomized, double-blinded, placebo-controlled Phase 3 study to confirm the efficacy and safety of RBX2660 for the prevention of recurrent CDI.

Up to 270 subjects may be randomized and treated in this study. Randomization will be at a 2:1 ratio (RBX2660:Placebo) which means approximately 180 subjects randomized to treatment with RBX2660 and 90 subjects randomized to Placebo. Consented subjects who meet all inclusion and none of the exclusion criteria will be randomized. Potential subjects who are consented but do not meet the inclusion and/or exclusion criteria will be considered screen failures and will not count towards total randomized. Subjects who are randomized but exit prior to the administration of the first blinded enema may be replaced with additional subjects which could cause overall number of subjects randomized to be greater than the 270 anticipated, however no more than 270 subjects will be treated with a blinded enema. Replacement subjects will be randomized to ensure maintenance of proper blinding.

Potential subjects are expected to already be taking or just have been prescribed antibiotics to control recurrent CDI symptoms at the time of enrollment per the investigator's standard of care. This means patients who have already completed their prescribed course of antibiotics to treat recurrent CDI, cannot be considered for enrollment unless they have another recurrence.

Once enrolled (informed consent obtained), in order to be randomized and treated;

1. Subject must meet all the inclusion and none of the exclusion criteria;
2. Antibiotics will have been administered for a minimum of 10 consecutive days prior to the washout period;
3. CDI symptoms must be under control leading into the antibiotic washout period.

Control of CDI symptoms is defined as no longer meeting the symptomatic criteria for CDI diarrhea which is 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 while taking antibiotics. Thus, at minimum the diary must show that symptoms are under control the two days prior to the washout period in order for the subject to be treated.

Once screening is completed and all inclusion and exclusion verified, the subject can be randomized. The assigned study treatment will be scheduled to consist of a single blinded study enema according to the randomization assignment. Study treatment is to be completed as soon as possible, but no more than 14 calendar days following randomization. A minimum of 24hr to maximum of 72hr antibiotic washout period is required prior to administration of the assigned study treatment. Ultimately, the study treatment needs to be administered within 21 days of the Screening visit.

In-office study follow-up visits occur at weeks 1-, 4- and 8 after completing the blinded study treatment. Telephone assessments for adverse events occur during weeks 2, 3 and 6 after the study enema and at months 3 and 6. Subjects are required to keep a detailed diary to assess for solicited events from the date of enrollment (informed consent) to the 1-week follow-up visit. The diary will be collected and reviewed at the baseline visit prior to blinded enema administration. The subject will continue to complete the diary following enema administration and it will be collected and reviewed at the 1-week follow-up visit.

Subjects who are deemed failures following the blinded treatment per the pre-specified treatment failure definition may elect to receive an unblinded RBX2660 enema. This unblinded enema is to be administered within 21 calendar days of failure determination. If a subject receives an unblinded RBX2660 enema, the follow-up requirements will restart from the day of the unblinded RBX2660 enema received according to the same schedule as required for the blinded portion of the study.

A primary efficacy and safety analysis will be conducted when 100% of the randomized subjects in each group have completed their 8-week follow-up assessment after receiving the blinded treatment. One or more interim analyses will be conducted to evaluate the primary efficacy endpoint for possible early study stopping for success or futility. The first interim analysis will occur after a minimum of 160 subjects have been treated and evaluated for efficacy. A second interim analysis could occur when 220 subjects have been treated and evaluated for efficacy if success is not achieved at the first interim analysis. The details of the planned interim analyses are included in the statistical analysis plan.

A final analysis and report will be completed once the last subject has completed the 6-month follow-up visit for their study treatment. This includes 6-month follow-up after an unblinded RBX2660 study treatment. At that time the study will be considered complete.

See Figure 3-1 for an illustration of the Study Design.

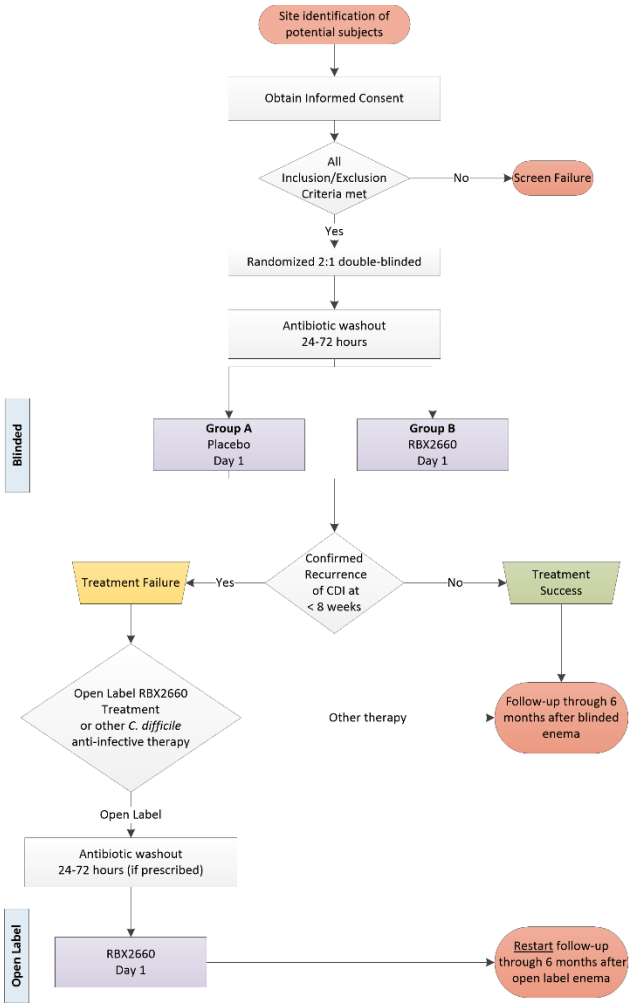


Figure 3-1: Phase 3 Study Design. 2:1 randomization refers to two subjects randomized to receive RBX2660 (Group B) for every one subject randomized to Placebo (Group A)

3.3. Definition of Recurrent CDI for Study Entry

The definition of recurrent CDI for study entry is a documented diagnosis of:

1. CDI diarrhea; the passage of three or more unformed/loose stools in 24 or fewer consecutive hours for at least two consecutive days, that began within 8 weeks after completion of previous CDI treatment;
2. *and* at least one positive stool test for the presence of toxigenic *C. difficile*; which must be documented within 30 days prior to or on the date of enrollment (informed consent).

To be considered for enrollment, a subject must have medical record documentation of recurrent CDI per the above study definition that includes either:

a. at least one recurrence after a primary episode and has completed at least one round of standard-of-care oral antibiotic therapy or;
b. had at least two episodes of severe CDI resulting in hospitalization within the last year.

3.4. Definition of CDI Diarrhea for Use in Enrolled Subjects Throughout the Study

1. 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;
2. *and* a positive stool test for the presence of *C. difficile* toxin; documented at the time of the diarrhea.

3.5. Definition of Treatment Success

Treatment success is defined as:

- The absence of CDI diarrhea for 8 weeks after completing a study treatment.

3.6. Definition of Sustained Clinical Response

Sustained clinical response is defined as:

- Treatment success of the presenting CDI recurrence and no new CDI episodes through 6 months after completing a blinded treatment.

3.7. Definition of Treatment Failure

Treatment failure (CDI recurrence) is 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.

If a recurrence is suspected, an in-office visit is required, and the subject must provide a fresh stool sample. Site staff will send this stool sample to the central laboratory for analysis. To ensure consistency across clinical sites for the determination of study failures, the central laboratory will perform the required C. DIFF QUIK CHEK COMPLETE® Test rapid enzyme immunoassay for glutamate dehydrogenase (GDH) and toxins A and B. If the test is inconclusive, the central laboratory will conduct a second confirmatory test by PCR.

Specifically, regarding interpretation of results, if the GDH and toxin are both positive per the rapid enzyme immunoassay test during the presence of diarrhea then the subject is considered a treatment failure.

However, if the subject experiences diarrhea and the GDH and toxin are both negative per the test, then the subject is not considered a treatment failure as the presence of *C. difficile* was not established. The study investigator will need to determine the appropriate treatment for the subject as to avoid the possibility of serious adverse events.

Alternatively, if the GDH and toxin results per the rapid enzyme immunoassay test are inconclusive (one is positive and the other is negative) the central lab will perform a PCR test. If the PCR test is negative, the subject will not be considered a treatment failure as the presence of C. *difficile* was not established. If the PCR test is positive, then the subject will be considered a treatment failure.

Finally, if the rapid enzyme immunoassay test provides an invalid result such that the control line is not visible, the test will be repeated.

For suspected treatment failures, a sample must be sent to the central laboratory. In the case of suspected treatment failure where there is an immediate concern for subject safety, including the potential for serious adverse events, a C. DIFF QUIK CHEK COMPLETE® Test will be permitted to be conducted at the site or other laboratory known to the site in addition to sending a sample to the central laboratory for testing. If the C. DIFF QUIK CHEK COMPLETE® Test is not available, a testing algorithm that directly assesses the presence of *C. difficile* toxin for laboratory confirmation of recurrent CDI should be used. In the event, the test results from the central laboratory differ from that of a local laboratory, the results from the central laboratory will be used in determination of treatment failure. For subjects who are suspected of treatment failure, but for whom there is not a test result from the central laboratory for the suspected episode, a deviation will be added to the database, and due documentation of the subject's symptoms and all available data will be sent to the Endpoint Adjudication Committee (EAC) for independent adjudication of treatment failure.

