CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 13-0045
Study Title:
Phase 1/2 Placebo Controlled, Partially-Blinded Clinical Trial to Assess the Safety and Efficacy of Microbial Restoration by Enema with Banked and Thawed Processed Stool in Individuals with One or More Recurrences of *Clostridium difficile* Associated Disease (CDAD)

NCT03548051

Version 1.0

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STUDY TITLE

Protocol Number Code:	**DMID Protocol: 13-0045**
Development Phase:	Phase ½
Products:	Fecal Microbiota Preparation-cryopreserved filtered human feces
Form/Route:	Fecal microbial transplant
Indication Studied:	Clostridium *difficile* Associated Disease
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	September 6, 2018
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	July 20th, 2020
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Classification
C	Celsius
CDAD	Clostridium *difficile* Associated Disease
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ER	Emergency Room
ESBL	Extended Spectrum Beta-Lactamase
F	Fahrenheit
FMPE	Fecal Microbiota Preparation Enema
FMPP	Fecal Microbiota Preparation Placebo
FMT	Fecal Microbiota Transplant
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonisation
ISM	Independent Safety Monitor
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
N	Number (typically refers to subjects)
NIH	National Institutes of Health
NOCMC	New Onset Chronic Medical Condition
PCR	Polymerase Chain Reaction
PI	Principal Investigator

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List of Abbreviations *(continued)*

PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
ULN	Upper Limit of Normal
VRE	Vancomycin-Resistant Enterococcus
WBC	White Blood Cell
WHO	World Health Organization

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1. PREFACE

The Statistical Analysis Plan (SAP) for "Phase 1/2 Placebo Controlled, Partially-Blinded Clinical Trial to Assess the Safety and Efficacy of Microbial Restoration by Enema with Banked and Thawed Processed Stool in Individuals with One or More Recurrences of *Clostridium difficile* Associated Disease (CDAD)" (DMID Protocol 13-0045) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses to be performed by the Statistical and Data Coordinating Center (SDCC) and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the analyses. It does not describe the analysis for the exploratory outcome measure of gut microbial diversity which will be described in a separate SAP. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this analysis plan will be described and justified in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

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2. INTRODUCTION

Clostridium difficile is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus acquired through ingestion of spores after disruption of normal gut flora typically from exposure to antimicrobials. *Clostridium difficile* associated disease (CDAD) can be mild but can progress to a severe disease with pseudomembranous colitis and toxic megacolon requiring colectomy [4] and even resulting in death.

In recent years, there has been a change in the epidemiology of CDAD. Currently, CDAD is the leading nosocomial infection in the United States [19]. The Centers for Disease Control and Prevention estimate that there are 453,000 cases annually in the US resulting in 29,000 deaths [16]. Also, CDAD is increasingly reported in populations thought previously to be at low risk for infection such as young, healthy persons living in the community and peripartum women [5 , 3 , 24]. The attributable mortality increased from 5.7 to 23.7 deaths per 1 million persons from 1999 to 2004 [23]. CDAD results in $4.8 billion in excess costs in US acute care facilities annually [7]; each episode costing $6,774-$10,212 for CDAD requiring admission, $2,992-$29,000 for hospital-acquired CDAD [9]. The increase in severity and incidence of CDAD is due mostly to the emergence of an epidemic strain designated as North American PFGE pulse-field type 1 [NAP1]/restriction endonuclease analysis type BI/PCR ribotype 027 or NAP1/BI/027 [18]. The epidemic strain is characterized by fluoroquinolone resistance and higher levels of toxin production [26] than conventional strains, causing a 3-fold higher mortality rate than matched controls infected with less virulent strains [22].

Permanent cure of CDAD requires some combination of immunity and restoration of normal colonic microflora, needed to eliminate or suppress CDAD. Antibiotic treatment of C. difficile helps to ameliorate symptoms while allowing gradual restoration of the normal gut flora but may in itself further alter the colonic microbiota. Most initial episodes respond to either fidaxomicin [17], vancomycin [30], or metronidazole [27, 25] courses. However, CDAD recurrence is common [12] with 15%–30% of patients experiencing a relapse in symptoms after effective initial therapy, usually in the first few weeks after treatment is discontinued.

Fecal microbiota transplantation (FMT), the reconstitution of normal flora by a “stool transplant” from a healthy individual to a *C. difficile*-infected recipient, was first described in 1958 [8]. The procedure is quite effective and can be done through different routes: enema (the most common technique used until 1989) nasogastric or nasojejunal tube, upper tract endoscopy since 1991 and colonoscopy since 1998 [20]. In the first randomized clinical trial, there was resolution of recurrent CDAD in 81% of patients after one infusion with donor feces versus 31% of patients treated with vancomycin alone and 23% of patients receiving vancomycin and bowel lavage [28]. Four out of five other randomized clinical trials showed 80-93% efficacy for FMT against recurrent CDAD [2, 29, 15, 13]. Only one clinical trial [10] was terminated at interim analysis for lack of efficacy; however the study offered a single FMT administration with longer timeframe for FMT preparation, randomized patients with active CDAD, did not use a bowel preparation, and 37.5% of patients were not able to retain at least 80% of the enema therefore receiving less than 40 grams of transplanted stools. Another larger trial using the enema route for FMT administration enrolled 232 patients who received 1 to 5 FMT either from frozen or fresh stools with an efficacy of more than 83% per protocol for both arms. However, the study had a short follow up period [15]. A recent systemic review of 536 patients treated with FMT showed 87% resolution of diarrhea. Diarrhea resolution rates varies according to the site of infusion: 81% in the stomach; 86% in the duodenum/jejunum; 93% in the cecum/ascending colon; and 84% in the distal colon [2] and amount of fecal material transplanted.

Further research is needed to explore the optimal preparation, route, timing, and number of administrations as well as the long-term safety of FMT. The current study will use standardized frozen fecal samples

transplanted be enema route after bowel preparation, allowing multiple FMT administrations and looking both at the efficacy and long-term safety of FMT in patients with recurrent CDAD.

2.1. Purpose of the Analyses

This is a phase I/II study to investigate the safety and efficacy of FMT delivered via enema after thawing of frozen, banked fecal microbiota to patients with recurrent CDAD.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives:

- To evaluate the safety of FMT(s) delivered by enema vs. placebo delivered by enema.
- To determine efficacy of FMT delivered by enema vs. placebo delivered by enema.

3.1.2. Secondary Objectives:

- To evaluate the sustained clinical response rate of FMTs delivered by enema vs. placebo delivered by enema.
- To evaluate the rate of recurrent CDAD.
- To evaluate the time to recurrent CDAD.

3.1.3. Exploratory Objectives:

- To evaluate changes in the fecal microbiome as a function of clinical response and CDAD recurrence.
- To determine the rate of development of metabolic syndrome.

3.2. Endpoints

3.2.1. Primary Safety Outcome Measures:

- Number of subjects with an AE through 30 days after completing treatment for recurrent CDAD.
- Number of subjects with a SAE through 365 days after completing treatment for recurrent CDAD.
- Number of subjects with a new onset of related chronic medical condition through 365 days after completing treatment for recurrent CDAD.
- Number of subjects with newly acquired transmissible infectious diseases which are considered AESI through 365 days after completing treatment for recurrent CDAD.

3.2.2. Primary Efficacy Outcome Measure:

- Proportion of subjects with clinical response through Day 30 (±3) after randomization.

3.2.3. Secondary Efficacy Outcome Measures:

- Proportion of subjects with sustained clinical response through Day 60 (±5) after randomization.
- Sustained clinical response is defined as those subjects who responded by Day 30 with no recurrence of CDAD through 60 days after randomization.
- Number of recurrences of CDAD through Days 30 and 60 after completing treatment for recurrent CDAD.
- Time (in days) from randomization until the study day when first CDAD reoccurred (through 60 days).

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3.2.4. Exploratory Outcome Measures:

- Changes in gut microbial diversity through 365 days after completing treatment for recurrent CDAD.
- Number of subjects with abnormal clinical laboratory tests (hematology, biochemistry) through 30 days after completing treatment for recurrent CDAD.
- Number of subjects with new onset metabolic syndrome through 365 days (year 1) after completing treatment for recurrent CDAD.
- Agreement of PCR test results and toxin assay results in subjects with a clinical suspicion of CDAD

3.3. Study Definitions and Derived Variables

3.3.1. Study Definitions

1. Clinical response is defined as those subjects who have no recurrence of CDAD through Day 30 (±3) after randomization.
2. The date of "completing treatment for recurrent CDAD" is the date of the first effective enema OR if there is no effective enema then the date of last ineffective enema. An effective enema is defined as the enema that was followed by no diarrhea by Day 8 OR with diarrhea at Days 5-8 but without a positive PCR test for *Clostridium difficile*. An ineffective enema is defined as the enema followed by diarrhea at Days 5-8 but with a positive PCR test for *Clostridium difficile*.
3. CDAD is defined as bowel movements as determined by ≥3 unformed stools (soft or watery) within 24 consecutive hours with a positive PCR test for *Clostridium difficile*.
4. Recurrence is defined as the re-establishment of diarrhea (frequency of passed unformed stools >3 unformed stools within 24 consecutive hours) with positive PCR test for *C. difficile*.
5. Sustained clinical response is defined as those subjects who have initial response by Day 8 and through Day 30 after randomization with no recurrence of CDAD through 60 days after randomization.
6. An AE is defined as any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions, as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical trial, regardless of their relationship to investigational product.
7. AEs will be assessed by the clinician using a protocol defined grading system (Table 5 and Table 6). For events not included in the protocol defined grading system, the following guidelines will be used to quantify intensity.
    - Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
    - Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
    - Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
8. AE relationship to test article is assessed by the clinician using the following guidelines:

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- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event

9. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
   - Death;
   - Life-threatening adverse event*;
   - Inpatient hospitalization or prolongation of existing hospitalization;
   - Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life function, or;
   - A congenital anomaly/birth defect.

   *Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event which, had it occurred in a more severe form, might have caused death.
10. New onset of related chronic medical conditions (NOCMCs) are defined as any new ICD-10 diagnosis that is applied to the subject during the duration of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.
11. Adverse Events of Special Interest (AESI) are defined as newly acquired transmissible infectious agents or infectious diseases related to study product and the following agents: HIV type 1 and 2, Hepatitis A, B, C, Treponema pallidum, HTLV-1, -2, Cyclospora, Salmonella, Shigella, Campylobacter, E. coli 0157:H7, Shiga-toxin producing E. coli, Ova and enteric parasites including Isospora, Vancomycin-resistant Enterococcus (VRE), extended spectrum beta-lactamase (ESBL), carbapenemase producing gram-negative rods, methicillin-resistant Staphylococcus aureus (MRSA), Helicobacter pylori, Rotavirus, Adenovirus, Norovirus, Vibrio, Giardia lamblia, Cryptosporidium, and Microsporidia.
12. New onset metabolic syndrome will be defined using the following definition from the International Diabetes Federation [32]:
    - Increased waist circumference, with ethnic-specific waist circumference cut-points

    Additionally, any two of the following:
    - Triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides
    - HDL cholesterol <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or treatment for low HDL
    - Systolic blood pressure ≥130, diastolic blood pressure ≥85, or treatment for hypertension
    - Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes

3.3.2. Derived Variables

1. For safety assessments, such as clinical laboratory measurements, multiple observations within a specific visit period are accepted. In the case of multiple observations within a specific window, the assessment value that is closest to the scheduled visit window will be used in the analyses for the post-baseline records. For screening and baseline visits, the last assessment value will be used. All the recorded data will be listed. If observations have the same distance to the scheduled assessment, the latest one will be used.
2. The time in days until first CDAD recurrence through 60 days will be calculated by subtracting the date of first enema administration from the date of first positive PCR test. Those without a positive PCR test will be censored at 60 days or their last visit date, whichever occurs first.

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4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multi-center, randomized, placebo controlled, partially blinded trial comparing the safety and efficacy of fecal microbiota transplantation versus placebo both delivered by rectal enema in subjects 18 years of age or older with recurrent CDAD (i.e., ≥ 2 episodes of CDAD within the previous 6 months, including the last episode). 162 (108 in the FMT group, 54 in the placebo group) male or female subjects will be enrolled in the study. CDAD is defined as bowel movements as determined by ≥3 unformed stools (soft or watery) within 24 consecutive hours with a positive PCR test for *Clostridium difficile*. Subjects must have had treatment for most recent CDAD with at least 10 days of either metronidazole po/IV (500 mg tid), oral vancomycin (at least 125 mg qid), or oral fidaxomicin (200 mg bid) and have no diarrheal symptoms (<3 unformed stools per 24-hour period) off antibiotics during the washout period.

Once enrolled, subjects will be randomized at each site to receive either FMT by enema or placebo by enema in a 2:1 ratio. Subjects in the FMT arm will receive FMT by enema, but if CDAD develops between Days 5-8 after the enema then the subject will be classified as a treatment failure and receive 10-14 days of oral vancomycin. After a washout period of at least 2 but no more than 4 days without diarrheal symptoms (<3 unformed stools per 24 consecutive hour period) another FMT by enema will be administered. If the subject fails the second FMT by enema, then he/she will be referred for treatment from locally available options but will be followed long-term (up to 1 year) only for safety.

The subjects in the placebo arm will crossover and receive FMT by enema if CDAD is present between Days 5-8 after receiving placebo, at which time the subject is classified as a treatment failure. The subject might then receive one more FMT by enema depending on clinical response as detailed above. If the subject fails the second FMT by enema, then he/she will be referred for treatment from locally available options but will be followed long-term (up to 1 year) only for safety.

If a subject in the placebo group or in the FMT arm fails after Day 8, he/she will be referred for treatment from locally available options and will be followed long-term (up to 1 year) only for safety.

The study is described as partially blinded because by design subjects are to be blinded only to a certain point such that after the second ineffective enema the subject will become aware as to which group they were originally assigned. Moreover, all subjects following scenarios 2, 3, or 4 (Figure 1) will receive a second enema containing active FMT (FMPE) and thus will not be blinded to the nature of the second enema.

Subjects will be followed for clinical response (efficacy) and safety. The clinical response is defined as those subjects who have no recurrence of CDAD by Day 30 after randomization. Sustained clinical response is defined as those subjects who have responded by Day 30 with no recurrence of CDAD through 60 days after randomization.

AEs will be collected from enrollment through 30 days after completing treatment for recurrent CDAD. New-onset AESIs will be collected up to 365 days after completing treatment for CDAD. SAEs will be collected through the whole study period. Investigators will look for signs and symptoms of CDAD from enrollment until 60 days after treatment of recurrent CDAD. If there is no recurrence of CDAD 60 days after treatment, subjects will be contacted every 2 months by telephone calls until 365 days after treatment of recurrent CDAD.

Blood samples will be obtained for assessment of safety and for exploratory endpoints (metabolic syndrome markers & infectious agents). The blood samples will be obtained at screening, enrollment and Days 9, 30, 60,

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and 365, after completing treatment for recurrent CDAD. Leftover blood specimens from the assays will be stored and may be used for future research.

Stool samples will be obtained at screening, enrollment and Days 9, 30, 60 and 365 after completing treatment for recurrent CDAD and at the time of recurrence (for subjects who experience a recurrence). Samples will be used for *C. difficile* PCR and toxin testing (when symptoms of CDAD are present), assessment of safety (infectious agents) as well as microbiome determination and other exploratory endpoints. Leftover stool specimens will be stored and may be used for future research.

