Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of a Single Infusion of Bezlotoxumab (MK-6072, Human Monoclonal Antibody to C. difficile Toxin B) in Children Aged 1 to <18 Years Receiving Antibacterial Drug Treatment for C. difficile Infection (MODIFY III)
NCT number:	NCT03182907
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Title Page

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of a Single Infusion of Bezlotoxumab (MK-6072, Human Monoclonal Antibody to C. difficile Toxin B) in Children Aged 1 to <18 Years Receiving Antibacterial Drug Treatment for C. difficile Infection (MODIFY III)

Protocol Number: 001-01

Compound Number: MK-6072

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

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Regulatory Agency Identifying Number(s):

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Approval Date: 07 February 2019

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment -01

Overall Rationale for the Amendment:

The main reason for this protocol amendment is to modify the enrollment strategy, as described in the Summary of Changes Table, with the aim of shortening the overall enrollment timelines.

Based on population pharmacokinetic (PK) considerations, the Sponsor considers it unlikely that a dose modification will be needed within an age cohort, and therefore the initially planned pause in enrollment after 12 participants have a complete set of PK samples in Panel A of an age cohort has been removed. Patients will continue to be enrolled in Panel A until the PK analysis is completed, and the dose has been confirmed, enrollment in Panel B of the age cohort will commence. Furthermore, the Sponsor considers it unlikely that PK data from Panel A of Age Cohort 1 (12 to <18 years of age) will result in a modification of the planned dose (10 mg/kg) for Age Cohort 2 (1 to <12 years of age), and therefore enrollment in Panel A of Age Cohort 2 will commence after the first 12 participants in Panel A of Age Cohort 1 have completed all study visits. There is no change in the 2 planned evaluations of safety data to be conducted by the Data Monitoring Committee (DMC) after the first 12 participants in Age Cohort 1 complete the study and after the first 12 participants in Age Cohort 2 complete the study.

Additional changes have been made as well, as outlined in the Summary of Changes table.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1.2 – Enrollment Strategy 5.2 – Number of Participants 5.5.1 – Starting Dose for This Trial 7.1 – Treatments Administered 7.2 – Dose Modification (Escalation/Titration/Other) 7.5.1 – Dose Preparation 10.1 – Statistical Analysis Plan Summary 10.5.3 – Efficacy Population	The enrollment strategy has been modified as follows: • Enrollment into Age Cohort 2 will be initiated after 12 participants in Age Cohort 1 Panel A have completed all study visits. The initial dose for Age Cohort 2 will be 10 mg/kg. • Enrollment into Panel A of each age cohort will not be paused during the time PK assessments in each age cohort are conducted.	This change will shorten the overall enrollment period by removing the enrollment pauses that were initially planned for the PK evaluation and the DMC safety review. Blinded safety information from the trial is reviewed by the Sponsor on an ongoing basis to identify any unexpected safety findings; therefore, safety oversight will not be impacted. An evaluation of safety data from the first 12 participants in each age cohort who complete the study will still be conducted by the DMC as planned in the original version of the protocol. Based on the adult population PK studies, neither intrinsic factors (including age) nor extrinsic factors affect the efficacy or safety of bezlotoxumab. The weight-based dose (10 mg/kg) adequately controls for differences in bezlotoxumab pharmacokinetics related to body weight. An evaluation of PK data from approximately 12 participants in each age cohort who provide all protocol-required serum samples for PK analysis will still be performed to determine if dose modifications are needed for that age cohort. Enrollment into Panel A will continue while this evaluation is performed, as it is unlikely that the doses will need to be modified in the older age cohort based on the age range, mechanism of action, PK properties, and/or the established exposure-response relationships. Moreover, it is unlikely that data from 12 to <18-year-old adolescents will inform dosing information in the younger age cohort. Thus, there is no need to wait for the PK evaluation in the older cohort before initiating enrollment in the younger cohort.