3.8. Management of Treatment Failure

Following blinded treatment, subjects meeting the protocol definition of treatment failure may be scheduled for administration of an unblinded RBX2660 enema within 21 calendar days of failure determination. In order to receive the unblinded RBX2660 enema, the site must provide documentation of meeting all treatment failure criteria as defined by the protocol. If the subject has a subsequent treatment failure after the unblinded RBX2660 enema, the subject can be given another therapy as deemed appropriate by the treating investigator.

Without conclusive failure documentation, an unblinded RBX2660 will not be provided for administration.

Treatment failures are required to be entered in the study database shortly after determination of failure to allow for sponsor awareness and assurance that an unblinded RBX2660 can be provided if requested.

If antibiotics are given to control symptoms, a 24-72hr washout period prior to administration of an unblinded RBX2660 enema is required. If the subject will have the unblinded enema, it needs to be administered within 21 calendar days of failure

determination. The use of antibiotics prior to an unblinded RBX2660 enema is at the discretion of the investigator.

If a subject receives an unblinded RBX2660 enema, the follow-up requirements will restart from the day of the unblinded RBX2660 enema according to the same schedule as required for the blinded portion of the study. This results in completion of a new subject diary for up to 7 days after treatment; in-office visits at 1-, 4- and 8-weeks as well as telephone calls at 2-, 3- and 6- weeks and at 3 and 6 months after the last RBX2660 treatment.

Treatment failures who do not receive an unblinded RBX2660 enema will continue to follow their original schedule of assessments for the duration of the study based on the blinded study enema.

3.9. Determination of Treatment Success/Failure

The site investigator makes the initial determination of treatment success or failure based on the pre-defined study definitions. The site investigator's assessment will then be provided to the EAC for independent, blinded adjudication of treatment success or failure that will be utilized for study analysis and reporting purposes. This may be done in an on-going basis or a single meeting as deemed appropriate. Details of the EAC logistics, activity and responsibilities will be included in a EAC charter.

3.10. Endpoint Adjudication Committee

The Endpoint Adjudication Committee (EAC) provides independent, blinded adjudication of treatment success or failure that will be used for study analysis and reporting purposes. The EAC is comprised of three physicians specializing in infectious diseases or gastroenterology who have experience managing subjects with recurrent CDI and are not investigators in the study. Details of the EAC logistics, activity and responsibilities will be included in a EAC charter.

3.11. Data and Safety Monitoring Board

The DSMB will review safety data for trends and may be unblinded as needed to adjudicate certain adverse events and for review of both the primary efficacy and safety analysis and the final analysis. Details regarding DSMB responsibilities related to analysis oversight and data reporting will be provided in the DSMB Charter.

3.12. Medical Monitor

The Medical Monitor provides blinded review of serious adverse events or events reported by the site as related to the investigational product or enema procedure to assess accuracy of reporting as related to seriousness and causality, and periodic review of adverse events for trends. Details of this review are documented in a Safety Management Plan. The Medical Monitor will remain blinded throughout the study. The

Medical Monitor's review will be provided to the DSMB for analysis purposes and as applicable for the proper adjudication of potential study stopping rules.

3.13. Blinding

Subjects, site personnel, the DSMB, EAC and the Medical Monitor are blinded to the randomization assignment. Blinding will be maintained through the data cutoff for the primary efficacy and safety analysis after which the blind may be lifted for the DSMB. The DSMB may be unblinded to individual assignments earlier as needed to adjudicate certain adverse events. Individual randomization assignments will not be revealed to the subjects, site personnel, EAC or the Medical Monitor until the study is completed. Sites will be provided an emergency unblinding code if it becomes medically necessary to know the treatment group assigned for a particular subject.

Subjects will be randomized to receive either RBX2660 or placebo through an Interactive Response Technology (IRT) System 4-14 calendar days prior to the blinded study treatment. Randomization assignment is revealed to Rebiotix Operations Department personnel for product preparation and shipment. The Rebiotix Kit is shipped to the site in a sealed carton that is only opened by the IP administrator at the time of administration, out of view of the subject and other site personnel. While the IP administrator will not have access to the actual randomization assignment, it may be possible to guess through visualization at the time of enema preparation and administration. To limit study bias, the IP administrator should not perform any of the subject study assessments from completion of the enema administration visit through the subject's final study visit.

The Rebiotix Kit remains sealed at the site until opened at the time of administration by the IP Administrator. The IP bag is blinded by an opaque brown sleeve secured over it at Rebiotix at the time of shipment, and the tube set is covered by another brown opaque sleeve, which is placed by the IP Administrator at the time of preparation at the site; preparation occurs out of sight from the subject and other site personnel. The IP is covered by the opaque sleeves throughout the administration process to avoid inadvertent visualization by the subject or other personnel who may accidentally view it. Subjects will be instructed to disregard the presence or absence of odor or color, as these characteristics may or may not indicate which product is being administered. Product is placed in an opaque biohazard bag that is sealed to avoid accidental visualization.

4. Subject Selection and Withdrawal

4.1. Inclusion Criteria

All responses must be "yes" to include a subject in the study:

1. ≥ 18 years old.
2. Medical record documentation of recurrent CDI per the study definition, that includes either: a) at least one recurrence after a primary episode and has completed at least one round of standard-of-care oral antibiotic therapy or b) has had at least two episodes of severe CDI resulting in hospitalization within the last year.
3. A positive stool test for the presence of toxigenic *C. difficile* within 30 days prior to enrollment.
4. Is currently taking or was just prescribed antibiotics to control CDI related diarrhea at the time of enrollment.
   Note: Subject's CDI diarrhea must be controlled (<3 unformed/loose, i.e. Bristol Stool Scale type 6-7, stools/day for 2 consecutive days) while taking antibiotics during screening
5. Willing and able to have an enema(s).
6. Willing and able to complete the stool and serum testing required for the study.
7. Agrees not to take non-dietary probiotics through 8 weeks after receiving the last study enema (including OTC and prescription).
8. Agrees not to take any oral vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide and 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 recurrent CDI diagnosis.
9. Agrees to practice a form of effective contraception during study participation, does not apply to persons with documented non-child bearing potential.
10. Has a negative urine pregnancy test at the time of enrollment and on the day of each enema prior to administration (persons of child-bearing potential only).
11. Willing and able to provide informed consent and local privacy authorization as applicable.
12. Willing and able to complete the required Subject Diary.
13. Willing and able to meet all study requirements, including attending all assessment visits and telephone calls.

4.2. Exclusion Criteria

All responses must be "no" to include a subject in the study:

1. A known history of refractory CDI.
2. Currently has continued CDI diarrhea despite being on a course of antibiotics prescribed for CDI treatment.
3. Requires antibiotic therapy for a condition other than CDI.
4. Previous fecal transplant, RBX2660 treatment, receipt of CDI vaccine or treatment with CDI monoclonal antibodies prior to study enrollment.

5. History of inflammatory bowel disease (IBD), e.g., ulcerative colitis, Crohn's disease, or microscopic colitis.
6. Diagnosis of irritable bowel syndrome (IBS) as determined by Rome III criteria.
7. History of chronic diarrhea.
8. History of celiac disease.
9. Disease symptoms (diarrhea) caused by a confirmed intestinal pathogen other than *C. difficile*.
10. Currently has a colostomy.
11. Intraabdominal surgery within the last 60 days.
12. Evidence of active, severe colitis.
13. History of short gut syndrome or motility disorders.
14. Requires the regular use of medications to manage bowel hypermotility.
15. Planned therapy in the next 3 months that may cause diarrhea (e.g., chemotherapy).
16. Planned surgery requiring perioperative antibiotics within 6 months of study enrollment.
17. Life expectancy of < 6 months.
18. Compromised immune system (e.g., HIV infection with CD4 count <200/mm^3; inherited/primary immune disorders; immunodeficient or immunosuppressed due to a medical condition or medication).
    Note: Eligible HIV patients who have a CD4 count >200/mm^3 who are on stable, highly active anti-retroviral therapy may be considered for enrollment.
19. Taking systemic steroids > 20 mg prednisone a day or prednisone-equivalent, or is 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 be enrolled only after consultation with the Medical Monitor, and only if the doses have been stable (except for drug therapeutic monitoring adjustments for calcineurin inhibitors) for 90 days and have not been associated with diarrhea prior to the current episode of CDI.
20. An absolute neutrophil count of <1000 cells/µL during screening.
21. Known or suspected current (< 90 days) illicit drug use. *Note: marijuana use is allowed.*
22. Participant is unable to discontinue opioids (unless on a stable dose with no increase in dose planned for the duration of the study).
    Note: Opioids are permitted as needed as long as participants are on a stable dose at the time of randomization and expect to maintain the same dose until the 8 week follow-up visit OR if the participant has been on short-term (i.e., ≤ 14 days) opioid treatment and there is anticipation of a dose decrease or cessation of use during the course of the study. Participants who only receive a few doses at the time of presentation of CDI may be

considered for participation. Investigator should consult on any clarification of the opioid doses/treatment with the Medical Monitor.

23. Pregnant, breastfeeding, or intends to become pregnant during study participation.
24. Participating in a clinical trial of another investigational product (drug, device or other) and has not completed the required follow-up period.
25. Subject, in the opinion of the investigator, for whatever reason, should be excluded from the study.