Information regarding the co-administration of any oral or parenteral antibacterials or probiotics, any acid blockers (H2 blockers and PPIs), NSAID, antineoplastic, lipid lowering agents, antihistamines or any antiperistaltics will be recorded through 365 days after completing treatment for recurrent CDAD.

The safety and efficacy of the trial will be overseen by a Data and Safety Monitoring Board (DSMB). Statistical analysis will be performed by The Emmes Company, LLC. The DSMB will monitor, review, and evaluate the results of the interim analysis and advise the sponsor regarding continuation of the trial as per the DSMB Charter.

4.2. Discussion of Study Design, Including the Choice of Control Groups

FMT, as described in Section 2, despite its efficacy has been initially slow to be widely adopted in the treatment of recurrent CDAD due to safety and acceptability concerns but also logistical challenges and lack of standardization [1].

FMT is generally well tolerated and safe with transient abdominal discomfort and bloating after the procedure. However little data on long-term safety exist; the majority of patients receiving FMT were typically being followed for more than 2 months but less than a 1 year.

Although reluctance initially present, the aesthetically unpleasing aspect of the procedure did not alter the patients' interest or willingness to try FMT [31] and currently physicians are also more willing to refer patients with recurrent CDAD for FMT evaluation [11].

Centralization of the screening and processing steps would make the treatment cheaper, safer, less variable and more convenient with a readily available pool of donors [1]. Though no head-to-head trial has compared different routes of FMT administration, transplant by lower route seems to be superior in efficacy. Colonoscopy, with its ability to deliver enough volume of FMT throughout the entire colon is appealing; however, the procedure is time consuming, resource intensive and may be unsafe in active CDAD by increasing the risk of perforation or with the risk of sedation associated with the procedure. Rectal enema on the other hand is a simple and cheap procedure not requiring an endoscopist, or anesthetist. However, since enemas only reach the splenic flexure, there may be a need for repeated instillation.

Further research is needed to explore the optimal preparation, route, timing, and number of administrations as well as the long-term safety of FMT.

The current study will use standardized frozen fecal samples transplanted by enema route after bowel preparation, allowing multiple FMT administrations and looking both at the efficacy and long-term safety of FMT in patients with recurrent CDAD.

Previous research has shown the need for additional enemas to ensure a take. The study design was chosen to allow multiple FMT administrations in a controlled manner with no more than two FMTs and only if relapse occurs in the first week since it is known that early relapse occurs in up to 50% of cases [33]. Additionally, knowing that FMT is efficacious, the choice of 2:1 (FMT:placebo) randomization as well as planning for an

interim analysis to stop for efficacy were employed in an effort to minimize the number of subjects receiving placebo.

4.3. Selection of Study Population

This study will be conducted in male and female subjects 18 years of age or older who are diagnosed with recurrent CDAD. Subjects will be recruited from within the larger health care system surrounding the clinical sites (inpatient and outpatient). Only subjects who meet all inclusion criteria and no exclusion criteria will be eligible for enrollment into this study.

4.3.1. Inclusion Criteria

1. Providing permission to access the medical record.
2. Male or non-pregnant female 18 years or older at the time of enrollment.
3. Able to provide signed and dated informed consent.
4. ≥2 episodes of CDAD in the past 6 months, including the last episode if present at screening[1].

   [1]Defined by ≥1 confirmed positive CDAD by diagnostic methods and another occurrence substantiated by medical history.
5. Completed treatment course of at least 10 days of oral vancomycin, oral/IV metronidazole, or oral fidaxomicin for the most recent episode prior to enrollment.
6. Controlled diarrheal symptoms (<3 unformed stools per 24 consecutive hour period).
7. Deemed likely to survive for 1 year after enrollment.
8. Women of childbearing potential[2] in sexual relationships with men must use an acceptable method of contraception[3] from 30 days prior to enrollment until 4 weeks after completing study treatment.

   [2]Not sterilized via tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year of the last menses if menopausal. Also includes females who are postmenopausal <1 year.
   [3] Includes, but is not limited to, barrier with additional spermicidal foam or jelly, intrauterine device, hormonal contraception (started at least 30 days prior to study enrollment), intercourse with men who underwent vasectomy.
9. Males must agree to avoid impregnation of women between Day 1 and 28 days following each administration of the study product.
10. Negative urine or serum pregnancy test within 24 hours of enrollment and randomization.
11. Is able to provide blood and fecal specimens.
12. Is able to complete a test of comprehension.

4.3.2. Exclusion Criteria

1. Previous FMT within the previous 12 months prior to study enrollment.
2. Any heart, lung, pancreas, or intestinal transplant recipient or any HIV positive transplant recipient[1].

   [1] not excluded from the trial are subjects who are kidney, liver, or liver/kidney transplant recipients AND are more than 6 months from transplantation AND have not had a rejection episode in the past 6 months AND have been stable on immunosuppressive regimen for the past 6 months (any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, will not be considered a deviation of this criterion).

3. Requiring antibiotics in the past 2 weeks prior to receiving the enema for a condition other than CDAD or scheduled to be used in the upcoming 2 weeks.
4. Unable to tolerate enema for any reason.
5. Any GI cancer in the past year or any actively treated malignancy[2],[3].

   [2]Not excluded from the trial are subjects with actively treated basal and squamous cell cancers without any systemic treatment.
   [3]Subjects with recently treated malignancy (past 2 months) should have an absolute neutrophil count ≥ 1000 /µL since treatment. Subjects with leukemia cannot be enrolled in the study.
6. Patients with a history of severe anaphylactic food allergy.
7. Patients with decompensated cirrhosis[4].

   4 Decompensated cirrhosis is defined as cirrhosis with any history of the following: variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, hepatorenal syndrome, or hepatopulmonary syndrome.
8. Untreated HIV disease[5].

   [5]If no HIV screening results are available in the medical record from within the last six months, a HIV screening test will be performed during screening.
9. Other severe immunosuppression or immunodeficiency conditions[6].

   [6] not excluded from the trial are, subjects who take daily dose of systemic corticosteroid equivalent to <20mg prednisone for any duration, or ≥20 mg prednisone for <14 days, or alternate-day corticosteroid therapy at any dose, OR methotrexate ≤0.4 mg/kg/week, OR azathioprine ≤3 mg/kg/day, OR 6-mercaptopurine ≤1.5 mg/kg/day.
10. Severe OR acute disease at the time of enrollment[7]

    [7]Temperature >100.4˚F (38.0˚C) or heart rate less than 45 bpm or greater than 130 bpm, or systolic blood pressure less than 80 mm Hg or greater than 155 mm Hg, or diastolic blood pressure greater than 100 mm Hg, or at the discretion of the investigator
11. Major surgery of the GI tract in the past 2 months.
12. Having a non tolerance[8] to or any component of vancomycin, loperamide or GoLYTELY.

    [8]tolerance is defined as the absence of immunoglobulin E-mediated allergy (e.g., urticaria, angioedema, bronchospasm, or anaphylaxis) and the absence of severe allergy (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis)
13. Active[9] inflammatory bowel disease (IBD) including ulcerative colitis, Crohn's disease, indeterminate colitis or celiac disease.

    [9] Active IBD is defined as any IBD requiring any steroid use in the past 6 months OR any increase in dose or frequency of medications in the past 6 months (any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, will not be considered a deviation of this criterion).
14. Uncontrolled irritable bowel syndrome (IBS)[10] or any active uncontrolled gastrointestinal disorders or diseases[11]

    [10] Uncontrolled IBS refers to any IBS with diarrhea on average more than once a week for the past 3 months prior to last CDAD episode.
    [11]GI obstruction, ileus, gastric retention, bowel perforation, toxic colitis or toxic megacolon, persistent infectious gastroenteritis, persistent or chronic diarrhea of unknown etiology, or refractory/severe Clostridium difficile infection (severe CDAD identified as leukocytosis with a white blood cell count greater than 15,000 cells/mL or an increase in the serum creatinine level to 1.5 times the premorbid level), chronic diarrhea of unknown cause for 6 weeks or more.
15. Unable to comply with protocol requirements.

16. Participation in any other clinical drug research trial within 30 days prior to enrollment or for the 1 year after enrollment that might interfere with the safety and efficacy assessment.
17. A condition that would jeopardize the safety or rights of the subject, would make it unlikely for the subject to complete the study, or would confound the results of the study.

4.4. Treatments

4.4.1. Treatments Administered

Fecal Microbiota Preparation Enema (FMPE)

Fecal microbial transplant (FMT) is the process by which the reconstitution of normal flora is delivered by a "stool transplant" from a healthy individual to an individual who has experienced ≥2 episodes of CDAD. The FMPE will be used for the FMT process and is described as human feces filtered to 330 microns suspended in sterile Sodium Chloride (0.9% USP), Glycerol (12.5%, USP) and deionized water.

Fecal Microbiota Preparation Placebo (FMPP)

The FMPP by enema will be Sodium Chloride (0.9%, USP), Glycerol (12.5%, USP), 8-12 drops brown food coloring (AmeriColor 204) (<1%) and deionized water.

Vancomycin

Vancomycin is a tricyclic glycopeptide antibiotic and is a product of the organism *Amycolatopsis orientalis*. The bactericidal action of vancomycin against the vegetative cells of *C. difficile* results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis.

Loperamide

Loperamide hydrochloride, 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-a,a-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use. Loperamide prolongs the transit time of the intestinal contents. It reduces daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes.

GoLYTELY

GoLYTELY oral solution is a combination of polyethylene glycol 3350, osmotic laxative, and electrolytes. It will be used for the bowel preparation and is indicated for bowel cleansing prior to colonoscopy and barium enema X-ray examination.

4.4.2. Identity of Investigational Product(s)

Fecal Microbiota Preparation

Enema (FMPE)

The FMT study product, FMPE, will be formulated as 100 grams of human feces homogenized in 250 mL of sterile Sodium Chloride (0.9%, USP), Glycerol (12.5%, USP) and deionized water. The active product will be packaged in a PET Nalgene Bottle with HDPE screw-cap.

Placebo (FMPP)

The placebo, FMPP, will be formulated at 250 mL sterile Sodium Chloride (0.9%, USP), Glycerol (12.5%, USP), brown food coloring (<1%) (AmeriColor 204 or similar), and deionized water. The placebo product will be packaged in an identical container as the active product.

Vancomycin

Vancomycin will be supplied as 125-mg capsules for oral administration.

Loperamide

Loperamide will be supplied as 2-mg capsules for oral administration.

GoLYTELY

GoLYTELY solution contains: 236 grams of polyethylene glycol (PEG) 3350, 22.74 grams sodium sulfate (anhydrous), 6.74 grams of sodium bicarbonate, 5.86 grams of sodium chloride, and 2.97 grams of potassium chloride. It will be supplied as a 4-L jug containing white powder for reconstitution with water.

All study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use."

FMPE and FMPP will be provided by OpenBiome and upon request by DMID, will be transferred to DMID-Clinical Materials Services, Fisher BioServices. Vancomycin, loperamide, GoLYTELY will be supplied by Fisher BioServices. Study product(s) will be shipped to the investigational site upon request and approval by DMID.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Randomization will be performed through the enrollment module in the electronic data capture system, maintained by the SDCC. Eligible subjects will be randomized and assigned in a 2:1 ratio to FMPE or FMPP, with stratification by site. The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the treatment groups during the study.

4.4.4. Selection of Doses in the Study

Previous studies have shown that at least 50g of human feces are needed in FMT in order to achieve efficacy. For this study, 100g of human feces was chosen as it is twice the quantity of the standard 50g formulation used by FMT practitioners with the goal of accounting for any enema retention issues.

4.4.5. Selection and Timing of Dose for Each Subject

FMPE and Placebo (FMPP) must be prepared on the same day as administration. To avoid contamination and risk, standard protocols for handling biohazardous material will be employed. Additionally, during material transfer peri-procedure, sterile microbiological technique will be employed.

FMPE by Enema

Bowel preparation with GoLYTELY is performed one day prior to administration of enema. On the day of FMT, loperamide 4mg administered orally as a single dose will be given 1-3 hours prior to administration of the enema.

The FMPE is thawed over the course of 1 hour in a warm water bath (approximately 30°C) or at room temperature for 4.5 hours. After thawing, swirl moderately for 10 seconds to resuspend particulates and transfer to an enema container.

The FMPE will be administered rectally by retention enema (target dwell time of 1-3 hours).

The procedure is performed by nursing staff under investigator's supervision.

Placebo (FMPP) by Enema

Bowel preparation with GoLYTELY is performed one day prior to administration of enema. On the day of FMT, loperamide 4mg administered orally as a single dose will be given 1-3 hours prior to administration of the enema. The placebo (FMPP) is thawed over the course of 1 hour in a warm water bath (approximately 30°C) or at room temperature for 4.5 hours. After thawing, swirl moderately for 10 seconds to resuspend particulates and transfer to an enema container.

The placebo will be administered rectally by retention enema (target dwell time of 1-3 hours).

The procedure is performed by nursing staff under investigator's supervision.

4.4.6. Blinding

This study is considered to be partially blinded due to constraints by the design of the study. The study is double-blinded until a subject has a second ineffective enema. At that time point, the subject and site coordinator will be unblinded to the subject's randomization assignment when it is determined whether or not they are eligible for a third enema.

The study treatment will be prepared by an unblinded pharmacist. The pharmacist at each site will refer to the Treatment Key provided for the trial by the SDCC to determine the randomized treatment for the subjects. The pharmacist will maintain an open label code (provided by the SDCC) under locked/secured conditions and will follow the randomization code. The enemas will be packaged to appear identical and the placebo enema fluid itself will be colored to match the active study product. For the first enema visit, an unblinded RN under the supervision of an unblinded investigator will perform the enema. The unblinded staff and investigator will not be involved in any subsequent study assessment.

Study subjects or legally authorized representative will remain blinded and not be provided any information until all subjects have completed the trial and the database has been locked. However, the study is designed to be blinded only to a certain point because after the second ineffective enema the subject will become aware as to which group they were originally assigned (FMPE vs. FMPP). Moreover, all subjects in scenarios 2, 3, or 4 will receive a second enema containing active FMT (FMPE) and thus will no longer be blinded.

In the case of a medical emergency, the PI or ISM may deem it medically necessary to unblind the subject's treatment assignment. If the PI or ISM believes that unblinding would benefit the medical care of the subject and time permits, DMID will be consulted prior to unblinding, and concurrence will be obtained. After DMID has approved the unblinding, an independent medical doctor or appropriate designee at the site, who is NOT the principle investigator or blinded staff, should contact the SDCC. If the independent medical doctor or designee cannot make contact with Emmes staff, and/or time does not permit, the unblinding process can occur on-site by contacting the unblinded pharmacist.

The analysis for FMPE efficacy will include clinical response at Day 30 (primary) and Day 60 (secondary) after randomization. The cross-over study design impacts blinding and the primary efficacy analysis will only include results after a single enema.