4.3. Subject Recruitment and Screening

Subjects are recruited by qualified and trained site personnel when they are identified as recently diagnosed with or experiencing recurrent CDI within 8 weeks of completing the treatment for a previous CDI episode. Potential subjects are to be fully informed as to this study's purpose, requirements, randomization schedule, blinding, anticipated risks, etc., and are to be given the chance to review the informed consent form and receive satisfactory answers to all questions. Subjects sign the study-specific, IRB/REB-approved Informed Consent and local privacy authorization, which is the point at which the potential subject is considered enrolled in the study.

Subjects are eligible to receive study treatment upon confirmation that they have met all inclusion/exclusion criteria listed in Sections 4.1 and 4.2. Antibiotics being taken for their recurrent CDI symptoms must be stopped for a 24-72 hour washout period prior to receiving the blinded study enema.

5. Investigational Product

5.1. RBX2660 Description

RBX2660 microbiota suspension 50 g/150 mL in an enema bag. Each bag of RBX2660 provides one enema. Each enema of RBX2660 consists of a suspension of minimum 10^7 live organisms/mL in polyethylene glycol 3350/0.9% Sodium Chloride Irrigation, USP, solution.

5.2. Placebo Description

The Placebo is an enema of normal saline. Placebo packaging and labeling are identical to the packaging and labeling for RBX2660 to support the study blinding.

5.3. Rebiotix Kit Description

Investigational product is supplied in a single-enema bag fitted with a spike port and a rectal tube assembly that is used to administer IP as an enema; these components are packaged together in the Rebiotix Kit. Rebiotix Kit components include:

- 1 bag of RBX2660 or Placebo with a spike port contained in a brown opaque sleeve
- 1 rectal tube assembly
- 1 brown opaque sleeve for the tube assembly
- 1 adhesive strip to secure opaque sleeves
- 1 biohazard disposal bag
- 1 Instructions for Use

5.4. Treatment Regimen

Randomization is to occur about 4-14 calendar days prior to the blinded study treatment to allow for notification to Rebiotix and shipment of product. Ultimately, the study treatment needs to be administered within 21 days of the Screening visit. Subjects are randomized to one of the following groups:

- Group A: Placebo
- Group B: RBX2660

Randomization will occur in a 2:1 fashion with two subjects randomized to receive RBX2660 for every one subject randomized to Placebo.

Once completed, assigned study treatment consists of a single blinded enema of either RBX2660 or Placebo as per the randomization assignment. Product is to only be administered by the authorized IP Administrator who must be a qualified and trained health care professional following the Instructions for Use and standard site procedures. Subjects are to remain at the site under supervision for at least one hour post-enema administration for vital sign assessment (temperature, heart rate, blood pressure, respiratory rate) and observation.

Subjects with a documented treatment failure following blinded treatment may be scheduled for administration of an unblinded RBX2660 enema. In order to receive an unblinded RBX2660 enema, a subject must have documentation of meeting all treatment failure criteria as defined by the protocol (Section 3.7).

If, in the opinion of the investigator, antibiotics are warranted for the control of CDI symptoms prior to receiving the unblinded RBX2660 enema, they can be administered but need to be stopped 24-72 hours before enema administration. The total time from a treatment failure (CDI recurrence) determination to administration of an unblinded enema is within 21 calendar days.

See Section 6 for the Schedule of Study Procedures and detailed description of the requirements.

5.5. Subject Follow-up Requirements

Subjects are assessed at office visits at 1, 4 and 8 weeks and via telephone calls from the study coordinator at 2, 3 and 6 weeks and 3 and 6 months from their last study enema. See Section 6 for follow-up assessments and phone calls, and Section 6.16 for subject withdrawal/termination.

5.6. Concomitant Therapy

The subject must agree not to take any oral vancomycin, metronidazole, fidaxomicin, rifaximin, nitazoxanide, and 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 recurrent CDI diagnosis. Medication information will be collected at the screening visit and changes in medications will be recorded throughout the study. Subjects should be encouraged to notify their general practitioners of study participation and the requirements for concomitant therapy as able.

5.7. Preparation of Investigational Product

Instructions for Use with detailed directions for IP preparation and administration are in each Rebiotix Kit.

5.8. Packaging

Investigational product is supplied in an enema bag fitted with a spike port and a rectal tube assembly that is used to administer the product via enema; these components are packaged together in the Rebiotix Kit.

5.9. Ordering, Receipt and Storage, Dispensing, Returning, and Tracking Investigational Product

5.9.1. Ordering Investigational Product

Authorized site personnel will randomize subjects using the Interactive Response Technology (IRT) System which automatically triggers ordering of IP. If a subject is a confirmed treatment failure and will proceed to unblinded RBX2660 treatment, the site will document the failure in the IRT which automatically triggers ordering of RBX2660 IP.

5.9.2. Receipt and Storage of Investigational Product

Note: Each unit of IP is designated to be administered to a specific subject on a specific date; administration of IP designated for one subject to another subject is prohibited. The Rebiotix Kit must only be opened by the IP Administrator and only at the time of product preparation immediately before administration away from subjects and other study personnel.

Personnel from the Rebiotix Operations Department confirm the randomization assignment and ship a unit of IP to the authorized person/ department as specified on the Delegation of Authority log at the site in a temperature-controlled shipping package. The authorized person opens the shipping package, visually confirms that the unit of IP arrived intact, confirms that the temperature indicator has not been tripped and records receipt and inspection on the Product Accountability Log. IP is to be thawed and stored in the refrigerator until administration.

IP must be kept in a secure location under the control of the Investigator or authorized designee at all times; see Section 5.9.5 for details. IP must be administered to the subject by the expiration date as specified on the label. If it is not administered by the expiration date, it must be destroyed by site staff per the institution's processes and be recorded on the Product Accountability Log.

5.9.3. Dispensing and Administering Investigational Product

Dispensing procedures vary from site to site, but each site's study investigator is responsible for delegating the administration of IP to a qualified and trained health care professional; this person(s) ("IP Administrator") must be identified on the Delegation of Authority Log and receive product-specific training on IP administration.

IP is to be administered by the IP Administrator after the site Investigator confirms all inclusion/exclusion criteria have been met, the subject had a negative pregnancy test (if applicable) and the 24-72 hour washout period has been completed. Administration is via enema following the Instructions for Use in each product package and the site's standard procedures.

5.9.4. Returning IP

Do not return IP to Rebiotix. For IP received but not administered to a subject, it must be destroyed by site staff per the institution's processes. Destruction must be recorded on the Product Accountability Log.

5.9.5. Product Accountability and Tracking

Each unit of IP is sent to the site for administration to an assigned subject and is labeled with a batch number to be recorded in the eCRF and on the Product Accountability Log. Each unit must be tracked on the Product Accountability Log by the person(s) authorized on the Delegation of Authority Log to perform that step. IP must be kept in a secure location under the control of the site investigator or authorized designee as recorded on the Delegation of Authority Log. The Product Accountability Log and Delegation of Authority Log are to be maintained by the site and confirmed during

monitoring visits. The steps to be tracked include dates of receipt and dispensing, batch number, subject number, storage in refrigerator, and destruction if not administered to a subject. The IP Administrator must ensure the correct batch number is administered to the correct subject.

6. Study Procedures

6.1. General Information

Study information is collected on study-specific electronic case report forms (eCRFs) by the site. Study monitoring occurs at regular intervals to ensure the protection of subject rights and safety, data integrity and accuracy, and proper study conduct in compliance to the protocol and applicable regulations including 21 CFR 312 and ICH E6 GCPs. Study visits and telephone assessments must occur with the window specified in Table 6-1; visits and calls out of window or missed are to be reported as protocol deviations. The study-required procedures are to be conducted as shown in Table 6-1.

Table 6-1 Schedule of Events

Activity	Screening (Enrollment)	Baseline / Enema Administration (≤ 21 days from screening)	Follow-up Visits 1-, 4- and 8-Week (± 3 days) Assessments[1]	Weekly Phone Assessment (Weeks 2, 3 and 6 (± 3 days)	Unscheduled Possible Recurrence Visit	Unblinded Enema Administration[1] (≤ 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[3]	X[3]	X					
Central Lab CMP & CRP testing	X						
C. difficile testing[4]	X[4]				X[4]		
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[5]						
24-72hr 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[6]			X	
Employment status assessed	X		X[7]				X
Concomitant medications	X	X	X	X	X	X	X
Medical History Assessment	X		X[7]		X		X
Adverse events assessed		X	X	X	X	X	X
Solicited events assessed[2]		X	X[2]			X[2]	
Protocol deviations (if applicable)	X	X	X	X	X	X	X

[1] Documented treatment failures may receive an unblinded RBX2660 enema. If an unblinded enema is administered, the follow-up visit requirement re-start based on the date of last enema administration.

[2] Solicited events are collected in the Subject Diary from the day of administration of any study enema (blinded or unblinded) until the day prior to the 1-week visit. The Subject Diary is collected and reviewed at the 1-week visit. Solicited events that increase in severity from screening should be assessed for a possible adverse event.

[3] Exclusion criteria for absolute neutrophil count should be assessed based on the CBC collected at the screening visit.

[4] Perform within 30 days prior to or at enrollment and if CDI recurrence is suspected.

[5] Randomization should occur after screening criteria have been assessed and eligibility confirmed (4-14 calendar days from randomization to blinded study treatment).

[6] Subject Diary is reviewed only at the 1-week follow-up visit.

[7] Collected at the 8-week follow-up visit only.

6.2. Informed Consent

All subjects must sign the study-specific IRB/REB-approved Informed Consent/HIPAA Form; see Section 4.3. The original signed Form is to be placed in the subject's study file. A copy of the signed Form is also to be given to the subject for his/her records.

6.3. Subject Diary

The Subject Diary serves as a tool for the subject to record pre- and post-treatment health and information that may indicate adverse events or the recurrence of CDI. The subject also documents changes in medications.

At the time of enrollment (informed consent) subjects are provided a Subject Diary that they are to complete until the day prior to the blinded study enema. This may mean up to 21 days depending on how long it takes to determine subject eligibility for the study. The diary will be collected and reviewed at the baseline visit prior to enema administration.

A diary is also given to the subject on the day of the blinded study enema administration and is collected at the 1-week office visit. The Subject Diary is reviewed for solicited event occurrence and severity, changes to medications, occurrence of adverse events, and possible recurrence of CDI. The following information is entered into the study database:

- solicited event severity
- changes to medication
- occurrence of adverse events

If a subject is a documented treatment failure and s/he elects to receive unblinded RBX2660 treatment, the follow-up visit requirements start over with the receipt of an unblinded enema. The subject will be given additional diary pages to complete beginning on the day of the unblinded enema until the 1-week visit. This additional information is also entered into the study database.

6.4. Optional Stool Samples for Additional Testing by Rebiotix

Subjects are requested to provide stool samples directly to Rebiotix at:

- Screening (between the time of enrollment and prior to treatment)
- at the time of the 1, 4 and 8 week office visits;
- at the time of the 3 and 6 month phone calls;
- at the time of possible treatment failure symptoms.

Subjects collect the samples at home in pre-labeled containers given to them by the study team. Rebiotix provides the study sites with kits containing all the materials for collecting and shipping the samples, including subject directions, container labels, and prepaid, preaddressed mailing labels. Samples are identified by the label on the container that contains only the subject's study identification number and date/time of the sample; samples will not contain any personal information that would identify the subject. Samples may be stored for approximately five years. The stool samples will be used for research about the microorganisms in the human gut. Some of the research will include testing for microorganisms (*Clostridium difficile* and vancomycin-resistant enterococcus) both before and after receiving the study enema. Failure to send in a sample does not require a protocol deviation, however subjects should be reminded of this request.

6.5. Screening Visit

The following study activities/data will be collected at the screening visit:

- Subjects are told about the study and informed consent is obtained (enrollment)
- Standard demographics (gender, ethnicity, date of birth, race.)
- Detailed medical history, including Charlson Comorbidity Index variables
- Assess inclusion/exclusion criteria, including *C. difficile* stool testing
    - At the time of enrollment or study entry, a positive stool test for toxigenic *C. difficile* must be or have been performed and documented no more than 30 days before entry and must be on file at the site. *C. difficile* laboratory testing according to the site's standard of care is acceptable for enrollment, however, the use the C. DIFF QUIK CHEK COMPLETE® Test rapid enzyme immunoassay test for enrollment is preferred. If the rapid enzyme immunoassay test is utilized, the same interpretation of results as defined for treatment failures is required.
- Core laboratory blood sample is collected for CBC w/differential and comprehensive metabolic panel (CMP: Sodium, potassium, chloride, BUN, creatinine, albumin, AST, ALT, alkaline phosphatase, bilirubin (direct, indirect and total), glucose) and C-reactive protein (CRP) testing
- Onsite urine pregnancy test for subjects of child bearing potential
- For subjects who consented to the Optional Stool Sample collection, remind them to obtain and ship a stool sample to Rebiotix anytime between their enrollment date and their blinded enema administration visit
- Assess vital signs: height, weight, temperature, blood pressure, pulse, respiration.
- Complete the Cdiff32 health-related quality of life questionnaire

- Document concomitant medications
- Completion of the Subject Diary is explained and how to complete it is demonstrated; see Section 6.3.
- Verify employment status
- Assess for protocol deviations

6.6. Randomization

Once enrolled (informed consent obtained), in order to be randomized and treated:

1. Subject must meet all of the inclusion and none of the exclusion criteria;
2. Antibiotics will have been administered for a minimum of 10 consecutive days prior to the washout period;
3. CDI symptoms must be under control leading into the antibiotic washout period.

After enrollment and confirmation of inclusion/exclusion criteria compliance, including criteria confirmed by central laboratory testing, the study coordinator or other trained and authorized site staff randomize the subject in the Interactive Response Technology (IRT) System and ensures study treatment is completed within 4-14 calendar days of randomization. Ultimately, the study treatment needs to be administered within 21 days of the Screening visit.

The randomization schedule will be created using randomized blocks within four strata based on antibiotics used at screening (Vancomycin alone, Vancomycin in combination, Fidaxomicin or Other), and randomized subjects will be assigned one of two treatments (Group A or Group B) within the appropriate stratum. The randomization will not be stratified by site, so each site will draw from the same set of blocks. A subject will be assigned the next available treatment allocation from the randomization list. The randomization code and the date and time of randomization will be captured in the IRT.

Enrolled (consented) subjects who are randomized but exited prior to attempting the blinded treatment may be re-enrolled if another CDI recurrence occurs and thus randomized under a different subject identification numbers (re-randomized). If this occurs, they will be included in the analysis using their second randomization assignment and subsequent assessments and will only be counted once towards the total randomized.

Treatment will be assigned in the following proportions: 2:1 to yield a total of up to 270 randomized and treated subjects, or approximately 180 subjects randomized to treatment with RBX2660 and 90 subjects randomized to Placebo. Subjects who are randomized but exit prior to the administration of the first blinded enema may be replaced with additional subjects which could cause overall number of subjects randomized to be greater than the 270 anticipated, however no more than 270 subjects will be treated with

a blinded enema. The assignment is transmitted to the Rebiotix Operations Department, who will ship the correct IP to the site for each treatment. Replacement subject will also be randomized to ensure proper blinding.

6.7. Baseline Visit and Enema Administration

The baseline visit is performed on the day of the blinded enema administration. Randomization and IP administration must occur within 21 days of the screening visit. Antibiotics for the control of CDI symptoms are prescribed or continued until 24-72 hours before administration of the blinded study enema.

The following study activities/data will be collected at the baseline visit prior to enema administration:

- Inclusion/exclusion criteria are confirmed including the following:
  - The control of symptoms during antibiotic use is confirmed by review of the subject diary
  - Compliance to the washout period (discontinuation of the antibiotics for 24-72 hours prior to the baseline visit) is confirmed
- Modified physical exam (no genitourinary exam unless medically indicated) is performed to establish baseline health status (findings that can be attributed to the subject's medical history will not be documented as adverse events)
- Central laboratory blood sample collection for CBC w/differential, HIV, Hepatitis A (IgG) Hepatitis B Anti-Hepatitis B surface antigen, Hepatitis C antibody, and Treponema Antibody. *NOTE: the results are **not** needed before proceeding to treatment per the protocol*
- Central laboratory stool sample is collected. *NOTE: the results are **not** needed before proceeding to treatment per the protocol*
- Onsite urine pregnancy test for subjects of child bearing potential
- Assess vital signs: temperature, pulse, blood pressure, respiration
- Changes to concomitant medications since the last visit
- Review subject diary
- Assess recurrence of CDI
- Assess for adverse events since enrollment
- Assess for protocol deviations

Following successful completion of the baseline visit, investigational product is then administered via enema per the Instructions for Use and standard site procedure by the authorized IP Administrator; see Section 5.9.3. Subjects remain at the site under supervision for at least one hour post-IP administration for vital sign assessment (temperature, heart rate, blood pressure, respiratory rate) about every 15 minutes and

observation. If the subject's vital signs do not return to the pre-administration values ± 20%, assess the subject for a possible AE. The subject is sent home after completion of study procedures and a review of the Subject Diary instructions, and is requested to call the study coordinator if symptoms recur or at the onset of an adverse event.

Table 6-2: Subject Baseline Stool and Blood Testing Conducted by Central Laboratory

Test Name	Material Tested
Norovirus	Stool
Rotavirus	
Adenovirus	
Enteric pathogens *(Shigella, Salmonella, Campylobacter, sorbitol-negative E. coli., Aeromonas, Plesiomonas, Yersinia,* and *shiga toxins)*	
Giardia antigen	
*Cryptosporidium a*ntigen	
Acid-fast staining *(Cyclospora, Isospora)*	
Ova and parasites	
Vancomycin-resistant *enterococci* (VRE)	
Methicillin-resistant *Staphylococcus aureus* (MRSA)	
Vibrio	
Listeria	
Clostridium difficile	
Carbapenem-resistant Enterobacteriaceae Culture (CRE)	
CBC with Differential	Blood
HIV	
Hepatitis A (IgG)	
Hepatitis B Anti-Hepatitis B surface antigen	
Hepatitis C Antibody	
Treponema Antibody	

6.8. In Office Visit (1-Week)

Timely and complete follow-up visits will ensure the scientific integrity of the data is maintained and allow for continued oversight of subject safety.

The following study activities/data will be collected at the 1-week follow-up visit:

- Review of the subject diary for solicited events as defined in Section 7.4
- Assess recurrence of CDI
- Subject's weight
- Adverse event collection, including new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders
- Cdiff32 health-related quality of life questionnaire
- Changes to concomitant medications since the last visit
- Assess for protocol deviations
- For subjects who consented to the Optional Stool Sample collection, remind the subject to collect and ship a stool sample to Rebiotix

6.9. In Office Visit (4-Week)

The following study activities/data will be collected at the 4-week follow-up visit:

- Assess recurrence of CDI
- Subject's weight
- Adverse event collection, including new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders
- Cdiff32 health-related quality of life questionnaire
- Changes to concomitant medications since the last visit
- Assess for protocol deviations
- For subjects who consented to the Optional Stool Sample collection, remind the subject to collect and ship a stool sample to Rebiotix

6.10. In Office Visit (8-Week)

The 8-week follow-up visit is the primary efficacy endpoint timeline of the study. As such, every attempt should be made to ensure subjects understand the importance of this visit and are scheduled within the appropriate visit window.