4.4.7. Prior and Concomitant Therapy

The following concomitant medications (by prescription or over the counter) will be recorded, ranging from 90 days prior to screening and for 365 days after completing treatment for recurrent CDAD:

- Anti-infectives
- Any probiotics
- Any medications used in the treatment of CDAD
- Any acid blockers (H2 blockers and PPIs)
- Any antiperistaltics
- Any NSAID
- Any antihistamines
- Lipid lowering agents
- Antineoplastic agents
- Glucocorticoids

There are no prohibited treatments/medications except for FMT outside the current study and antibiotics other than to treat CDAD in 30 days prior to receiving enema.

4.4.8. Treatment Compliance

All subjects are to receive at least one enema administered in the clinic. Subjects randomized to the placebo arm may receive at most three enemas, whereas subjects randomized to the active arm may receive at most two enemas. All enemas are to be administered in the clinic.

4.5. Efficacy and Safety Variables

4.5.1. Safety Variables

Safety will be assessed by the occurrence of solicited adverse events through 8 days after each enema, non-serious AEs starting from treatment initiation through 30 days after completing treatment for recurrent CDAD, SAEs starting from treatment initiation through 365 days after completing treatment for recurrent CDAD, NOCMCs starting from treatment initiation through 365 days after completing treatment for recurrent CDAD, newly acquired transmissible infectious diseases which are considered adverse events of special interest (AESIs) starting from treatment initiation through 365 days after completing treatment for recurrent CDAD, abnormal clinical laboratory tests starting from treatment initiation through 30 days after completing treatment for recurrent CDAD, and new onset metabolic syndrome starting from treatment initiation through 365 days after completing treatment for recurrent CDAD.

Solicited adverse events occurring from the time of each study enema through 8 days after each study enema include fever, chills, nausea, diarrhea, vomiting, constipation, abdominal cramps, abdominal bloating, flatulence, malaise (fatigue), and loss of appetite. Bowel movements will be recorded through 30 days after the last study enema utilizing a stool log. The number of vomiting episodes will be recorded using an emesis log.

Clinical laboratory tests to be evaluated include: potassium, creatinine, liver function tests (ALT), hemoglobin, WBC, neutrophil count, and platelets. Only Grade 3 abnormal clinical laboratory tests through 30 days after completing treatment for recurrent CDAD will be reported as AEs.

The fecal and blood (serum and plasma) aliquots collected for safety assessment will be stored and only analyzed for select infectious agents following a report of an AESI related to newly acquired transmissible infectious agents (Figure 3). The assays for individual infectious agents will be performed at a local lab.

4.5.2. Efficacy Variables

Clinical response evaluation will include a quantification of the symptoms of CDAD to assess clinical response by Day 8 and through Day 30 after randomization and an evaluation of sustained clinical response through 60 days after randomization. Clinical response will be determined by the Investigator based on the subject reported memory aid with a physical evaluation, as needed, and a PCR test.

Clinical response is defined as those subjects who have no recurrence of CDAD. Subjects will be provided with a memory aid (through 30 days after completing CDAD treatment) to record information on the number and consistency of the stools passed and any other symptoms that they may be experiencing.

Stool and blood samples will be collected at different visits as per the schedule of events (Table 1, Table 2, and Table 3). If a stool sample cannot be obtained during the visit, then the subject will be allowed to bring in a stool sample at the study visit (+1 day).

Stool samples may be split into five aliquots: (1) for C. difficile PCR, (1) toxin assay (at screening and for clinical suspicion of CDAD), (1) for microbiome determination, (1) for safety assessment following AESI related to newly acquired transmissible infectious agents (Figure 3) and (1) for future use.

PCR and toxin testing will only be done if the signs and symptoms of CDAD are present.

If the fecal sample collected for PCR and toxin testing is not available, an additional fecal sample should be collected and aliquoted prior to enrollment.

If the fecal sample collected at screening is unformed or liquid it will be analyzed for presence of C. difficile using PCR and toxin testing at the site's local laboratory within 48 hours of sample collection.

In addition, after enrollment has been completed stool samples will be analyzed from a subset of qualifying subjects, who provided a complete set of samples, to identify and measure the major constituents of the intestinal microbiota (i.e. microbiome determination).

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5. SAMPLE SIZE CONSIDERATIONS

Sample size considerations are based on the primary efficacy endpoint. Sample size estimation is based on a group sequential design with two interim analyses of aggregate data with the opportunity to stop early for efficacy.

The goal of this trial is to establish efficacy of FMT given by enema compared to a placebo enema while limiting the number of subjects allocated to the placebo arm. A group sequential design with two interim reviews will allow enrollment into the placebo arm to be halted prior to the planned full enrollment if the FMT is shown to be efficacious.

To detect a difference in clinical response of 0.25 between the treatment (FMT) and control (placebo) groups, assuming a placebo group proportion of 0.50, with 80% power using a two-sided significance level of 0.05, will require a total sample size of 147 (98 in the FMT group, 49 in the placebo group). Assuming a drop-out rate of 10%, the required sample size is 162 (108 in the FMT group, 54 in the placebo group).

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate, by visit number within subject. All summary tables will be structured with a column for each treatment in the order (FMPE, FMPP) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

The first interim analysis was planned to be performed when approximately 40% of subjects had met the primary efficacy endpoint. If the first interim analysis did not result in termination of enrollments to the placebo arm, the second interim analysis was planned to take place when approximately 70% of subjects have met the primary efficacy endpoint.

A CSR was planned to be generated after all primary and secondary endpoint data are available, to include all primary and secondary endpoint data, as well as the data from any available exploratory endpoints.

The study was stopped early due to low enrollment and other unforeseen challenges, and thus the CSR will be generated once the last subject last visit has occurred and data monitoring and cleaning is complete.

6.3. Analysis Populations

A tabular listing of all subjects, visits, and observations excluded from the efficacy analysis will be provided in the CSR (Listing 4).

6.3.1. Modified Intention-to-Treat (mITT) Population

The modified intention-to-treat (mITT) analysis population will include all randomized subjects who received the study treatment and were followed through the Day 30 visit. Subjects who were not able to retain at least 50% of the enema within 1-3 hours, and either refused a second enema, or were not able to retain at least 50% of the second enema within 1-3 hours will be excluded from this population. Subjects will be analyzed according to the treatment arm to which they were randomized. This analysis set will be used for all efficacy analyses.

6.3.2. Safety Population

The safety analysis population will include all subjects who receive the study treatment and have at least one post-treatment safety assessment. In the case of miss-randomization, subjects will be analyzed according to the actual treatment received. This analysis set will be used for all safety analyses.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

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6.5. Missing Data

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values.

6.6. Interim Analyses and Data Monitoring

An unblinded group sequential interim analysis was originally planned for when approximately 40% of enrollment is completed. The trial could be terminated and completed at that time for efficacy or continued until the second planned interim analysis. If the trial was terminated for efficacy, the plan would be to stop enrolling placebo subjects and continue enrolling subjects to receive FMT to accumulate additional safety data, at which point the trial essentially becomes an observational study. If the trial was not terminated, the second interim analysis would take place when approximately 70% of enrollment is completed. An unblinded group sequential analysis of the cumulative data at that time would be conducted, which may result in the termination of the trial for efficacy, or continuation until the final estimated number of subjects are enrolled. The study would not be halted during interim analyses.

At the interim analyses the Wald test statistic for the primary endpoint would be calculated as follows:

$$Z_1 = \frac{\hat{p}_t - \hat{p}_c}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t)}{n_t} + \frac{\hat{p}_c(1-\hat{p}_c)}{n_c}}} + \frac{\frac{1}{n_t} + \frac{1}{n_c}}{2}$$

where the second term is a continuity correction, $\hat{p}_t$ $\widehat{\mathrm{p_t}}$ and $\hat{p}_c$ $\widehat{\mathrm{p_c}}$ are the observed event rates and n_t and n_c are the sample sizes in the treatment and control groups, respectively, at the interim. At the discretion of the DSMB, one of the following actions will be taken based on the result of the primary endpoint.

1. If $Z_1 > u_1$ the trial is stopped for efficacy and the null hypothesis of no treatment effect is rejected, and we conclude the treatment is effective.
2. If $Z_1 \leq u_1$ the trial is continued until the time of the second interim analysis, at which point Z_2 will be calculated in the same way as Z_1 with all data up to that point.

The efficacy boundary (u_1) for the primary endpoint will be derived from the O'Brien-Fleming error spending function [14, 21], and the appropriate amount of type I error will be spent during the unblinded interim analysis to ensure that the overall one-sided type I error remains 0.025. While the interim analysis is planned to occur once 40% of the patients have completed through 30 days post-treatment, it may not occur exactly at this time point. As the exact boundaries are dependent on the information available at the interim analysis, they will be derived at the time of the interim analysis using the O'Brien-Fleming error spending function for u_1.

At the time of this SAP, the study was stopped after 10 subjects enrolled due to enrollment challenges. No interim analyses for efficacy occurred.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for product administration and assessment of safety and efficacy endpoints.

6.8. Multiple Comparisons/Multiplicity

As no unblinded interim analyses were conducted, there will be no adjustments for multiple comparisons or multiplicity in the final analysis.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 10 will present a summary of the reasons that subjects were screened but not enrolled.

The composition of analysis populations, including reasons for subject exclusion, by treatment group, is presented in Table 8.

The disposition of subjects in the study will be tabulated by treatment group (Table 7). The table shows the total number of subjects screened, enrolled, receiving each enema, and the number completing the study.

A flowchart showing the disposition of study subjects, adapted from the CONSORT Statement will be included (Figure 2). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by treatment group.

A listing of subjects who terminated from study follow-up and the reason will be included in Listing 1.

7.2. Protocol Deviations

A summary of subject specific protocol deviations will be presented by deviation category, type, and treatment group for all subjects (Table 4). All subject specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 2 and Listing 3, respectively).

8. EFFICACY EVALUATION

Efficacy variables will be listed by subject and site. Data will be summarized by treatment group. N, Mean, Standard Deviation, Minimum and Maximum will summarize continuous efficacy variables, whereas number and percent will summarize categorical efficacy variables.

All primary and secondary efficacy analyses will be conducted in the mITT population.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint of the proportion of subjects with clinical response through Day 30 post randomization will be summarized by treatment group presenting the number, proportion, and corresponding two-sided Wilson (Score) 95% confidence intervals in Table 16. The protocol calls for a formal test of hypothesis comparing FMT to placebo. The null hypothesis is that there is no difference in proportions between study arms, with a two-sided alternative. A two-sided Wald test with a continuity correction was planned to test the hypothesis with an O'Brien-Fleming alpha adjustment for the planned interim analyses, however, due to the early closure of the study without an interim analysis, the number of subjects is likely too small to use an asymptotic test. Instead, a two-sided Fisher's exact test will be used to test the hypothesis with no alpha adjustment.

The difference in proportions will be computed by subtracting the proportion for the placebo group from the proportion for the FMT group. The denominator for each group will consist of all subjects randomized to the respective group in the mITT population. The numerator will then be those who have a clinical response through the Day 30 visit (as evidenced by no positive PCR test results through this visit). If a subject requires a second enema before the Day 30 assessment, they will be considered a failure for this endpoint.

A list of all PCR test results as well as toxin assay results is presented in Listing 8.

8.2. Secondary Efficacy Analyses

8.2.1. Sustained Clinical Response through Day 60

The secondary efficacy endpoint of the proportion of subjects with sustained clinical response through Day 60 will be summarized by treatment group presenting the number, proportion, and corresponding two-sided Wilson (Score) 95% confidence intervals in Table 16. The proportion in each group will be computed by the number of subjects in the mITT population as the denominator. The numerator will be those with a sustained clinical response through the Day 60 visit (as evidenced by no positive PCR test results through this visit), without requiring an additional FMT. If the number of subjects with a sustained clinical response permits, a two-sided Fisher's exact test will be used to test the hypothesis with no alpha adjustment.

The difference in proportions will be computed by subtracting the proportion for the placebo group from the proportion for the FMT group.

8.2.2. Number of Recurrences of CDAD through Days 30 and 60

The number of recurrences of CDAD at 30 and 60 days after completing treatment for recurrent CDAD will be described for each treatment group in Table 17. If there are subjects who receive additional enema(s) then this table will include summaries of this endpoint for each unique scenario as shown in Figure 1. By the time treatment for recurrent CDAD has been completed, treatment groups may not be comparable depending on the number of FMTs and antibiotics received for each scenario. For this reason, no formal comparisons are planned between groups.

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8.2.3. Time to First CDAD Recurrence through Day 60

The time (in days) until first CDAD recurrence (using the date of first positive PCR test post-enema) will be analyzed using time-to-event methods. Kaplan-Meier estimates will be presented and a Log-Rank permutation test for small samples will be used to compare treatment groups. Subjects without a recurrence will be censored at their last known contact date or at 60 days, whichever occurs first. A summary table will be presented in Table 18 and a Kaplan-Meier plot will be displayed in Figure 4.

8.3. Exploratory Efficacy Analyses

8.3.1. Changes in Gut Microbial Diversity

A separate detailed statistical analysis plan that covers the planned microbiome exploratory analysis will be developed and finalized prior to database lock.

8.3.2. Agreement of PCR and Toxin Assay Results in Subjects with a Clinical Suspicion of CDAD

Agreement between PCR and toxin-based assay results will be assessed by creating two 2x2 contingency tables, one for PCR positivity and GDH Antigen positivity, and one for PCR positivity and Toxin A/B positivity (Table 19 and Table 20). Per protocol, these tests were only conducted when symptoms of CDAD were present, and therefore the number of tests per subject are few. Because of this, in addition to the small number of subjects available, tests from multiple visits per subject will be pooled to determine agreement. All subjects from both treatment groups will be pooled. Cohen's Kappa statistic will be computed to measure the degree of agreement between two tests, where a 1 indicates perfect agreement and a 0 indicates agreement that is expected by chance.

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9. SAFETY EVALUATION

The analyses of safety data will be primarily descriptive. All summaries and analysis of safety data will be presented for the safety analysis population. Safety summaries will be presented overall and by treatment group.

Listings will be sorted by subject ID, parameter (if applicable), and visit.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. All categorical measures will be summarized by the frequency and percentages (based on the non-missing sample size) of observed levels.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by treatment group, overall, and by site (Table 11, Table 12, Table 13, and Table 14). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics (Listing 5).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 22.1 or higher.

Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 15).

Individual subject listings will be presented for all pre-existing medical conditions (Listing 6).

9.1.2. Prior and Concomitant Medications

Summaries of medications recorded per Section 4.4.7 that were started prior to treatment administration and continuing at the time of administration, as well as medications started post-administration, will be presented by WHO Drug Levels 1 and 2 and treatment group (Table 74).

Individual subject listings will be presented for all concomitant medications (Listing 18).

9.2. Measurements of Treatment Compliance

All subjects were to receive at least one enema administered in clinic. The dates of first treatment are presented by site and treatment group in Table 9. The number of enemas administered to subjects will be presented by treatment group as part of the subject disposition table (Table 7).

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total number of subjects in the safety population. All adverse events reported will be included in the summaries and analyses.

An overall summary of adverse events is presented in Table 21.

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9.3.1. Solicited Events and Symptoms

Solicited adverse events are collected prior to product administration, 30 minutes post-administration and then daily for 7 days after each administration and graded on a scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe). In addition, a stool log will be used to record the number and consistency of bowel movements 30 days after each enema, however, only diarrhea through Day 8 will be summarized for consistency with the solicited even reporting period. Solicited events include: fever, chills, nausea, diarrhea, vomiting, constipation, abdominal cramps, abdominal bloating, flatulence, loss of appetite, and malaise/fatigue. Grading scales for all solicited events and symptoms are included in Table 5.