The following study activities/data will be collected at the 8-week follow-up visit:

- Assess recurrence of CDI
- Subject's weight
- Adverse event collection, including new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders

- Changes to concomitant medications since the last visit
- Cdiff32 health-related quality of life questionnaire
- Verify employment status
- Assess changes in medical history, including Charlson Comorbidity Index variables. Worsening of conditions are to be captured as an adverse event with appropriate source documentation. An improvement in a condition may not have physician diagnosis or source documents to support improvement; subject self-reported improvement in a condition does not require medical documentation to support the improvement.
- Assess for protocol deviations
- For subjects who consented to the Optional Stool Sample collection, remind the subject to collect and ship a stool sample to Rebiotix

6.11. Telephone Assessments (Weeks 2, 3 and 6)

Qualified and trained site staff, as recorded on the Delegation of Authority Log, make the phone calls and may follow the script provided. All data collected are to be recorded and reported as required in Section 6.15. These phone calls must occur within the window specified in Table 6-1; phone calls out of window or missed phone calls are to be reported as protocol deviations.

The following study activities/data will be collected at the telephone assessment calls:

- Assess recurrence of CDI
- Adverse event collection, including new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders
- Changes to concomitant medications since the last visit
- Assess for protocol deviations

6.12. Telephone Assessments (3- and 6- Months)

Qualified and trained site staff, as recorded on the Delegation of Authority Log, make the phone calls and may follow the script provided. All data collected are to be recorded and reported as required in Section 6.15. These phone calls must occur within the window specified in Table 6-1; calls out of window or missed calls are to be reported as protocol deviations.

The following study activities/data will be collected at the telephone assessment calls:

- Assess recurrence of CDI
- Subject’s weight, self-reported
- Adverse event collection, including new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders

- Changes to concomitant medications since the last visit
- Cdiff32 health-related quality of life questionnaire
- Verify employment status
- Assess changes in medical history, including Charlson Comorbidity Index variables. Worsening of conditions are to be captured as an adverse event with appropriate source documentation. An improvement in a condition may not have physician diagnosis or source documents to support improvement; subject self-reported improvement in a condition does not require medical documentation to support the improvement
- Assess for protocol deviations
- For subjects who consented to the Optional Stool Sample collection, remind the subject to collect and ship a stool sample to Rebiotix

The last phone call occurs 6 months after the date of the last administration of IP whether it was blinded or unblinded.

6.13. Unscheduled Possible Recurrence Visit

If CDI recurrence is suspected any time within 8 weeks of the last study enema due to documentation of three or more unformed/loose (i.e. Bristol Stool Scale type 6-7) stools within 24 or fewer consecutive hours for at least two consecutive days, possible treatment failure must be assessed. An in-office visit is required and the subject must provide a fresh stool sample to test for the presence of *C. difficile* toxin as defined by the protocol.

The following study activities/data will be collected at the Unscheduled Possible Recurrence visit:

- Collect fresh stool sample to send to the central laboratory for analysis
- Assess recurrence of CDI
- Vital signs: temperature, pulse, blood pressure, respiration
- Adverse event collection, including the new onsets of obesity, metabolic syndrome, pre-diabetes, diabetes and/or autoimmune disorders
- Changes to concomitant medications since last visit
- Cdiff32 health-related quality of life questionnaire
- Assess changes in medical history, including Charlson Comorbidity Index variables. Worsening of conditions are to be captured as an adverse event with appropriate source documentation. An improvement in a condition may not have physician diagnosis or source documents to support improvement; subject self-reported improvement in a condition does not require medical documentation to support the improvement.
- Assess for protocol deviations

- For subjects who consented to the Optional Stool Sample collection, remind the subject to collect and ship a stool sample to Rebiotix.

Treatment failure (CDI recurrence) is 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 using the study required *C. difficile* testing algorithm.

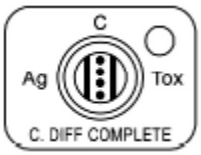
To ensure consistency across clinical sites for the determination of study failure, the central laboratory will perform the required C. DIFF QUIK CHEK COMPLETE® Test (QCC Test) rapid enzyme immunoassay test for glutamate dehydrogenase (GDH) and toxins A and B.

In the case of suspected treatment failure where there is an immediate concern for subject safety, including the potential for serious adverse events, a C. DIFF QUIK CHEK COMPLETE® Test will be permitted to be conducted at the site or other laboratory known to the site **in addition to** sending a sample to the central laboratory for testing.

If the C. DIFF QUIK CHEK COMPLETE® Test is not available by the site or other laboratory, a testing algorithm that directly assesses the presence of *C. difficile* toxin for laboratory confirmation of recurrent CDI may also be used to test a sample, in addition to sending a sample to the central laboratory for testing.

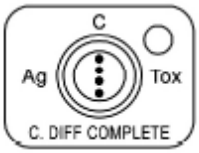
Specifically, if the antigen and toxin are both positive per the QCC Test during the presence of diarrhea then the subject is considered a treatment failure.

Treatment Failure:



However, if the subject experiences diarrhea and the antigen and toxin are both negative per the QCC Test, then the subject is not considered a treatment failure as the presence of *C. difficile* was not established. The study investigator will need to determine the appropriate treatment for the subject as to avoid the possibility of serious adverse events.

Treatment Success:



Finally, if the antigen and toxin results per the QCC Test are inconclusive (one is positive and the other is negative), the stool sample will be sent to a central lab to perform a PCR test. If the PCR test is negative, the subject will not be considered a treatment failure as the presence of C. *difficile* was not established. If the PCR test is positive, then the subject will be considered a treatment failure.

Inconclusive Test, send sample for PCR testing:

Finally, if the QCC Test provides an invalid result such that the control line is not visible, the test will need to be repeated.

Invalid result, repeat testing immediately with new QCC Test:

6.14. Unblinded RBX2660

Subjects with a documented treatment failure meeting the protocol definition in the blinded portion of the study may be scheduled for administration of an unblinded RBX2660 enema. In order to receive the unblinded RBX2660 enema, a subject must have documentation of the following:

- Meeting all treatment failure criteria as defined by the protocol
- Compliance to the washout period (discontinuation of antibiotics for 24-72 hours prior to administration visit) is confirmed
- Negative urine-dipstick pregnancy test for subject of childbearing potential to confirm that they are not pregnant on the date of administration
- Unblinded enema administration is to occur within 21 calendar days of failure determination

While subjects may choose to receive and understand they are receiving an unblinded RBX2660 enema; neither they nor the study site will be unblinded to their original treatment.

If antibiotics are given to control symptoms, a 24-72hr washout period prior to administration of an unblinded RBX2660 enema is required, however the unblinded enema must still be administered within 21 calendar days of failure determination.

If a subject receives an unblinded RBX2660 enema, the follow-up requirements will restart from the day of administration of the unblinded RBX2660 enema according to the same schedule as required for the blinded portion of the study. This results in completion of a new subject diary from the day of unblinded RBX2660 enema administration until the day prior to the 1-week visit; in-office visits at 1-week (see Section 6.8), 4- week (see Section 6.9) and 8-week (see Section 6.10) as well as telephone calls at 2, 3 and 6 weeks (see Section 6.11) and at 3 and 6 months (see Section 6.12) after the unblinded RBX2660 treatment.

The study will be considered complete when all subjects have reached their 6-month follow-up after the last study enema received, including unblinded enemas, or have exited, whichever is earlier.

6.15. Study Exit

A Study Exit eCRF will be completed for each subject who is randomized. Data to be collected at this visit includes exit date and reason for study exit. This visit may occur in conjunction with the 6-month Follow-Up visit for subjects who complete the study and do not have ongoing adverse events.

The following information will be collected on the Study Exit eCRF:

- Exit date
- Reason for study exit
    - Completed Study
    - Screen Failure
    - Withdrawal by subject
    - Study Terminated by Sponsor
    - Investigator withdrawal
    - Adverse Event
    - Death
    - Lost to Follow-Up
    - Other: (specify)

Additional data will be collected when the following occur:

- Medication changes
- Adverse Events

6.16. Subject Withdrawal or Termination

A subject's study participation is considered complete once the 6-month telephone call is conducted after starting the last course of study drug or the subject exits the study, whichever comes first. A subject may withdraw at any time for any reason or be withdrawn from the study prematurely for the following reasons:

- Withdrawal of consent by subject
- Lost to follow-up
- Failure to comply to study requirements
- Termination of study by the sponsor
- Death
- Other (to be specified).

The reason for withdrawal is recorded on the Study Exit eCRF. In the event that a subject requests to withdraw from the study, every attempt should be made to have the subject return for an early withdrawal visit and to complete the required visit questionnaires prior to withdrawal.

For a subject who is suspected of being lost-to-follow-up, a minimum of three attempts must be made to contact subjects using two different contact methods (e.g., telephone, email, text, and letter); one attempt must be a registered postal letter or traceable courier notice (e.g., FedEx Express) to the subject's last known address. The contact attempts and methods are to be recorded on the Study Exit eCRF. The date the subject is regarded as lost to follow-up is the date of last actual encounter with the subject, such as the last phone call contact or visit.

Completion of a Study Exit eCRF is required for all randomized subjects when they exit the study regardless of reason, including completion of all study requirements, visits and assessments. Subjects who were randomized but were determined to be screen failures or otherwise exited prior to receiving a dose of the study drug should also be documented on a Study Exit eCRF.

7. Assessment of Safety

7.1. Adverse Event Management

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent. Subjects should be instructed to report any adverse event that they experience to the investigator. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF.

However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g. electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Recurrence of CDI is not to be reported as an AE unless hospitalization ≥ 24 hours is required to treat it. If a hospitalization of ≥ 24 hours is not required, it is to be recorded on the Follow-up eCRF and applicable CDI Form which will be reviewed as a component of the efficacy assessment. If hospitalization ≥ 24 hours is required, it is to be reported as an SAE.

Adverse events should be followed until the event resolves or the subject exits the study. Events lasting > 3 months are considered to be chronic in nature.

7.2. Definitions

- Adverse event: an adverse event (AE) is any untoward medical occurrence in a clinical investigation subject associated with the use of IP, which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP.
    - All adverse events, including observed or volunteered problems, complaints, or symptoms are to be recorded on the eCRF within 10 days of site awareness.

- Adverse reaction: All noxious and unintended responses to IP should be considered an adverse reaction. “Responses” to IP means that a causal

relationship between IP and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

- Serious adverse event (SAE): An adverse event or adverse reaction is considered serious if, in the view of either the investigator, Medical Monitor or sponsor, it results in any of the following outcomes:
  - Death
  - Life-threatening adverse event
    NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
  - Hospitalization ≥ 24 hours or prolongation of an existing hospitalization
    NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event (SAE) under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
  - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - Congenital anomaly/birth defect.
  - Important medical event
    NOTE: Important medical events that may not result in death, be life-threatening, or do require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.
- Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information.
- Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

7.3. Anticipated Adverse Events

The following is list of anticipated adverse events that may or may not be causally related to IP, the enema procedure, or CDI:

- gas (flatulence)
- belching
- abdominal distension or bloating
- increased diarrhea
- abdominal cramping or pain
- constipation
- colitis
- fever ≥ 37.8° C (100.0°F)
- fatigue
- chills
- transmission of disease from the donor to recipient
- rectal irritation or pain
- rectal bleeding
- nausea
- vomiting
- hypotension
- puncture of the intestine

7.4. Solicited Events

The following list of anticipated events are solicited from subjects via the Subject Diary:

- gas (flatulence)
- abdominal distension or bloating
- rectal irritation or pain
- chills/severe shivering
- abdominal pain or cramping
- increased diarrhea
- constipation
- rectal bleeding
- nausea
- vomiting
- fever ≥ 37.8° C (100.0°F)

Through the completion of the Subject Diary, subjects are asked specific questions regarding frequency and severity of the solicited AEs.

7.5. Preexisting Condition

A preexisting condition, including abnormal physical exam findings, is one that is present at the start of the study and is to be recorded at the time of the screening visit. A preexisting condition is only to be recorded as an adverse event if the frequency, intensity or the character of the condition worsens during study participation.

7.6. Serious Adverse Event Reporting – Procedures for Investigators

7.6.1. Initial Reports

All SAEs occurring from the time of informed consent until 6 months after administration of the last study enema of IP must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All serious adverse events that the investigator considers related to study drug occurring after 6 months after administration of the last enema of IP must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at **medpace-safetynotification@medpace.com** or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:
Medpace Clinical Safety

Medpace SAE hotline – USA:
[redacted]

7.6.2. Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. Chronic is defined as a condition lasting >3 months.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.7. Grading Event Severity

Identified, subject reported and unsolicited adverse events are to be graded, according to severity, by the site investigator. For this classification of events, severity is not the same as seriousness, which is defined in Section 7.1. Severity is an indication of the *intensity* or a specific event (e.g., mild, moderate or severe). Classification of an event as serious relates to an event's outcome or intervention criteria and is usually associated with events that pose a threat to a subject's life or functioning. An event can be severe but not serious, such as a migraine.

Using the definitions in Table 7-1, the site investigator will categorize the severity of a solicited or unsolicited event on the AE eCRF. If a particular event is not listed on this table, the NIH/NCI Common Terminology Criteria for Adverse Events found at online at the following address may be utilized.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Table 7-1: Severity Grading Table*

Parameter	Grade1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially Life-threatening
Flatulence (gas)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	NA	NA
Belching (burping)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	NA	NA
Abdominal distension or bloating	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Increased diarrhea	Increase of ≤ 3 stools over baseline per 24-hour period	Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea if not present at baseline OR increase of ≥ 7 stools over baseline per 24-hour	Life-threatening consequences, e.g., hypotensive shock

Parameter	Grade1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially Life-threatening
			period OR IV fluid replacement indicated if not indicated at baseline	
Abdominal cramping/pain	Discomfort/pain causing no or minimal interference with usual social and functional activities	Discomfort/pain causing greater than minimal interference with usual social and functional activities	Discomfort/pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care OR inpatient hospitalization ≥ 24 hours
Constipation	Occasional or intermittent symptoms, occasional use of stool softeners, laxatives, dietary modifications or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms causing inability to perform usual social and/or functional activities	Life-threatening consequences, e.g., obstruction, toxic megacolon
Colitis	No symptoms, regardless of pathologic or radiographic evidence of inflammation	Abdominal pain, mucus or blood in the stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences, e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon
Fever	37.8 – 38.6°C (100.0 – 101.5° F)	38.7 – 39.3°C (101.6 – 102.8° F)	39.4 – 40.5°C (102.9 – 104.9° F)	> 40.5°C (104.9° F)
Fatigue/malaise	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Rectal discomfort or irritation	No symptoms or symptoms not	Symptomatic with medical intervention	Symptoms causing inability to perform usual social and	NA

Parameter	Grade1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially Life-threatening
	requiring medical intervention	(topical medications / treatments) indicated	functional activities or requiring medical intervention other than topical medications / treatments	
Rectal bleeding	Mild or intermittent without transfusion	Persistent without transfusion	Requires transfusion	Life-threatening consequences
Nausea	Transient (≤ 24 hours) or intermittent nausea with nor or minimal interference with oral intake	Persistent nausea resulting in decreased intake for 24-48 hours	Persistent nausea resulting in decreased intake > 48 hours OR aggressive rehydration indicated, e.g., IV fluids	Life-threatening consequence, e.g., hypotensive shock
Vomiting	Transient (≤ 24 hours) or intermittent vomiting with nor or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated, e.g., IV fluids	Life-threatening consequence, e.g., hypotensive shock
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Adverse event not identified elsewhere in this table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment,

Parameter	Grade1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially Life-threatening
				persistent disability, or death

*****Adapted from *Division of AIDS Table for Grading of Severity of Adult and Pediatric Adverse Events* and *Addendum 3: Rectal Grading Table for Use in Microbicide Studies; May 2012.*

7.8. Causality

For all adverse events, the investigator must pursue and obtain adequate information to determine the outcome of the adverse event and to assess whether the AE meets the criteria for classification as an SAE, serious suspected adverse reaction, suspected adverse reaction, unexpected adverse event, or unexpected suspected adverse reaction. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. For adverse events with a causal relationship to the IP or the enema procedure, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

The Investigator will make a causality assessment for all AEs and decide whether there is a reasonable possibility that the AE may have been caused by the study product or procedure, including an assessment of biologic plausibility, presence or absence of alternative causal explanations (such as continuation or exacerbation of the subject's recurrent CDI symptoms), and temporal relationship to product administration and/or the procedure. Relatedness to RBX2660 or the enema procedure is defined as:

Unrelated: The event is due to an underlying or concurrent illness or effect of concomitant therapy and is not related to the study product or procedure (*e.g.*, has no temporal relationship to study product or procedure, or has a much more likely alternative etiology)

Possible: There is some temporal relationship between the event and the administration of the study product or procedure, though the event could also be explained by the subject's medical condition or other therapies.

Probable: The temporal relationship between the event and administration of the study product or procedure is suggestive, and the event is unlikely to be explained by the subjects' medical condition or other therapies alone.

Definite: The event follows a reasonable temporal sequence from administration of the study product or procedure, follows a known or suspected response pattern to the study product and/or procedure, improves upon stopping the study product, and reappears upon repeated exposure, if that occurs.

If an investigator is unsure about whether to report a finding as an adverse event, s/he is encouraged to enter the finding as an AE into the study database.

7.9. Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study after IP administration, the investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the investigator for completion.

The subject or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

7.10. Medical Monitor

An independent Medical Monitor reviews all serious adverse events and other events reported by the site as related to the investigational product or enema procedure to provide an objective, qualified judgment of the events. The Medical Monitor is a physician not participating as an investigator in this study. The Medical Monitor has the responsibility to review and evaluate the information relevant to product safety throughout the development and implementation of the protocol. The Medical Monitor will remain blinded throughout the study. The Medical Monitor performs the following functions:

- Reviews SAEs and other adverse events as requested;
- Reviews the study protocol and Investigator's Brochure for adequacy of safety oversight;
- Confers with site investigators, DSMB and the Rebiotix Clinical Department as applicable regarding potential safety concerns;
- Provides medical surveillance and provides appropriate recommendations for the conduct of the study as needed.

Details of the Medical monitor activities and expectations will be documented in a Safety Management Plan.