The proportion of subjects reporting at least one solicited adverse event will be summarized for each solicited adverse event and any symptom. Wilson (Score) two-sided 95% CIs will be presented by treatment group for each enema (Table 23).

For each solicited event and any solicited event, the maximum severity per subject over the 8-day reporting period will be summarized for the safety population. The number and percentage of subjects reporting each event will be summarized by the maximum severity and treatment group, separately for each enema administration and over all administrations. For each event, the denominator is the number of subjects with non-missing data for the specific event (Table 24).

The number of subjects reporting a solicited adverse event will be summarized for each day post-administration both in a summary table beginning in Table 25 and concluding with Table 27 and graphically in a bar chart (Figure 5).

Solicited adverse events by subject will be presented in Listing 9. Data collected from the stool log and emesis log will be presented in Listing 10 and Listing 11, respectively.

9.3.2. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class (SOC) and preferred term for each administration and over all administrations. Denominators for percentages are the number of subjects who received the enema being summarized (Table 28, Table 29, and Table 30).

Adverse events by subject will be presented in Listing 12.

The following summaries for unsolicited adverse events will be presented by MedDRA SOC, preferred term, and treatment group:

- Summary of adverse events occurring in ≥5% of subjects (Table 22);
- Subject incidence and total frequency of adverse events over time by enema with 95% CI (Days 1-8, Days >8) (Table 28, Table 29, and Table 30);
- Summary of severity and relationship to study product (Table 31, Table 32, and Table 33);
- Subject incidence and total frequency of related adverse events over time (Days 1-8, >8) (Table 34);
- Subject listing of serious adverse events (Table 35);
- Subject listing of non-serious adverse events of moderate or greater severity (Table 36);
- Listing of other significant adverse events (Table 37);
- Bar chart of related adverse events by MedDRA SOC and severity (Figure 6)

- Bar chart of the incidence of related adverse events by MedDRA SOC and maximum severity (Figure 7)

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

The following listings will be presented including Subject ID, Adverse Event Description, Last Enema Received/Days Post Enema and Duration, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, and Outcome:

- Deaths and Serious Adverse Events (Table 35);
- Adverse Events of Special Interest (Table 37);
- New Onset Chronic Medical Conditions (Table 37).

9.5. Pregnancies

For any subjects in the safety population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A table summarizing the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births by treatment will be presented. In addition, a listing of pregnancies and outcomes will be presented (Listing 19, Listing 20, Listing 21, Listing 22, and Listing 23).

9.6. Clinical Laboratory Evaluations

The distribution of laboratory results by time point, treatment group, and maximum severity will be presented in Table 40, Table 41, Table 42, and Table 43 for chemistry parameters and in Table 50, Table 51, Table 52, Table 53, and Table 54 for hematology parameters. If the number of observations permits, laboratory results will also be summarized using shift tables in Table 44, Table 45, and Table 46 for chemistry parameters and in Table 55, Table 56, Table 57, and Table 58 for hematology parameters. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for each laboratory parameter, will be summarized for raw values and changes from baseline in Table 47, Table 48, and Table 49 for chemistry parameters and in Table 59, Table 60, Table 61, and Table 62 for hematology parameters.

Listing 13 and Listing 14 will provide a complete listing of individual clinical laboratory results with applicable reference ranges.

Listing 15 will provide a complete listing of metabolic syndrome markers (TG, HDL, LDL, HDL/LDL ratio, fasting glucose).

9.7. Vital Signs and Physical Evaluations

Vital sign measurements included systolic blood pressure, diastolic blood pressure, pulse, weight, and oral temperature. Vital signs were assessed at screening, Day 1, Day 8, Day 9, Day 30, Day 60, and Day 365 after each enema administration. In addition, waist circumference was obtained prior to enrollment and at subsequent enemas, Day 60, and Day 365 after last CDAD treatment. Vital signs with protocol-specified grading scales will be tabulated by time point, treatment group, and maximum severity starting in Table 63, Table 64, Table 65, Table 66, and Table 67. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for all vital signs, will be summarized for raw values and

changes from baseline in Table 68, Table 69, Table 70, Table 71, Table 72, and Table 73. Listing 16 will provide a complete listing of vital signs results.

A detailed physical examination is conducted at the screening visit and history driven physical exams as needed at enrollment and follow-up visits depending on interim medical history. The following body systems will be assessed: Abdomen, Cardiovascular/heart, Extremities, General Appearance, Genitourinary, HEENT, Lymph nodes, Musculoskeletal, Neck, Neurological, Pulmonary/Chest, and Skin (Listing 17).

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented (Listing 18). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the safety population (Table 74).

9.9. Other Safety Measures

Not applicable.

10. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

11. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

12. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

12.1. Changes in the Conduct of the Study

The first subject enrolled on protocol version 5.0. Subjects were also enrolled on protocol version 6.0 and 8.0. Substantive changes between these protocol versions are summarized below.

12.1.1. Inclusion and Exclusion Criteria

Several changes were made to inclusion and exclusion criteria to facilitate recruitment. From version 5.0 to 6.0 these changes included the following:

1. Updating exclusion criterion from excluding subjects with a previous FMT at any time excluding the current study to only excluding subjects with an FMT within the previous 12 months prior to enrollment.
2. Updating exclusion criterion from antibiotic use in the past 30 days or scheduled in the upcoming 3 months to antibiotic use in the past 2 weeks or scheduled in the upcoming 2 weeks.
3. Updating exclusion criterion from history of any GI cancer to any GI cancer in the past year.
4. Updating exclusion criterion from major surgery of the GI tract in the past year to past six months.
5. Updating exclusion criterion from having a known allergy to having a non-tolerance to any component of vancomycin, loperamide, or GoLYTELY.
6. Updating exclusion criterion from participation in another trial from 60 days prior to enrollment through the three-year duration of the study to 30 days prior to enrollment and one year after enrollment.

From version 7.0 to 8.0 these changes included the following:

1. Updating inclusion criterion #4 from 6 to 12 months.
2. Changing “Use of the following drugs in last 3 months: such as monoclonal antibodies to B and T cells, anti-TNF agents, glucocorticoids1, antimetabolites2, calcineurin inhibitors3, mycophenolate mofetil.

   [1] For example, > 20 mg of prednisone (or equivalent) given daily or on alternative days for 2 weeks or more
   [2]azathioprine, 6-mercaptopurine
   [3]tacrolimus, cyclosporine”

   to

   “Any heart, lung, pancreas, or intestinal transplant recipient or any HIV positive transplant recipient.

   [1] not excluded from the trial are subjects who are kidney, liver, or liver/kidney transplant recipients AND are more than 6 months from transplantation AND have not had a rejection episode in the past 6 months AND have been stable on immunosuppressive regimen for the past 6 months (any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, will not be considered a deviation of this criterion).”
3. Changing “Any GI cancer in the past year” to “Any GI cancer in the past 6 months.”
4. Changing “Any history of cirrhosis” to “Patients with decompensated cirrhosis.”
5. Changing “Major surgery of the GI tract in the past 6 months” to “Major surgery of the GI tract in the past 2 months.”

6. Changing "Any history of inflammatory bowel disease (IBD) including ulcerative colitis, Crohn's disease, indeterminate colitis or celiac disease" to "Active[9] inflammatory bowel disease (IBD) including ulcerative colitis, Crohn's disease, indeterminate colitis or celiac disease

   [9]Active IBD is defined as any IBD requiring any steroid use in the past 6 months OR any increase in dose or frequency of medications in the past 6 months (any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, will not be considered a deviation of this criterion)."

7. Changing "Irritable bowel syndrome (IBS) within the past 12 months or any active uncontrolled gastrointestinal disorders or diseases" to "Uncontrolled irritable bowel syndrome (IBS)[10] or any active uncontrolled gastrointestinal disorders or diseases[11]"

   [10] Uncontrolled IBS refers to any IBS with diarrhea on average more than once a week for the past 3 months prior to last CDAD episode."

12.1.2. Change in Subject Participation Duration

In version 8.0 substantive changes were made to limit the safety follow-up period from three years (1095 days) to one year (365 days). As such, secondary safety outcome measures intended to estimate long term safety after one year were removed.

12.1.3. Removal of Planned Interim Analyses

The protocol had originally called for two planned interim analyses for efficacy, one at 40% of enrollment and one at 70% of enrollment. In version 8.0, these planned interim analyses were removed as the study product was expiring and enrollment was anticipated to be closed early.

12.2. Changes in Planned Analyses

There are several changes from the protocol defined analyses that are included within this SAP. As mentioned above, secondary safety outcome measures were removed and thus, their associated analyses will not be conducted. Due to the early closure of the study, no interim analyses were conducted and therefore, no corrections for multiplicity will be applied in the final analysis. Furthermore, it was originally planned that the study would enroll 162 subjects allowing for larger sample statistical methods to be used. With only 10 subjects enrolled, it's anticipated that many of these tests will no longer be valid and many of the analyses will be primary descriptive or employ small sample techniques. Lastly, the protocol defines clinical response as having no recurrence of CDAD through Day 30 after completing treatment for recurrent CDAD, however this has been corrected in this SAP to reflect the intention of efficacy analyses to be conducted from the time of randomization comparing only the randomized treatments.

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14. LISTING OF TABLES, FIGURES, AND LISTINGS

Table and figure shells are presented below.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

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9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 1: Schedule of Study Procedures, Enema #1

	Screening Visit	Enrollment Visit (1st Enema)	Day 4[a]	Day 8	Day 9 post Enema	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a], Day 180[a], Day 240[a], Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
Visit	A00	A01	A02	A03	A04	A05, A06	A07	A08	A09, A10, A11, A12	A13	Supplemental
Window	(-21 to -1)	0	-1	-3	+3	±2	±3	±5	±7	±14	n/a
Informed Consent	X										
Inclusion/Exclusion	X	X		X[m]							
Test of Comprehension	X										
Medical history	X	X[k]		X[k]	X[k]		X[k]	X[k]		X[k]	X[k]
HIV screen if no known history of HIV + within the last 6 months	X										
Randomization		X									
Physical exam	X	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]
Vital signs [b]	X	X		X	X		X	X		X	X
Measuring waist circumference		X						X		X	
Clinical lab tests [c]	X	X			X		X	X		X	X[c]
Blood samples [d]		X			X		X	X		X	
Stool sample [e]	X	X		X	X		X	X		X	X
AEs/SAEs/ AESIs/Chronic Med. Conditions [f]		X	X	X	X	X	X	X	X	X	X
Bowel preparation and antiperistaltic Instructions	X			X							
Distribution of memory aid		X									
Review memory aid			X	X	X	X	X				[X][j]
Prior and/or concomitant medications [g]	X	X	X	X	X	X	X	X	X	X	X
Serum/Urine pregnancy test	X[l]	X		X							

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	Screening Visit	Enrollment Visit (1st Enema)	Day 4[a]	Day 8	Day 9 post Enema	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a], Day 180[a], Day 240[a], Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
Visit	A00	A01	A02	A03	A04	A05, A06	A07	A08	A09, A10, A11, A12	A13	Supplemental
Window	(-21 to -1)	0	-1	-3	+3	±2	±3	±5	±7	±14	n/a
Evaluation of signs and symptoms of CDAD[h]	X	X	X	X	X	X	X	X			X
Investigator Determination of clinical response			X	X	X	X	X	X			X
Enema administration		X									
Inquiry about interim diagnosis of CDAD									X	X	
Provide oral vancomycin				X[m]							

[a] Subject interviews may be conducted by telephone. Subjects will also be contacted at Day 4 after enema treatment to confirm clinical response and then weekly thereafter until recurrence or the 60-day post-treatment visit whichever comes first, to evaluate possible CDAD recurrence. Staff will evaluate for symptoms of CDAD during phone visit and consult with clinician if needed. Subject interviews will be supplemented by review of the subject's personal records (if hospitalized) and memory aid.

[b] Includes blood pressure, pulse, weight and body temperature. Height will be collected at screening visit only.

[c] Clinical labs include potassium, creatinine, liver function tests (ALT), hemoglobin, WBC, neutrophil count, and platelets.

[d] Metabolic Syndrome markers including triglyceride level, HDL, LDL, HDL/LDL ratio, fasting glucose (Days 1, 60 and 365), future use (Day 1, 9, 30, 60 and 365), storage of sera and plasma to look at infectious diseases potentially transmitted by FMT (Day 1) .

[e] Stool sample will be split into different aliquots; (1) for *C. difficile* PCR, (1) for *C difficile* toxin assay, (at screening and when signs and symptoms of CDAD are present), (1) for microbiome determination, (1) for safety assessment following AESI related to newly acquired transmissible infectious agents (Figure 2)

[f] AEs will be collected from the time of informed consent through Day 30 post completion of treatment. SAEs will continue to be collected and assessed through the Day 365. AESIs will be collected through 365 days after completing treatment for recurrent CDAD (Figure 2). New onset related chronic medical conditions will be collected from the time the first enema is administered through Day 365.

[g] The following concomitant medications will be recorded for 90 days prior to screening and throughout Day 365: anti-infectives, probiotics, any medications used in the treatment of CDAD, any medications that could affect peristalsis, any drugs with antacid properties, any NSAID, any antihistamines, any lipid lowering agents, antineoplastic agents.

[h] Clinician will evaluate for signs and symptoms of CDAD during clinic visit. Intercurrent diarrhea status is to be assessed during subject interviews, supplemented by review of the subject's personal records (if hospitalized), memory aid.

[i] A history driven physical exam performed depending on interim medical history

[j] Review of memory aid performed only if unscheduled visit occurs prior to Day 30.

[k] Interim medical history

[l] At screening only blood pregnancy test should be performed

[m] If the clinical suspicion is high vancomycin should be dispensed and started immediately however this scenario is based on the fact that the PCR will come back negative, but if the clinical suspicion is low, vancomycin will be dispensed.

Table 2: Schedule of Study Procedures, Enema #2

	Screening Visit	Enrollment Visit (1st Enema)	Day 4[a]	Day 8	FMT visit	Day 4[a]	Day 8	Day 9 Visit	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a] Day180[a] Day 240[a] Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
	Occurred under Scenario 1					***Post Last Enema***								
Visit	A00	A01	A02	A03	B04	B05	B06	B07	B08, B09	B10	B11	B12, B13, B14, B15	B16	Supplemental
Window			-1	-3	0	-1	-3	+3	±2	±3	±5	±7	±14	n/a
Informed Consent	X													
Inclusion/Exclusion	X	X		X[m]	X		X							
Test of Comprehension	X													
Medical history	X	X[k]		X[k]	X[k]		X	X[k]		X[k]	X[k]		X[k]	X[k]
HIV screen if no known history of HIV + within the last 6 months	X													
Randomization		X												
Physical exam	X	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]
Vital signs [b]	X	X		X	X		X	X		X	X		X	X
Measuring waist circumference		X			X						X		X	
Clinical lab tests [c]	X	X			X			X		X	X		X	X[c]
Blood samples [d]		X			X			X		X	X		X	
Stool sample [e]	X	X		X	X		X	X		X	X		X	X
AEs/SAEs/AESIs/Chronic Med. Conditions [f]		X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel preparation and antiperistaltic Instructions	X			X[m]			X							
Distribution of memory aid		X			X									
Review memory aid			X	X		X	X	X	X	X				[X][j]
Prior and/or concomitant medications [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine/Serum pregnancy test	X[l]	X		X	X		X							

	Screening Visit	Enrollment Visit (1st Enema)	Day 4[a]	Day 8	FMT visit	Day 4[a]	Day 8	Day 9 Visit	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a] Day180[a] Day 240[a] Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
	Occurred under Scenario 1					***Post Last Enema***								
Visit	A00	A01	A02	A03	B04	B05	B06	B07	B08, B09	B10	B11	B12, B13, B14, B15	B16	Supplemental
Window			-1	-3	0	-1	-3	+3	±2	±3	±5	±7	±14	n/a
Evaluation of signs and symptoms of CDAD[h]	X	X	X	X	X	X	X	X	X	X	X			X
Investigator Determination of clinical response			X	X		X		X	X	X	X			X
Provide oral vancomycin				X[m]			X[n]							
Enema administration		X			X									
Inquiry about interim diagnosis of CDAD												X	X	

[a] Subject interviews may be conducted by telephone. Subjects will also be contacted at Day 4 after enema treatment to confirm clinical response and then weekly thereafter until recurrence or the 60-day post-treatment Visit ,whichever comes first to evaluate possible CDAD recurrence. Staff will evaluate for symptoms of CDAD during phone visit and consult with clinician if needed. Subject interviews will be supplemented by review of the subject's personal records (if hospitalized) and memory aid.

[b] Includes blood pressure, pulse, weight and body temperature. Height will be collected at screening visit only.

[c] Clinical labs include potassium, creatinine, liver function tests (ALT), hemoglobin, WBC, neutrophil count, and platelets.

[d] Metabolic Syndrome markers including triglyceride level, HDL, LDL, HDL/LDL ratio, fasting glucose (FMT visit, Day 60 and Day 365), future use (FMT visit, Day 9, 30, 60 and 365), storage of sera and plasma to look at infectious diseases potentially transmitted by FMT (FMT visit).

[e] Stool sample will be split into different aliquots; (1) for *C. difficile* PCR, (1) for *C. difficile* toxin assay, (at screening and when signs and symptoms of CDAD are present), (1) for microbiome determination, (1) for safety assessment following AESI related to newly acquired transmissible infectious agents (Figure 2), and (1) for future use.

[f] AEs will be collected from the time of informed consent through Day 30 post-FMT treatment. SAEs will continue to be collected and assessed through Day 365. AESIs will be collected through 365 days after completing treatment for recurrent CDAD (Figure 2). New onset related chronic medical conditions will be collected from the time the first enema is administered through Day 365.

[g] The following concomitant medications will be recorded for 90 days prior to screening and throughout Day 365 post FMT: anti-infectives, probiotics, any medications used in the treatment of CDAD, any medications that could affect peristalsis, any drugs with antacid properties, any NSAID, any antihistamines, any lipid lowering agents, antineoplastic agents.

[h] Clinician will evaluate for signs and symptoms of CDAD during clinic visit. Intercurrent diarrhea status is to be assessed during subject interviews, supplemented by review of the subject's personal records (if hospitalized), memory aid.

[i] A history driven physical exam performed depending on interim medical history

[j] Review of memory aid performed only if unscheduled visit occurs prior to Day 30.

[k] Interim medical history

[l] At screening only blood pregnancy test should be performed

[m] If the clinical suspicion is high vancomycin should be dispensed and started immediately and if PCR test is positive the drug should be continued, but if the clinical suspicion is low, vancomycin will be dispensed but won't be started until the PCR results are back and subject is notified. For the GoLYTELY and loperamide - the subject will come and pick them from the clinic at least one day prior to the enema procedure.

[n] If the clinical suspicion is high vancomycin should be dispensed and started immediately however these scenarios are based on the fact that the PCR will come back negative at this timepoint or there is no more FMT to be offered, but if the clinical suspicion is low, vancomycin will be dispensed.

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Table 3: Schedule of Study Procedures, Enema #3

	Screening Visit	Enrollment Visit	Day 4[a]	Day 8	First FMT Visit	Day 4[a]	Day 8	2nd FMT Visit	Day 4[a]	Day 8 Visit	Day 9	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a] Day180[a] Day 240[a] Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
		Occurred under 2							***Post Last Enema***								
Visit	A00	A01	A02	A03	B04	B05	B06	C07	C08	C09	C10	C11, C12	C13	C14	C15, C16, C17, C18	C19	Supplemental
Window			-1	-3		-1	-3		-1	-3	+3	±2	±3	±5	±7	±14	n/a
Informed Consent	X																
Inclusion/ Exclusion	X	X		X[m]	X		X	X									
Test of Comprehension	X																
Medical history	X	X[k]		X[k]	X[k]		X[k]	X[k]		X[k]	X[k]		X[k]	X[k]		X[k]	X[k]
HIV screen if no known history of HIV + within the last 6 months	X																
Randomization		X															
Physical exam	X	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]
Vital signs[b]	X	X		X	X		X	X		X	X		X	X		X	X
Measuring waist circumference		X			X			X						X		X	
Clinical lab tests [c]	X	X			X			X			X		X	X		X	X[c]
Blood samples [d]		X			X			X			X		X	X		X	
Stool sample [e]	X	X		X	X		X	X		X	X		X	X		X	X
AEs/SAEs/AESIs/Chronic Med. Conditions [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel preparation and antiperistaltic Instructions	X			X[m]			X[m]										
Distribution of memory aid		X			X			X									
Review memory aid			X	X		X	X		X	X	X	X	X				[X][j]

	Screening Visit	Enrollment Visit	Day 4[a]	Day 8	First FMT Visit	Day 4[a]	Day 8	2nd FMT Visit	Day 4[a]	Day 8 Visit	Day 9	Day 15[a] Day 22[a]	Day 30 Visit	Day 60 Visit	Day 120[a] Day180[a] Day 240[a] Day 300[a]	Day 365 Visit	Unscheduled Visit for Recurrence
		Occurred under 2							***Post Last Enema***								
Visit	A00	A01	A02	A03	B04	B05	B06	C07	C08	C09	C10	C11, C12	C13	C14	C15, C16, C17, C18	C19	Supplemental
Prior and/or concomitant medications [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine/Serumpregnancy test	X[l]	X		X	X		X	X									
Evaluation of signs and symptoms of CDAD [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Investigator Determination of clinical response			X	X		X	X		X	X	X	X	X	X			X
Provide oral vancomycin				X[m]			X[m]										
Enema administration		X			X			X									
Inquiry about interim diagnosis of CDAD															X	X	

[a] Subject interviews may be conducted by telephone. Subjects will also be contacted at Day 4 after enema treatment to confirm clinical response and then weekly thereafter until recurrence or the 60-day post-treatment Visit , whichever comes first, to evaluate possible CDAD recurrence. Staff will evaluate for symptoms of CDAD during phone visit and consult with clinician if needed. Subject interviews will be supplemented by review of the subject's personal records (if hospitalized) and memory aid.

[b] Includes blood pressure, pulse, weight and body temperature. Height will be collected at screening visit only.

[c] Clinical labs include creatinine, potassium, liver function tests (ALT), hemoglobin, WBC, neutrophil count, and platelets.

[d] Metabolic Syndrome markers, including triglyceride level, HDL, LDL, HDL/LDL ratio, fasting glucose (FMT visit, Day 60 and Day 365), future use (FMT visit, Day 9, 30, 60 and 365, storage of sera and plasma to look at infectious diseases potentially transmitted by FMT (FMT visit).

[e] Stool sample will be split into different aliquots; (1) for *C. difficile* PCR, (1) for *C. difficile* toxin assay, (at screening and when symptoms of CDAD are present), (1) for microbiome determination, (1) for safety assessment following AESI related to newly acquired transmissible infectious agents (Figure 2), (1) for future use.

[f] AEs will be collected from the time of informed consent through Day 30 post-FMT treatment. SAEs will continue to be collected and assessed through Day 365. AESIs will be collected through 365 days after completing treatment for recurrent CDAD (Figure 2). New onset related chronic medical conditions will be collected from the time the first enema is administered through Day 365.

[g] The following concomitant medications will be recorded for 90 days prior to screening and throughout Day 365 post FMT: anti-infectives, probiotics, any medications used in the treatment of CDAD, any medications that could affect peristalsis, any drugs with antacid properties, any NSAID, any antihistamines, any lipid lowering agents, antineoplastic agents.

[h] Clinician will evaluate for signs and symptoms of CDAD during clinic visit. Staff will evaluate for symptoms of CDAD during phone visit and consult with clinician if needed. [i] A history driven physical exam performed depending on interim medical history.

[j] Review of memory aid performed only if unscheduled visit occurs prior to Day 30.

[k] Interim medical history

[l] At screening only blood pregnancy test should be performed

[m] If the clinical suspicion is high, vancomycin should be dispensed and started immediately and if PCR test is positive the drug should be continued, but if the clinical suspicion is low, vancomycin will be dispensed but won't be started until the PCR results are back and subject is notified. For the GoLYTELY and loperamide - the subject will come and pick them from the clinic at least one day prior to the enema procedure.

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10.2 Protocol Deviations

Table 4: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						
	Urine not collected						
	Stool not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						

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Category	Deviation Type	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Blinding policy/procedure	Any type						
	Treatment unblinded						
	Other						

N=Number of subjects in the Safety Population

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12.2.2 Displays of Adverse Events

Table 5: Solicited Adverse Event Grading Scale

Clinical Feature	Grade 1	Grade 2	Grade 3
Fever	38.0 – 38.4°C 100.4 – 101.2°F	38.5 – 38.9°C 101.3 – 102.0°F	≥ 39.0°C >102.0°F or ER visit or hospitalization
Chills	Mild	Moderate	Severe or ER visit or hospitalization
Nausea	Mild	Moderate	Severe or ER visit or hospitalization
Diarrhea	≥3 loose or liquid stools or ≥300-599 gm of loose or liquid stool /24 consecutive hours	4-5 loose or liquid stools or ≥600-800 gm of loose or liquid stool /24 consecutive hours	≥6 liquid stools or >800 gm of loose or liquid stool / 24 hours or ER visit or hospitalization or requires outpatient IV hydration
Vomiting	1-2 episodes in 24 hours	3-5 episodes in 24 hours	>5 episodes in 24 hours or ER visit or hospitalization or requires outpatient IV hydration
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental activities of daily living	Obstipation with manual evacuation indicated; limiting self-care activities of daily living
Abdominal Cramps	Mild	Moderate	Severe or ER visit or hospitalization
Abdominal bloating	Mild	Moderate	Severe or ER visit or hospitalization
Flatulence	Mild	Moderate	Severe or ER visit or hospitalization
Malaise, fatigue	Mild	Moderate	Severe or ER visit or hospitalization
Loss of appetite	Mild	Moderate	Severe or ER visit or hospitalization

Scoring guidelines:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Note: Definitions in the table will take precedence over the footnotes for diarrhea, vomiting, and constipation

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12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 6: Laboratory Adverse Event Grading Scale

Laboratory	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Potassium, high, mEq/L	5.2	5.3-5.4	≥ 5.5
Potassium, low, mEq/L	3.1	3.0	<3.0
Creatinine mg/dL	1.5-1.7	1.8-2.0	> 2.0
Liver Function Tests (ALT) increase by factor	1.1-2.5 x ULN*	>2.5-5.0 x ULN*	>5.0 x ULN*
Hgb (female), g/dL	11.0-11.3	9.5–10.9	<9.5
Hgb (male), g/dL	12.5-12.8	10.5- 12.4	<10.5
WBC, increase, cells, x 10^3u/L	10.8-15.0	15.1 - 20.0	>20.0
WBC, decrease, cells, x 10^3u/L	2.5-3.1	1.5-2.4	<1.5
Absolute Neutrophil Count (female), x 10^3u/L	0.800-0.909	0.600-0.799	≤0.599
Absolute Neutrophil Count (male), x 10^3u/L	0.650-0.669	0.600-0.649	≤0.599
Platelets, decrease, cells/mm^3	125,000-134,000	100,000- <125,000	<100,000

* ULN is upper limit of normal in lab.
Any clinical lab value Grade 3 (unless present at baseline) will be reported as an AE

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 7: Subject Disposition by Treatment Group

Subject Disposition	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received 1st Enema	x	xx	x	xx	x	xx
One attempt	x	xx	x	xx	x	xx
Two attempts	x	xx	x	xx	x	xx
Received 2nd Enema	x	xx	x	xx	x	xx
Received 3rd Enema						
Completed Study Day 30 Visit						
Completed Study Day 60 Visit						
Completed Follow-Up (Study Day 365)[a]						

N=Number of subjects enrolled
[a] Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.

Table 8: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
Modified Intention-to-Treat	Any Reason	x	xx	x	xx	x	xx
	Did not receive enema						
	Did not retain ≥50% of enema within 1-3 hours						
	Not followed through Day 30 visit						
Safety	Any Reason						
	Did not receive enema						
	Did not contribute post-enema safety data						

N=Number of subjects enrolled

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Table 9: Dates of First Treatment by Site and Treatment Group

Dates of Dosing	Hope Clinic of Emory FMPE (N=X)	Hope Clinic of Emory FMPP (N=X)	Duke University Medical Center FMPE (N=X)	Duke University Medical Center FMPP (N=X)	All Sites FMPE (N=X)	All Sites FMPP (N=X)	All Sites All Subjects (N=X)
Total (Entire period of enrollment)							
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x	x	x

Note: N= Number of subjects in the Safety Population

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Table 10: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but not enrolled		x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

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14.1.2 Demographic Data by Study Group

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Site

Variable	Characteristic	Hope Clinic of Emory (N=X)		Duke University Medical Center (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						

Note: N=Number of subjects enrolled

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Hope Clinic of Emory (N=X)	Duke University Medical Center (N=X)	All Subjects (N=X)
Age (years)	Mean	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx
	Maximum	xx	xx	xx
BMI (kg/m^2)	Mean	xx.xx	xx.xx	xx.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x

Note: N=Number of subjects enrolled

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Table 13: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group

Variable	Characteristic	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						

Note: N=Number of subjects enrolled

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Table 14: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group

Variable	Statistic	FMPE (N=X)	FMPP (N=X)	All Subjects (N=X)
Age (years)	Mean	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx
	Maximum	xx	xx	xx
BMI (kg/m^2)	Mean	xx.xx	xx.xx	xx.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x

Note: N=Number of subjects enrolled

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14.1.3 Prior and Concurrent Medical Conditions

Table 15: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

MedDRA System Organ Class	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

Note: N= Number of subjects in the Safety Population; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

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14.2 Efficacy Data

Table 16: Clinical Response by Time Point, Statistic, and Treatment Group, mITT Population

Time Point	Statistic	FMPE (N=xx)	FMPP (N=xx)
Day 30	Number with Clinical Response[a]	x	x
	Clinical Response Proportion	x.xx	x.xx
	95% CI	x.xx, x.xx	x.xx, x.xx
	Difference in Proportions	--	x.xx
	95% CI in Difference in Proportions	--	x.xx, x.xx
	p-value[c]	--	0.xxx
Day 60	Number with Sustained Clinical Response[b]	x	x
	Sustained Clinical Response Proportion	x.xx	x.xx
	95% CI	x.xx, x.xx	x.xx, x.xx
	Difference in Proportions	--	x.xx
	95% CI in Difference in Proportions	--	x.xx, x.xx
	p-value[c]	--	0.xxx

[a] Clinical response is defined as those subjects who have no recurrence of CDAD through Day 30 (±3) after randomization.
[b] Sustained clinical response is defined has having an initial response by Day 30 after randomization with no recurrence of CDAD through Day 60.
[c] Based on a two-sided Fisher's exact test

Table 17: Number of Recurrences of CDAD by Time Point, Statistics, and Treatment Group, mITT Population

Time Point	Statistic	FMPE (N=xx)	FMPP (N=xx)
Day 30	n	x	x
	Mean (Standard Deviation)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x
	Min, Max	x.x, x.x	x.x, x.x
Day 60	n	x	x
	Mean (Standard Deviation)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x
	Min, Max	x.x, x.x	x.x, x.x

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Table 18: Time (in days) to First CDAD Recurrence through Day 60 by Treatment Group, mITT Population

Statistic	FMPE (N=xx)	FMPP (N=xx)
Median[a]	x.x	x.x
Min, Max[a]	x.x, x.x	x.x, x.x
Kaplan-Meier Event Rate	x.x	x.x
95% CI	x.x, x.x	x.x, x.x
Log-Rank p-value	---	x.xxx

[a] Calculated among subjects who had a recurrence of CDAD.