7.11. Data and Safety Monitoring Board (DSMB)

The DSMB consists of three physicians specializing in infectious diseases or gastroenterology who have experience managing subjects with recurrent CDI and are not investigators in the study. A biostatistician who is not involved with study design or analyses may assist the DSMB. The DSMB will operate in accordance with applicable sections of the FDA Guidance for Clinical Trial Sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees.*

Details of the DSMB logistics, activity and responsibilities will be included in a DSMB charter. General responsibilities include oversight of subject safety through data review and assessment of trends. This includes the ability to stop the study based on pre-defined stopping rules. Additionally, the DSMB will provide an independent review of the efficacy data to ensure the benefits of providing this treatment to subjects outweighs the risks.

7.12. Study Stopping Rules for Safety

Medpace Safety personnel or designee will review all adverse events reported during the study to observe for trends and unanticipated events, either in severity, seriousness or incidence, and to assess if a study stopping rule may be triggered. Adverse event review includes the event description, onset date in relation to the treatment date, and the investigator's determination of causal relatedness to IP, the enema procedure, and pre-existing condition, as well as rating the event's severity and seriousness. Additionally, the Medical Monitor assessment of seriousness and causality will be provided and reviewed as it may be different from the site investigator report of the event. If necessary, the DSMB may be unblinded to adjudicate specific adverse events as per the study stopping rules, below. Anticipated AEs may trigger the study stopping rules.

The DSMB will determine whether enrollment should be paused, the study terminated, or other actions taken based on their assessment that:

a) There is probable cause that IP or enema procedure (e.g., due to transfer from an RBX2660 donor) contributed to a pathogenic intestinal infection in the stool of any subject, or

b) Any series of events of major significance such as death or other serious outcome for which a causal connection with the IP is plausible represents an excess of the important adverse event(s) in one of the study arms.

To support the DSMB assessment, the Rebiotix Operations Department may be asked to review the donor history and batch processing/release records for the product unit(s) administered in these cases, and forward its report to the DSMB Chair for review. The DSMB Chair will review the Operations Department report and may be unblinded to the

randomization assignment. If probable cause is suspected, the DSMB Chair will convene the entire DSMB for event review.

Upon the DSMB's determination of action, the Chair will notify the Rebiotix Clinical Department, who will notify the study sites.

If enrollment is stopped, Rebiotix and the study sites will assess for the occurrence of similar events, and evaluate IP and study records for possible root cause(s). Enrollment may be re-started upon further review and approval from the DSMB. As appropriate, the DSMB may recommend study termination or measures short of termination with the objective of reducing the risk of adverse events.

7.13. Sponsor Reporting of Adverse Events

The sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA & Health Canada, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional eight days.

All other suspected unexpected serious adverse reactions will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

The sponsor will also inform all investigators as required.

7.13.1. Timeline for Reporting Requirements

The following describes the expedited safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days of event discovery by Rebiotix**
  Rebiotix will notify FDA and Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than seven calendar days after the sponsor's initial receipt of the information.

- **Within 15 calendar days of event discovery by Rebiotix**
  The AE must meet all three of these criteria for expedited reporting.
  Any study event that is:
  - suspected adverse reaction
  - serious
  - unexpected

7.13.2. Additional Reporting Requirements

The sponsor will identify in IND safety reports all previous reports concerning similar adverse events and analyze the significance of the current event in light of the previous reports.

7.13.3. Reporting AEs to FDA and Health Canada

Rebiotix will report adverse events to FDA and Health Canada as required by applicable regulations. All adverse events will be reported in the annual and final clinical study reports.

8. Sample Size and Statistical Considerations

This study has a Statistical Analysis Plan which contains complete details of the statistical methodology and analyses that will be employed for this study.

8.1. Assessment of Efficacy

The primary efficacy parameter is treatment success, defined as the absence of CDI diarrhea through 8 weeks after completing a study treatment. Efficacy assessments will occur at the 1-, 4- and 8-week office visits.

Recurrence of CDI after 8 weeks from completion of the assigned study treatment is considered a new *C. difficile* infection, as defined by the Centers for Disease Control (CDC website http://www.cdc.gov/hai/eip/cdiff_techinfo.html; published August 30, 2012; accessed October 02, 2016).

Primary Efficacy Endpoint: Recurrence of CDI within 8 weeks of blinded treatment.

The primary efficacy analysis will be performed on all pre-defined analysis populations comparing the RBX2660 arm to the Placebo arm, Intent-to-Treat (ITT), modified Intent-to-Treat (mITT) and Per-Protocol (PP). However, the determination of meeting the pre-defined primary efficacy endpoint will utilize the mITT population results. The primary analysis of the study will be a Bayesian hierarchical model, which formally incorporates data from a previous randomized Phase 2b study (Protocol 2014-01) of RBX2660. This analysis will demonstrate the efficacy of RBX2660 by showing a sufficiently high posterior probability that the rate of success in the treatment group is superior to the rate of success in the control group. Secondary efficacy endpoints will also be completed on all analysis populations. Finally, all safety analyses will be performed on the Safety

population (SP) which includes all subjects in whom a blinded enema was at least opened and attempted.

A primary efficacy and safety analysis for primary efficacy and safety will be conducted when 100% of the applicable subjects in each group have completed their 8-week follow-up assessment after receiving the blinded treatment. Safety analysis will be completed for safety endpoints defined at or prior to 8 weeks following blinded treatment along with any longer term safety data available at the time of analysis. The analyses will be submitted to FDA for review. One or more interim analyses will be conducted to evaluate the primary efficacy endpoint for possible early study stopping for success or futility. The first interim analysis will occur after a minimum of 160 subjects have been treated and evaluated for efficacy. A second interim analysis could occur when 220 subjects have been treated and evaluated for efficacy if success is not achieved at the first interim analysis. The details of the planned interim analyses are included in the statistical analysis plan.

Final long-term safety results as well as unblinded RBX2660 efficacy data will be analyzed and reported in a final report after the last subject has completed the 6-month follow-up visit for their study treatment. This includes 6-month follow-up after an unblinded RBX2660 study treatment. At that time the study will be considered complete.

To demonstrate a 69% success with one dose of the RBX2660 treatment group vs. 47% success in the Placebo control group in a 2:1 randomization ratio, 240 subjects are required (power ≥90% with a nominal 2.5% type I error rate). Up to an additional 30 subjects will be enrolled to allow for a 10% loss-to-follow up rate, for a total of up to 270 subjects. Considering the 2:1 randomization, this results in approximately 180 subjects in the RBX2660 arm and 90 subjects in the Placebo arm. Potential subjects who have signed consent but do not meet all inclusion and/or exclusion criteria will be considered screen failures. Randomized subjects who withdraw for any reason prior to administration of the blinded enema will be replaced without counting toward the sample size cap which may result in more than 270 subjects being randomized, however no more than 270 subjects will be treated with a blinded enema. Replacement subjects will also be randomized to ensure proper blinding.

Subjects who are exited prior to randomization or randomized but exited prior to treatment may be re-enrolled and thus randomized under different subject identification numbers (re-randomized). If this occurs, they will be included in the analysis using their second randomization assignment and subsequent assessments only and will only be counted once towards the total randomized.

9. Study Administration

9.1. Institutional Review Board / Research Ethics Board Approval

The protocol, Informed Consent Form/HIPAA Form must be reviewed and approved by the respective IRB/REB and Rebiotix before subject recruitment and enrollment begins.

Prior to subject enrollment, a signed copy of the IRB/REB approval letter addressed to the investigator and a full copy of the IRB/REB-approved Informed Consent Form/HIPAA Form must be submitted to Rebiotix, certifying trial approval.

Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB/REC and forwarding copies of the approval letters to Rebiotix. The approval letters are to be kept in the Trial Master File (TMF) designated for this study.

US Sites

Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB and forwarding copies of the approval letters to Rebiotix. The approval letters are to be kept in the Trial Master File (TMF) designated for this study.

The investigator will notify the Rebiotix study manager within five (5) business days of withdrawal of IRB approval.

Institutional Review Boards will operate in accordance to 21 CFR 56 and their own standard operating procedures.

Canadian Sites

Prior to subject enrollment, a signed copy of the REB approval letter addressed to the investigator, a full copy of the REB-approved Informed Consent Form, and completed Research Ethics Board Attestation must be submitted to Mapi Group, the Agent for Rebiotix in Canada, and to Rebiotix. Investigators are responsible for submitting and obtaining initial approval and continuing approval from the REB and forwarding copies of the approval letters to Mapi Group and Rebiotix. The approval letters are to be kept in the Trial Master File (TMF) designated for this study.

The investigator will notify Mapi Group and Rebiotix within five (5) business days of withdrawal of REB approval.

Research Ethics Boards will operate in compliance with Health Canada regulations and their own standard operating procedures.

9.2. Form 1572 and Financial Disclosure

The principal investigator at each site (US and Canada) will complete and return a study-specific Form 1572 to the sponsor before beginning the study, as required by

federal regulations. In the event of a change in study personnel, the site will complete and submit a new Form 1572 to Rebiotix within 60 days of the change. The investigator agrees to be responsible for conducting the investigational study in accordance with the protocol, applicable FDA regulations including reporting and record-keeping requirements, GCPs, local IRB/REB requirements, and controlling dispensation and administration of RBX2660 and placebo. In addition, the investigator is responsible for ensuring that informed consent is obtained from each subject prior to participating in the study, as well as protecting the rights, safety and welfare of participating subjects.

All investigators will be required to sign a Financial Disclosure form, which certifies the investigator's and his/her immediate family's financial interest in Rebiotix and study outcomes. Investigators must inform Rebiotix of any changes to the information documented on the Financial Disclosure form throughout the course of the study and for a period of one year following completion of the study.