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Table 19: Agreement Between PCR and GDH Antigen Results

PCR Result	GDH Antigen Result		Statistic
	Positive	Negative	
Positive	x	x	Kappa: x.xxx
Negative	x	x	95% CI: x.xxx, x.xxx

Tables with similar format:

Table 20: Agreement Between PCR and Toxin A/B Results

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 21: Overall Summary of Adverse Events

	FMPE (N = xx)		FMPP (N = xx)		All Subjects (N = xx)	
Subjects[a] with	n	%	n	%	n	%
At least one solicited adverse event	x	x	x	x	x	x
At least one unsolicited adverse event from treatment initiation through 30 days after completing treatment for recurrent CDAD	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x
At least one serious adverse event[b] from treatment initiation through 365 days after completing treatment for recurrent CDAD	x	x	x	x	x	x
At least one related, serious adverse event from treatment initiation through 365 days after completing treatment for recurrent CDAD	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x
At least one new onset related chronic medical condition from treatment initiation through 365 days after completing treatment for recurrent CDAD	x	x	x	x	x	x
At least one new onset metabolic syndrome from treatment initiation through 365 days after completing treatment for recurrent CDAD	x	x	x	x	x	x
At least one newly acquired transmissible infectious disease which is considered an AESI from treatment initiation through 365 days after completing treatment for recurrent CDAD						
At least one abnormal clinical laboratory test (hematology or chemistry) from treatment initiation through 30 days after completing treatment for recurrent CDAD						
Mild (Grade 1)						
Moderate (Grade 2)						
Severe (Grade 3)						

N = Number of subjects in the Safety Population
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table X.
[c] As reported on the Adverse Event eCRF.

Table 22: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

MedDRA Preferred Term	MedDRA System Organ Class	FMPE (N=X)			FMPP (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.									
Other (Non-serious) Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc									

N = number of subjects in the Safety Population (number of subjects at risk).
n= number of subjects reporting event.
Events= total frequency of events reported.

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14.3.1.1 Solicited Adverse Events

Table 23: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Enema, and Treatment Group

Symptom	Post Enema 1 FMPE (N=X)			Post Enema 1 FMPP (N=X)			Post Enema 1 All Subjects (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Fever									
Chills									
Nausea									
Diarrhea									
Vomiting									
Constipation									
Abdominal cramps									
Abdominal bloating									
Flatulence									
Malaise, fatigue									
Loss of appetite									

N=Number of subjects in the Safety Population

Table 24: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Enema, and Treatment Group

Symptom	Severity	Post Enema 1 FMPE (N=X)			Post Enema 1 FMPP (N=X)			Post Enema 1 All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild									
	Moderate									
	Severe									
Fever	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild									
	Moderate									
	Severe									
Chills	None									
	Mild									
	Moderate									
	Severe									
Nausea	None									
	Mild									
	Moderate									
	Severe									
Diarrhea	None	x	xx		x	xx		x	xx	
	Mild									
	Moderate									
	Severe									
Vomiting	None									
	Mild									
	Moderate									
	Severe									

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Symptom	Severity	Post Enema 1 FMPE (N=X)			Post Enema 1 FMPP (N=X)			Post Enema 1 All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Constipation	None									
	Mild									
	Moderate									
	Severe									
Abdominal cramps	None									
	Mild									
	Moderate									
	Severe									
Abdominal bloating	None									
	Mild									
	Moderate									
	Severe									
Flatulence	None									
	Mild									
	Moderate									
	Severe									
Malaise, fatigue	None									
	Mild									
	Moderate									
	Severe									
Loss of appetite	None									
	Mild									
	Moderate									
	Severe									

Note: N = Number of subjects in the Safety Population who received the specified enema. Severity is the maximum severity reported during the solicited event reporting period post enema for each subject.

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Table 25: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Enema – FMPE, Post Enema 1 (N=X)

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Any Post-Enema*	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Fever	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Chills	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Nausea	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						

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Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Any Post-Enema*	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Diarrhea	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx				
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Vomiting	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Constipation	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Abdominal cramps	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Abdominal bloating	None																						
	Mild																						
	Moderate																						

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Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Any Post-Enema*	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																						
	Not Reported																						
Flatulence	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Malaise, fatigue	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						
Loss of appetite	None																						
	Mild																						
	Moderate																						
	Severe																						
	Not Reported																						

Note: N = Number of subjects in the Safety Population who received the specified enema. Severity is the maximum severity reported post enema for each subject for each day. *Indicates how many subjects had “None”, “Mild”, “Moderate”, “Severe”, or “Not Reported” for any day. A subject may be counted in more than one of these categories.

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Tables with similar format:

Table 26: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Enema – FMPP, Post Enema 1 (N=X)

Table 27: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Enema – All Subjects, Post Enema 1 (N=X)

14.3.1.2 Unsolicited Adverse Events

Table 28: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Enema Number– FMPE

MedDRA System Organ Class	MedDRA Preferred Term	Day 1-8 Post Enema 1 (N=X)				Day 9-30 Post Enema 1 (N=X)				Any Time Post Enema (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												
Note: N = number of subjects in the Safety Population who received the specified enema. This table presents number and percentage of subjects. A subject is only counted once per PT/time point.													

Tables with similar format:

Table 29: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Enema Number – FMPP

Table 30: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Enema Number – All Subjects

Table 31: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Maximum Severity, Relationship, and Treatment Group – FMPE

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity						Relationship to Treatment			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity and closest relationship.

Tables with similar format:

Table 32: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Maximum Severity, Relationship, and Treatment Group – FMPP

Table 33: Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Maximum Severity, Relationship, and Treatment Group – All Subjects

Table 34: Related Unsolicited Adverse Events Within 8 Days Post Enema by MedDRA System Organ Class, Preferred Term, Enema, and Treatment Group

MedDRA System Organ Class	MedDRA Preferred Term	FMPE Day 1-8 Post Enema 1			FMPP Day 1-8 Post Enema 1			All Subjects Day 1-8 Post Enema 1		
		n	%	Events	n	%	Events	n	%	Events
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT	x	xx	x	x	xx	x	x	xx	x
	[PT 1]									
	[PT 2]									

Note: N = Number of subjects in the Safety Population. This table presents number and percentage of subjects. For each time point, a subject is only counted once per PT.

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14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 35: Listing of Serious Adverse Events

Adverse Event	Associated with Enema No.	No. of Days Post Associated Enema (Duration)	No. of Days Post Enema the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:												
Comments:												
Subject ID: , Treatment Group: , AE Number:												
Comments:												

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Table 36: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Adverse Event	Associated with Enema No.	No. of Days Post Associated Enema (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

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Table 37: Listing of Other Significant Adverse Events

Adverse Event	Number of Enemas Received at Time of Event	No. of Days Post Associated Enema	Duration of Event	Severity	MedDRA System Organ Class	AESI?	NOCMC?	New Onset Metabolic Syndrome?	Relationship	Outcome
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

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14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 38: Listing of Abnormal Laboratory Results - Chemistry

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

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Table 39: Listing of Abnormal Laboratory Results - Hematology

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 40: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Any Chemistry Parameter Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP											
Day 9	FMPE											
	FMPP											
Day 30	FMPE											
	FMPP											
Day 60	FMPE											
	FMPP											
Day 365	FMPE											
	FMPP											
Max Severity Post Baseline	FMPE											
	FMPP											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

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Table 41: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Potassium

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP																	
Day 9	FMPE																	
	FMPP																	
Day 30	FMPE																	
	FMPP																	
Day 60	FMPE																	
	FMPP																	
Day 365	FMPE																	
	FMPP																	
Max Severity Post Baseline	FMPE																	
	FMPP																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

Tables with similar format:

Table 42: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Creatinine

Table 43: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Alanine Aminotransferase

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Table 44: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Potassium

		FMPE (N=XX) Baseline				FMPP (N=X) Baseline			
Time Point	**Grade**	**Normal n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Normal n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Day 9	None	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Mild	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Moderate	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Severe	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Day 30	None								
	Mild								
	Moderate								
	Severe								
Day 60	None								
	Mild								
	Moderate								
	Severe								
Day 365	None								
	Mild								
	Moderate								
	Severe								

Tables with similar format:

Table 45: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Creatinine

Table 46: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Alanine Aminotransferase

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Table 47: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Potassium

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	FMPE	x	xx.x	xx.x	xx.x	xx.x, xx.x
	FMPP					
Day 9	FMPE					
	FMPP					
Day 9, Change from Baseline	FMPE					
	FMPP					
Day 30	FMPE					
	FMPP					
Day 30, Change from Baseline	FMPE					
	FMPP					
Day 60	FMPE					
	FMPP					
Day 60, Change from Baseline	FMPE					
	FMPP					
Day 365	FMPE					
	FMPP					
Day 365, Change from Baseline	FMPE					
	FMPP					

Note: N=Number of subjects in the Safety Population

Tables with similar format:

Table 48: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Creatinine

Table 49: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Alanine Aminotransferase

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14.3.5.2 Hematology Results

Table 50: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Any Hematology Parameter Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP											
Day 9	FMPE											
	FMPP											
Day 30	FMPE											
	FMPP											
Day 60	FMPE											
	FMPP											
Day 365	FMPE											
	FMPP											
Max Severity Post Baseline	FMPE											
	FMPP											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

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Table 51: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Hemoglobin

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP											
Day 9	FMPE											
	FMPP											
Day 30	FMPE											
	FMPP											
Day 60	FMPE											
	FMPP											
Day 365	FMPE											
	FMPP											
Max Severity Post Baseline	FMPE											
	FMPP											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

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Table 52: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – White Blood Cell Count

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP																	
Day 9	FMPE																	
	FMPP																	
Day 30	FMPE																	
	FMPP																	
Day 60	FMPE																	
	FMPP																	
Day 365	FMPE																	
	FMPP																	
Max Severity Post Baseline	FMPE																	
	FMPP																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Tables with similar format:

Table 53: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Platelets

Table 54: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Neutrophils

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Table 55: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Hemoglobin

		FMPE (N=XX) Baseline				FMPP (N=XX) Baseline			
Time Point	**Grade**	**Normal n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Normal n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Day 9	None	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Mild	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Moderate	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Severe	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Day 30	None								
	Mild								
	Moderate								
	Severe								
Day 60	None								
	Mild								
	Moderate								
	Severe								
Day 365	None								
	Mild								
	Moderate								
	Severe								

Tables with similar format:

Table 56: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – White Blood Cell Count

Table 57: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Platelets

Table 58: Laboratory Shift Table by Parameter, Time Point, and Treatment Group – Neutrophils

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Table 59: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hemoglobin

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	FMPE	x	xx.x	xx.x	xx.x	xx.x, xx.x
	FMPP					
Day 9	FMPE					
	FMPP					
Day 9, Change from Baseline	FMPE					
	FMPP					
Day 30	FMPE					
	FMPP					
Day 30, Change from Baseline	FMPE					
	FMPP					
Day 60	FMPE					
	FMPP					
Day 60, Change from Baseline	FMPE					
	FMPP					
Day 365	FMPE					
	FMPP					
Day 365, Change from Baseline	FMPE					
	FMPP					

Note: N = Number of subjects in the Safety Population

Tables with similar format:

Table 60: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – White Blood Cell Count

Table 61: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Platelets

Table 62: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Neutrophils

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14.3.6 Displays of Vital Signs

Table 63: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Any Assessment

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP											
Day 8	FMPE											
	FMPP											
Day 9	FMPE											
	FMPP											
Day 30	FMPE											
	FMPP											
Day 60	FMPE											
	FMPP											
Day 365	FMPE											
	FMPP											
Max Severity Post Baseline	FMPE											
	FMPP											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

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Table 64: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Temperature

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP											
Day 8	FMPE											
	FMPP											
Day 9	FMPE											
	FMPP											
Day 30	FMPE											
	FMPP											
Day 60	FMPE											
	FMPP											
Day 365	FMPE											
	FMPP											
Max Severity Post Baseline	FMPE											
	FMPP											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

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Table 65: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Systolic Blood Pressure

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	FMPE	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	FMPP																	
Day 8	FMPE																	
	FMPP																	
Day 9	FMPE																	
	FMPP																	
Day 30	FMPE																	
	FMPP																	
Day 60	FMPE																	
	FMPP																	
Day 365	FMPE																	
	FMPP																	
Max Severity Post Baseline	FMPE																	
	FMPP																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Tables with similar format:

Table 66: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Diastolic Blood Pressure

Table 67: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Pulse

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Table 68: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Temperature

[Implementation note: If additional enemas are given then additional rows will be added for time points post second enema.]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	FMPE	x	xx.x	xx.x	xx.x	xx.x, xx.x
	FMPP					
Day 8	FMPE					
	FMPP					
Day 8, Change from Baseline	FMPE					
	FMPP					
Day 9	FMPE					
	FMPP					
Day 9, Change from Baseline	FMPE					
	FMPP					
Day 30	FMPE					
	FMPP					
Day 30, Change from Baseline	FMPE					
	FMPP					
Day 60	FMPE					
	FMPP					
Day 60, Change from Baseline	FMPE					
	FMPP					
Day 365	FMPE					
	FMPP					
Day 365, Change from Baseline	FMPE					
	FMPP					

Note: N = Number of subjects in the Safety Population

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Tables with similar format:

Table 69: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Systolic Blood Pressure

Table 70: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Diastolic Blood Pressure

Table 71: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Pulse

Table 72: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Weight

Table 73: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Waist Circumference

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14.4 Summary of Concomitant Medications

Table 74: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	FMPE (N=X)		FMPP (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	Any [ATC 1 – 2]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						

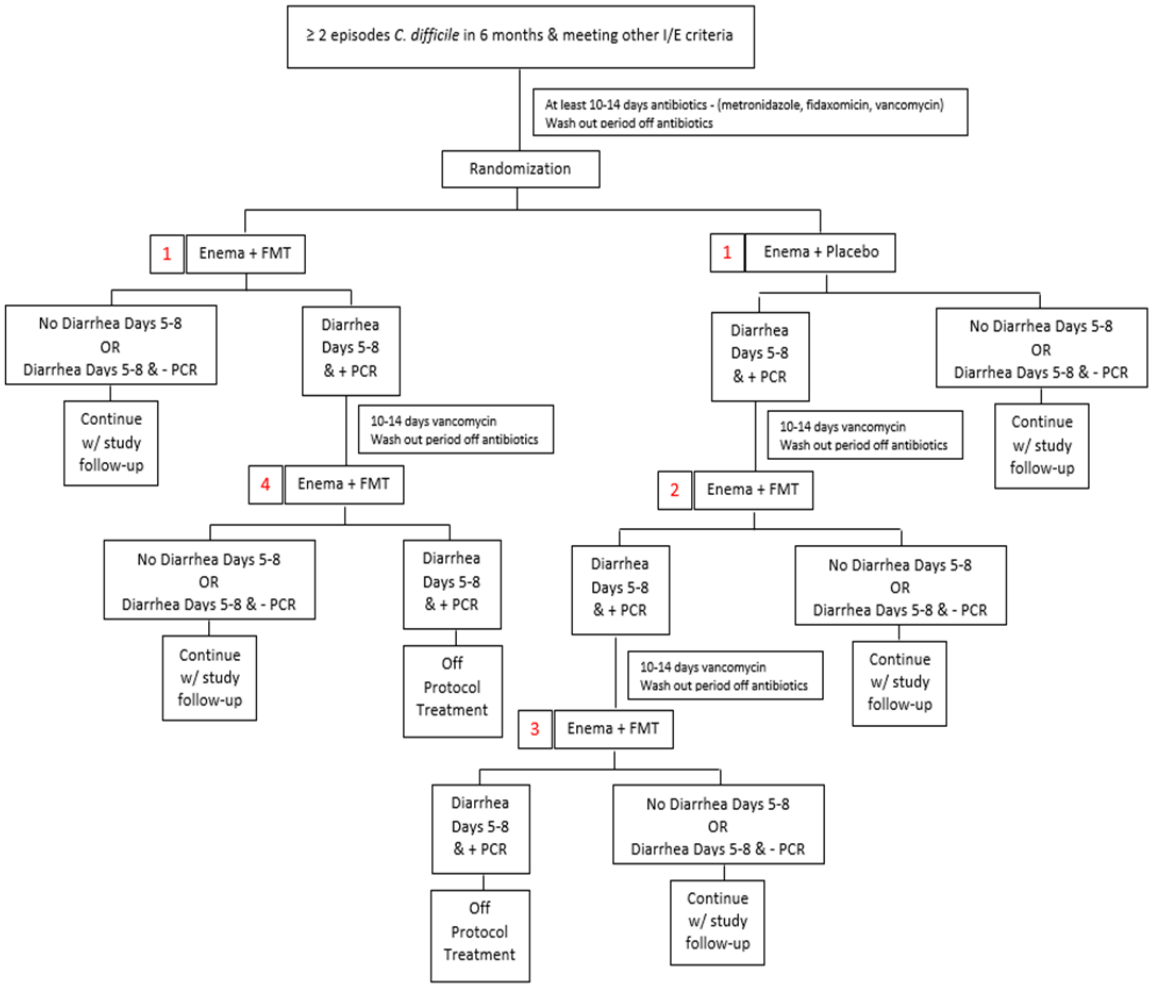
N = Number of subjects in the Safety Population; n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

9.1 Overall Study Design and Plan Description

Figure 1: Schematic of Study Design



Scenarios:

1= Receipt of placebo or FMT with no diarrhea or diarrhea with negative C. difficile testing by Day 8 after randomization.

2= Receipt of placebo with diarrhea and positive C. difficile testing Days 5-8 after randomization followed by no diarrhea or diarrhea with negative C. difficile testing by Day 8 after FMT.

3= Receipt of placebo with diarrhea and positive C. difficile testing Days 5-8 after randomization followed by diarrhea and positive C. difficile testing 5-8 days after first FMT.

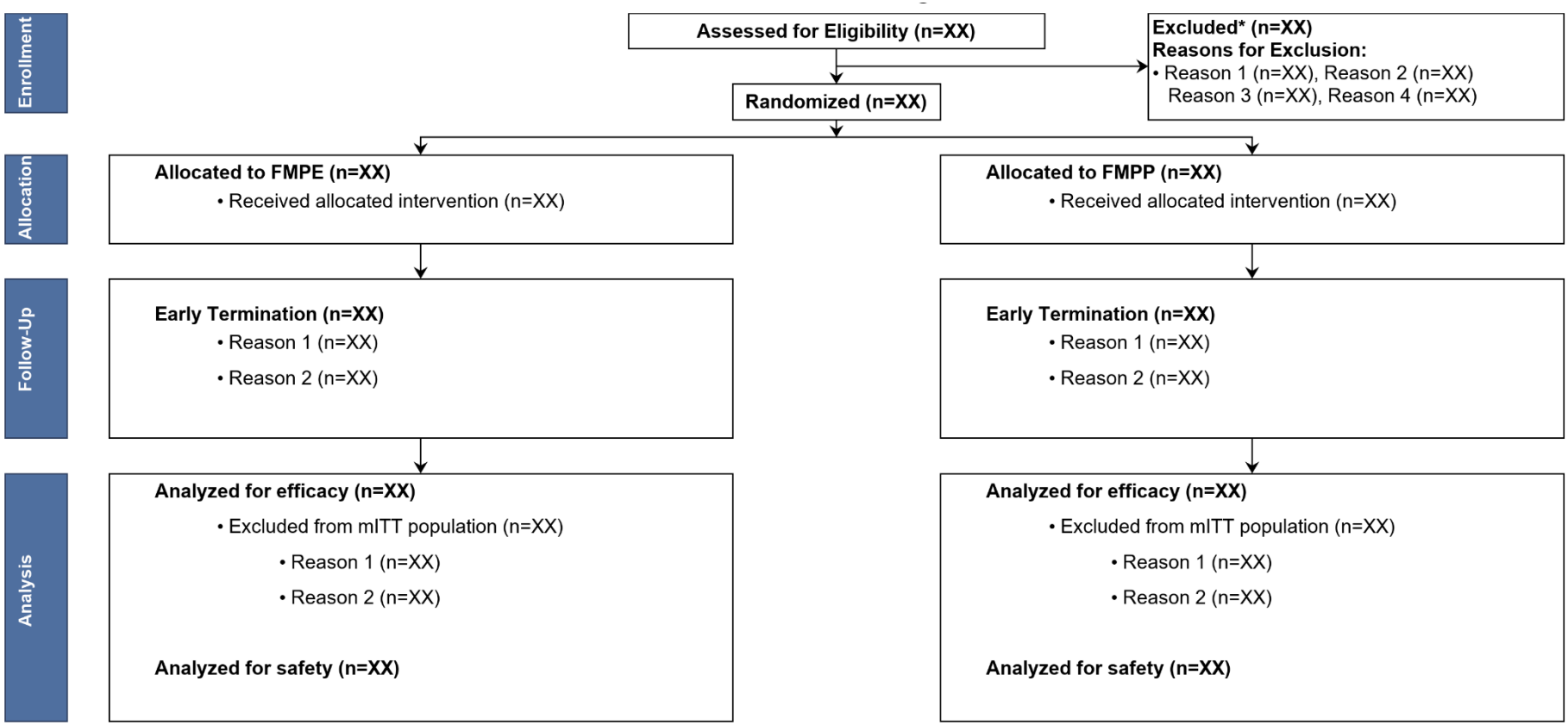
4= Receipt of FMT with diarrhea and positive C. difficile testing Days 5-8 after randomization

Note: If diarrhea develops after Day 8 and is C. difficile positive, a referral to standard medical care will be initiated and patient will follow up as needed

Washout period is defined as at least 2 days without CDAD treatment

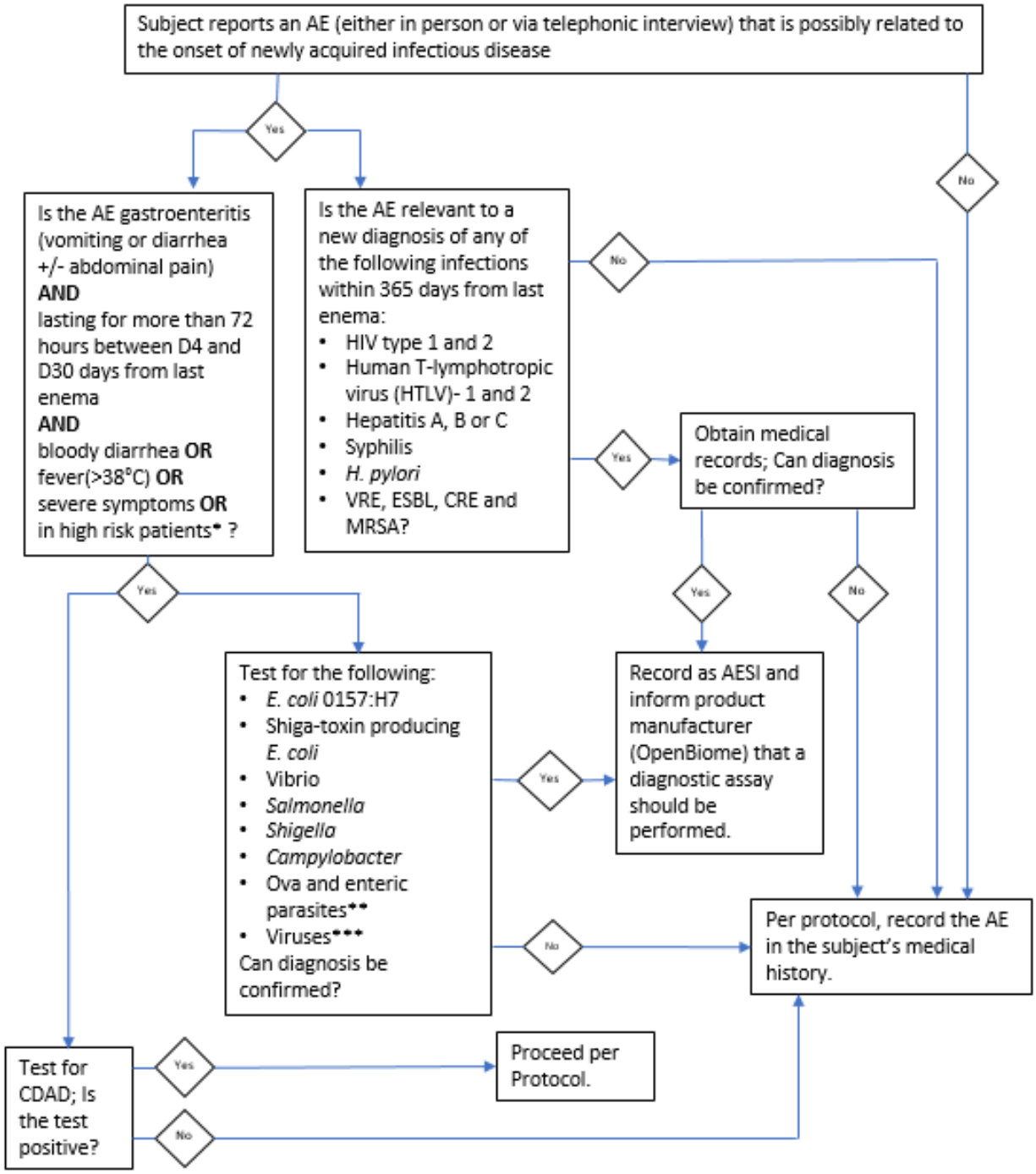
10.1 Disposition of Subjects

Figure 2: CONSORT Flow Diagram



12.2.2 Displays of Adverse Events

Figure 3: Algorithm for Adverse Events of Special Interest



*High risk patients include immunocompromised OR 70 years and above OR multiple comorbidities as determined by the investigator

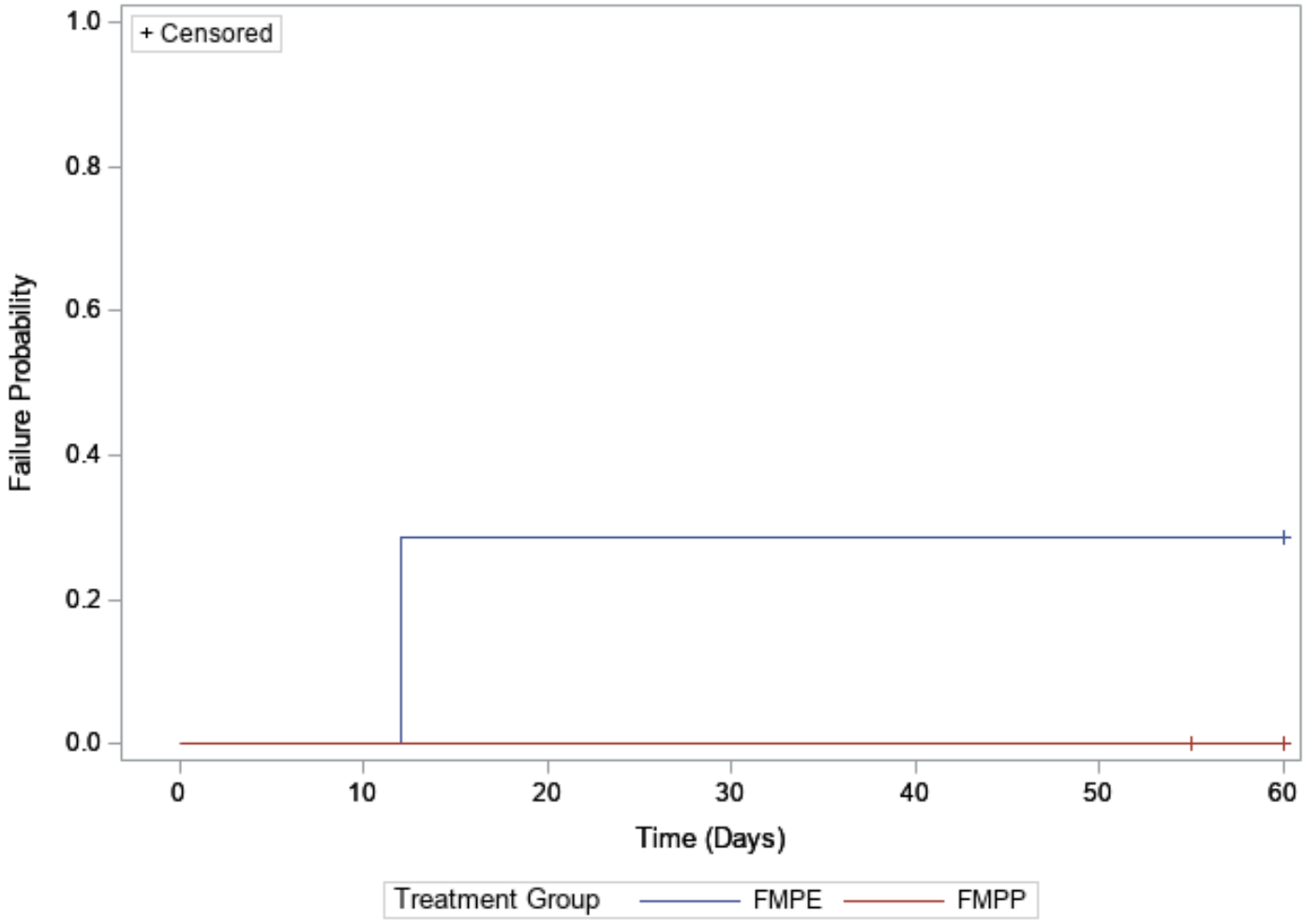
** Ova and enteric parasites include Cyclospora, Isospora, Giardia lamblia, Cryptosporidium and Microsporidia.