9.2.1. Canadian Sites: Qualified Investigator Undertaking Form

The principal investigator(s) at each Canada site will complete and return the Qualified Investigator Undertaking Form to Mapi Group before beginning the study, as required Health Canada. The investigator agrees to be responsible for conducting the investigational study in accordance with the protocol, applicable Health Canada regulations including reporting and record-keeping requirements, GCPs, local REB requirements, and controlling dispensation and administration of RBX2660 and placebo. In addition, the investigator is responsible for ensuring that informed consent is obtained from each subject prior to participating in the study, as well as protecting the rights, safety and welfare of participating subjects.

9.3. Subject Confidentiality

All information and data sent to Rebiotix, and/or its designees concerning subjects and their participation in this study are considered confidential by Rebiotix and its designees (subcontractors or contract research organization). Only authorized Rebiotix personnel or approved contracted agents of Rebiotix have access to some portions of these confidential files and will act in accordance with applicable regulations. The IRBs, REBs, FDA and Health Canada also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of the study will eliminate identifiable references to the subjects as much as possible.

9.4. Study Oversight

Clinical personnel at Rebiotix have knowledge of Good Clinical Practices, pertinent laws and regulations, and documented training in standard operating procedures

pertaining to study management and monitoring and will provide study oversight. Rebiotix can be contacted at;

Rebiotix Inc
2660 Patton Road
Roseville, MN 55113
Phone: 651-705-8770

9.5. Study Site Qualification

Investigational center qualification visits or phone calls will be conducted by Rebiotix prior to acceptance of a site into this study. The site qualification visit or phone call will be scheduled to include time with the study investigator, co-investigators, study coordinator and other study personnel. Areas of discussion include a review of personnel training, investigator qualifications, IP Administrator qualifications, adequacy of potential subject pool, FDA- or Health Canada-regulated study experience, this study's specific requirements for procedures and equipment, and a review of staffing availability and appropriateness. A written report of the qualification call/visit will be generated by the sponsor representative who conducts the call/visit. Resolution of any concerns and/or completion of any appropriate study activities identified during the qualification process will be documented and submitted to the study investigator.

9.6. Investigator / Site Training

The sponsor will provide appropriate training to each investigator, and IP Administrator, study coordinator(s), and other site personnel who will be involved in the study prior to study initiation. Training will address topics including ordering, secure storage and administration procedures, Subject Diary instructions, follow-up visit and phone call requirements, adverse event reporting, and accurate data collection. Training will include a detailed review of the protocol, eCRF completion, study-specific procedures, monitoring logistics, and regulatory requirements.

9.7. Data Management

Electronic case report forms specifically created for this study will be used to collect study data. The study investigator or his/her designee at each site is responsible for recording all data onto the study eCRFs as noted on the Delegation of Authority Log. The investigator must review and electronically sign all eCRFs as instructed; these responsibilities cannot be delegated to another person. Ongoing data review will be performed according to the study-specific Data Management Plan.

9.8. Monitoring

This study is monitored according to the study-specific Clinical Monitoring Plan. The investigator must allocate adequate time for such monitoring activities. The investigator must also ensure that the monitor or other compliance or quality assurance reviewers are given access to all study-related documents and study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. Study monitors and their activities are managed by the study manager or qualified designee; see Section 9.4. Study monitors will follow requirements as documented in monitoring procedures and the study-specific Monitoring Plan.

9.9. Direct Access to Source Data/Documents

The investigator is expected to facilitate study-related monitoring, audits, and inspections by the IRB/REB, sponsor and sponsor representatives, FDA, and Health Canada of all study-related documents including direct access to original source documents such as medical records and lab results, regulatory documents, study data, etc. The investigator will ensure access for the inspection of applicable study-related facilities, e.g., pharmacy, laboratory, exam rooms, etc.

Participation as a study investigator and study site in this study implies acceptance and support of inspections by FDA, Health Canada and/or Rebiotix or its designee(s).

9.10. Investigator Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the protocol, applicable FDA or Health Canada regulations for investigational new drugs, HIPAA (US only), GCPs and local IRB/REB requirements. Specific responsibilities are listed in this protocol.

Site study records and reports are kept in the Investigator Study File (ISF). Records and reports will remain on file for a minimum of two years (US sites) or 25 years (Canada sites) after either the completion/termination of this study or the date RBX2660 receives market approval for the indication being studied, whichever is later. The study investigator must contact Rebiotix before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. Rebiotix must be contacted if the study investigator plans to leave the site to ensure that arrangements for a new investigator or records transfer are made prior to investigator departure.

The investigator will promptly report to the IRB/REB all changes in the research activity and all unanticipated problems involving risk to subjects or others, and that he/she will not make any changes in the research without prior written approval from the sponsor and IRB. The investigator will adhere to all IRB/REB requirements imposed on this study.

9.11. Investigator Records

Records to be maintained by the investigator in the ISF include:

- Protocol and all amendments
- Signed Form 1572
- Signed Financial Disclosure Form(s)
- IRB approval letter including consent and HIPAA (US sites)
- IRB Membership list or Letter of Assurance (US sites)
- Signed Qualified Investigator Undertaking Form (Canadian sites)
- REB approval letter including the Informed Consent Form (Canadian sites)
- REB Attestation (Canadian sites)
- REB membership list or Letter of Assurance (Canadian sites)
- All correspondence relating to the study between the site/investigator/coordinator and the IRB/REB, sponsor, CRO, and Mapi Group, as applicable.
- CVs and professional licenses for all investigators and key study personnel
- Delegation of Authority Log/Site Signature Log
- Product Accountability Log (or electronic pharmacy equivalent)
- Study Visitor Sign-in Log
- Subject Screening/Enrollment log
- Reports submitted to Rebiotix and/or the IRB/REB

The following records must be maintained for each subject enrolled in the study:

- Signed Informed Consent/local privacy authorization as applicable
- Compete, accurate and current eCRFs
- Adverse event reports and any supporting documentation
- Protocol deviations
- Complete medical records, including procedure reports, lab reports, professional notes, etc.
- Records pertain to subject death during the investigation (including death records, death certificate, and autopsy report if performed).

Rebiotix reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study at any time.

9.12. Investigator Reports

Study investigators are required to submit the following reports at the times specified below:

- Adverse Events: report all AEs to the sponsor via eCRF within **ten (10) business days** of discovery.
- Serious Adverse Events and suspected adverse reactions: report to the sponsor via eCRF within 24 hours of discovery.

- Progress and Final reports: the investigator will submit annual study progress reports and a final study report when the study is terminated at the site to Rebiotix and the IRB/REB.

9.13. Study Site Termination

Rebiotix reserves the right to terminate a study site for any of the following reasons:

- Failure to properly secure subject informed consent or HIPAA Authorization prior to study enrollment or the conduct of any study-required procedures/assessments.
- Failure to report adverse events as required in Section 6.15.
- Protocol deviations.
- Repeated failure to appropriately and accurately complete eCRFs.
- Failure to enroll an adequate number of subjects.
- Loss of or unaccounted for product inventory.
- Administrative decision by the company.

9.14. Protocol Amendments

Neither Rebiotix, its designees (subcontractors or contract research organization) nor the study investigators may modify this protocol without obtaining written approval of the FDA, Health Canada, and/or IRB/REBs as required. No modifications may be made without prior written approval of Rebiotix.

9.15. Protocol Deviations

Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to Rebiotix within 48 hours of occurrence and to the respective IRB/REB as soon as possible, but in no event no later than five calendar days after the emergency occurs. Protocol deviations of any kind must be avoided as much as possible and those that do occur will be tracked in the clinical study database.

9.16. Inspection/Auditing

The investigator will permit study-related inspection/auditing by the IRB/REC, sponsor, FDA and/or Health Canada to ensure compliance to applicable regulations, GCPs, and the study protocol.

10.Publication Plan

Rebiotix has unrestricted publication rights of the study data. The study site and the investigator are not entitled to make any publication or release any information pertaining to this study or its results without the prior written consent of Rebiotix. The decision as to whether to provide such consent shall be made once Rebiotix has had an opportunity to review the contents of any proposed publication or release regarding the investigation and, if necessary, to delay any publication or release in order to protect the confidential or proprietary nature of any information contained therein. Merely the fact that the proposed publication or release contains statements unfavorable to Rebiotix shall not constitute grounds for prohibiting publication; however, all unfavorable statements must be based on adequate scientific evidence. Rebiotix reserves the right to give the data to third parties for publication or release and to name co-authors. Rebiotix retains the right to review and edit all proposed manuscripts, abstracts, publications, and presentations based upon this study or its results prior to submission to any organization, business, agency, person, publisher, society, or other entity.

11.References

Centers for Disease Control. http://www.cdc.gov/hai/eip/cdiff_techinfo.html; published August 30, 2012; accessed October 02, 2016.

Bakken JS. Feces transplantation for recurrent *Clostridium difficile* infection: US experience and recommendations. *Microb Ecol Health Dis*. 2015;26:27657. doi: 10.3402/mehd.v26.27657.

Department of Health and Human Services. http://www.hhs.gov/ash/initiatives/mcc; accessed October 02, 2016.

Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958;44:854 – 9.

Miller MA, Louie T, Mullane K, Weiss K, Lentnek A, Golan Y, et al. Derivation and validation of a simple clinical bedside score (ATLAS) for Clostridium difficile infection which predicts response to therapy. BMC Infect Dis. 2013;13:148.