*** Viruses include Rotavirus, Adenovirus and Norovirus

14.2.2 Efficacy Response Figures by Measure, Treatment, and Time Point

Figure 4: Time to First CDAD Recurrence through Day 60

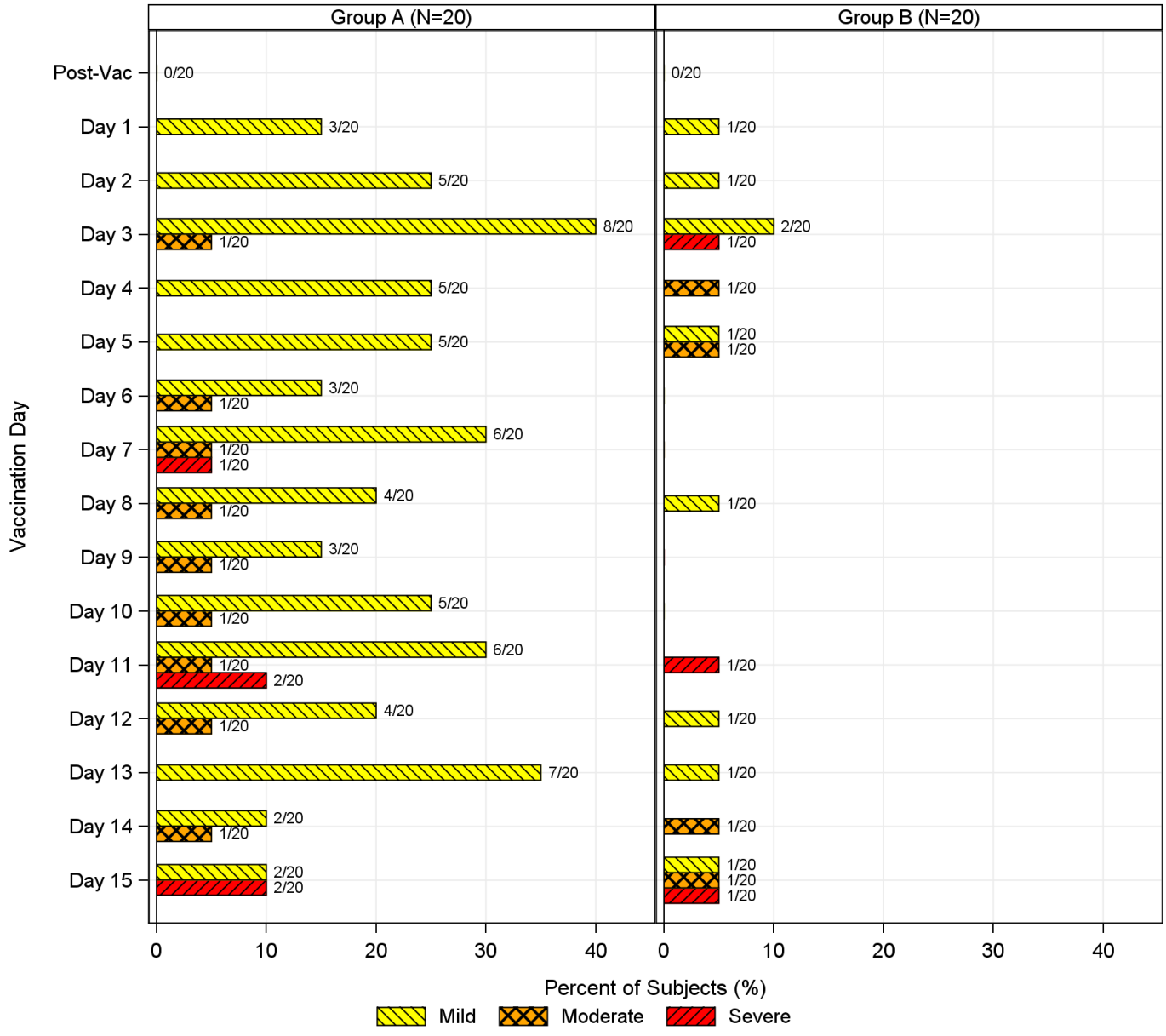
[Implementation note: The figure below is an example only. The y-axis will be labeled "CDAD Recurrence Probability".]



14.3.1.1 Solicited Adverse Events

Figure 5: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment and Treatment Group, Post Enema 1

[Implementation note: The figure below is an example only. The y-axis will be labeled "Post-Administration Day". The x-axis will indicate "Percentage of Subjects (%)". Each panel represents a treatment group with FMPE on the left and FMPP on the right.]



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14.3.1.2 Unsolicited Adverse Events

Figure 6: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[Implementation note: The figure below is an example only. This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending frequency. Each panel represents a treatment group with FMPE on the left and FMPP on the right.]

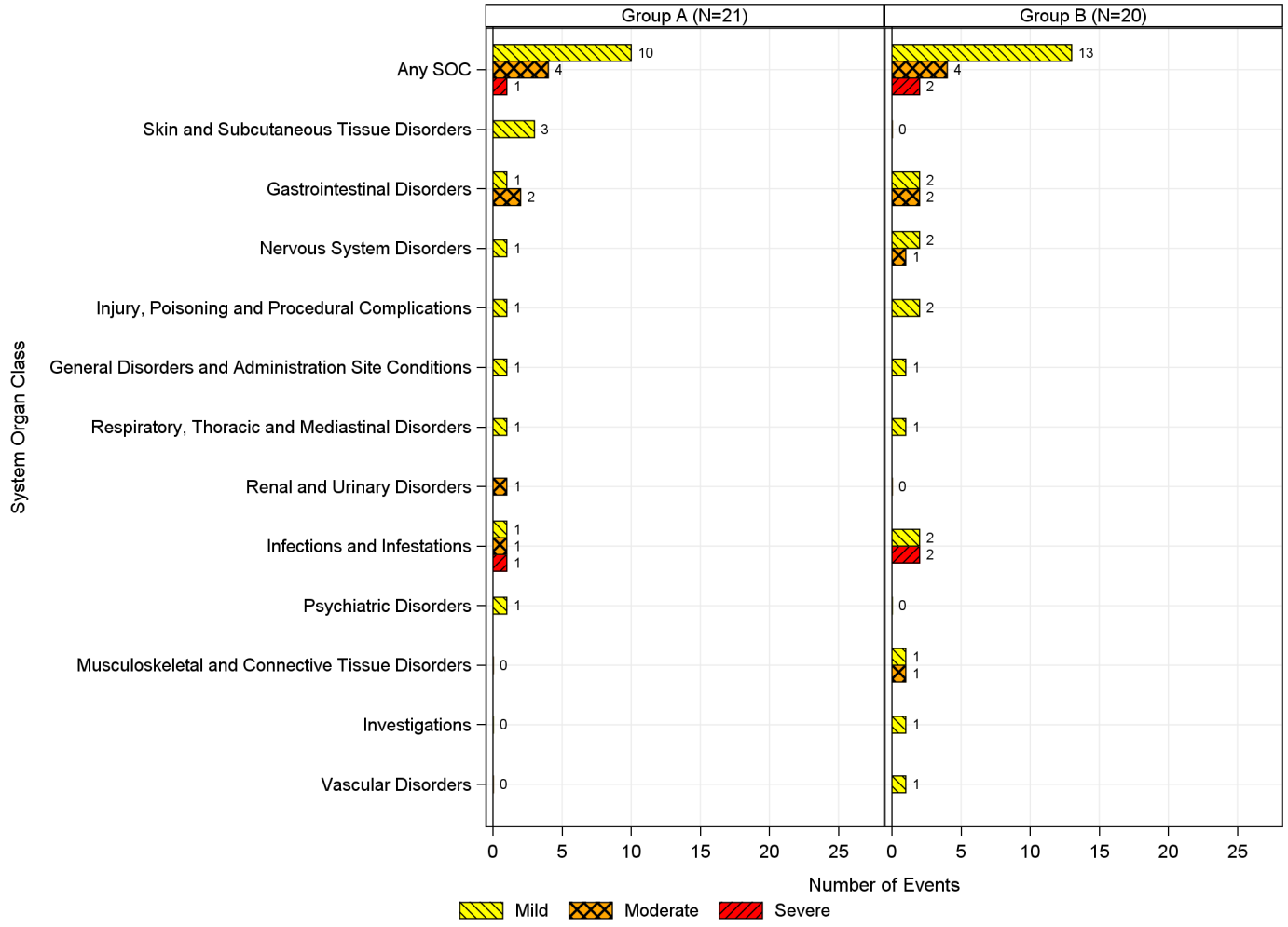
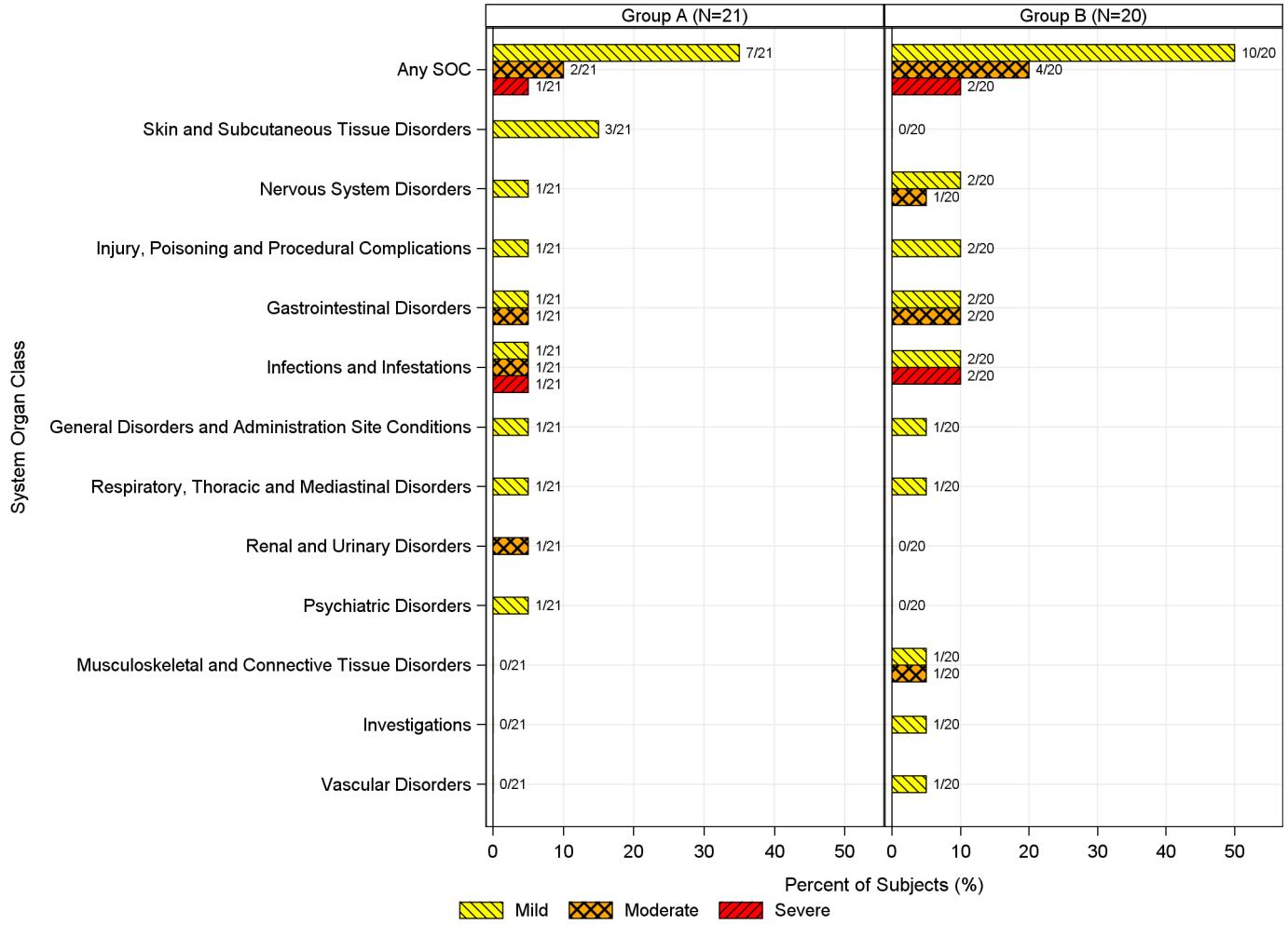


Figure 7: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

[Implementation note: The figure below is an example only. This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending incidence. Each panel represents a treatment group with FMPE on the left and FMPP on the right.]



APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

(not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
		[Category will be early termination or treatment discontinuation]		

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 3: 16.2.2.2: Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, mITT]	[e.g., Safety, mITT, Day x]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

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16.2.4 Demographic Data

Listing 5: 16.2.4.1: Demographic Data

Treatment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 6: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Listing 7: 16.2.5: Compliance and/or Drug Concentration Data

Not applicable.

16.2.6 Individual Efficacy Response Data

Listing 8: 16.2.6: Individual Efficacy Response Data

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	PCR Test Result	Toxin Assay Result

16.2.7 Adverse Events

Listing 9: 16.2.7.1: Solicited Events

Treatment Group	Subject ID	Enema Number	Post Enema Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
				MA				
				Clinic				

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
[b] Grade 3 events only.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

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Listing 10: 16.2.7.2: Stool Log

Treatment Group	Subject ID	Enema Number	Post-Enema Day	Collection Time	Consistency	Grade	Comments

Listing 11: 16.2.7.2: Emesis Log

Treatment Group	Subject ID	Enema Number	Post-Enema Day	Collection Time	Grade	Comments

Listing 12: 16.2.7.3: Unsolicited Adverse Events

Adverse Event		Associated with Enema No.	No. of Days Post Associated Enema (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
	Treatment Group: , Subject ID: , AE Number:											
	Comments:											
	Treatment Group: , Subject ID: , AE Number:											
	Comments:											

Note: For additional details about SAEs, see Table: xx.

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16.2.8 Individual Laboratory Measurements

Listing 13: 16.2.8.1: Clinical Laboratory Results – Chemistry

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

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Listing 14: 16.2.8.2: Clinical Laboratory Results – Hematology

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

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Listing 15: 16.2.8.3: Clinical Laboratory Results – Metabolic Syndrome Markers

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result	Clinically Significant?	Relationship to Study Product	If Unrelated, Alternate Etiology	Subject Discontinued Due to Result

16.2.9 Vital Signs and Physical Exam Findings

Listing 16: 16.2.9.1: Vital Signs

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Weight (kg)	Height (cm)	Waist Circumference (cm)

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Listing 17: 16.2.9.2: Physical Exam Findings

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 18: 16.2.10: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

Listing 19: 16.2.11.1: Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 20: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.
[a] Preterm Birth
[b] Term Birth

Listing 21: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Note: Congenital Anomalies are included in the Adverse Event listing.												

Listing 22: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 23: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion

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