Section # and Name	Description of Change	Brief Rationale
6.1 – Inclusion Criteria Appendix 5 – Contraceptive Guidance and Pregnancy Testing	• Added language to clarify that contraception methods classified as "acceptable" (ie, with a failure rate of >1% per year when used consistently and correctly) are sufficient for use in this study.	• This change was made to ensure it is clear that agreement to use a highly effective method of contraception is not required to participate in this study.
	• Added language in Table 14 to specify that acceptable contraceptive methods include progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.	• This change was made to allow for the use of progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, as an acceptable contraceptive method, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines.
	• Deleted the sentence in the Note in the Table 14 footnotes that stated, "Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies."	• Note was deleted to remove potential ambiguity about the choice of study-permitted contraceptive measures.
	• Corrected footnote "a" in Table 14 as follows: "Typical use failure rates are ~~lower~~ **higher** than perfect-use failure rates…"	• This change was made to correct a typo.
	• Deleted footnote "b" from Table 14, which stated, "If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment	• This footnote does not apply to this study treatment, as there is no known or expected interaction between bezlotoxumab and hormonal contraception.

Section # and Name	Description of Change	Brief Rationale
	period and for at least 12 weeks after the last dose of study treatment."	
	• Deleted footnote "c" from Table 14, which stated, "If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation."	• This footnote does not apply to this study treatment.
6.2 – Exclusion Criteria	Added exclusion of potential participants with a known hypersensitivity to any ingredients of bezlotoxumab.	This revision was implemented for consistency with the prescribing information in some markets that contraindicate the use of bezlotoxumab in patients with known hypersensitivity to any of the ingredients.

Section # and Name	Description of Change	Brief Rationale
6.2 – Exclusion Criteria 7.7 – Concomitant Therapy	Removed intravenous immune globulin (IVIG) as an excluded prior and concomitant treatment.	IVIG was originally excluded because this treatment contains a broad spectrum of antibodies and therefore has the theoretical potential to impact efficacy outcomes. However, efficacy is not the primary objective of this study, and participants who have received or may receive IVIG may still benefit from receiving bezlotoxumab. Excluding patients who have received IVIG but would otherwise be eligible decreases the pool of potential participants because some types of pediatric patients who have CDI receive IVIG due to their underlying condition. There are no anticipated safety concerns with the use of bezlotoxumab in participants who have received or will concomitantly receive IVIG. A supportive analysis of efficacy outcomes in an Efficacy Evaluable population has been added in this amendment; this population will exclude, among others, participants who receive IVIG.
6.2 – Exclusion Criteria	Clarified that surgery for CDI exclusion criterion is specific to surgery for the current CDI episode	Clarified so that participants who had surgery in the past for a prior episode of CDI are not excluded.
10.1 – Statistical Analysis Plan Summary 10.5.3 – Efficacy Population	Added an Efficacy Evaluable population.	Added such that supportive analyses of efficacy endpoints can be conducted in a subset of participants who do not have any important protocol deviations that may impact efficacy results (specific deviations will be determined prior to final unblinding of the database) or require any prior or concomitant treatment with IVIG.

Section # and Name	Description of Change	Brief Rationale
9 – Study Assessments and Procedures	Updated approximate total blood volume to be drawn over the 12 weeks of the trial from 21.5 mL to 29 mL.	Corrected to align with increased volume required for PK blood samples. The need for increased volume was identified after finalizing the original protocol and before enrolling the first participant in the trial. The maximum blood volume collected from each participant should be based on weight and should generally not exceed 1% of total blood volume on any 1 day or 3% of total blood volume (2.4 mL blood per kg of body weight) during a given 4-week trial period, unless appropriate justification is documented by the investigator.
9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Specified that *Clostridium difficile* infection (CDI) recurrence is not considered a reportable safety event unless it meets one or more SAE criteria.	CDI recurrence is being monitored as an efficacy endpoint and therefore does not also need to be reported as a nonserious AE.
9.3.7 – Events of Clinical Interest (ECI)	Specified that the ECI definition regarding AST, ALT, and bilirubin elevations is limited to postbaseline abnormalities that were not present at baseline or are clinically significantly worse than they were at baseline (as determined by the investigator).	Revised because participants with hepatic impairment are allowed to enroll in the trial, so it is important to clarify that baseline AST or ALT elevations will not be considered ECIs unless they clinically significantly worsen at a postbaseline time point.
2 – Schedule of Activities	Added weight measurement to screening visit.	Added to ensure adequate drug supply at site for future randomization and treatment.
6.1 – Inclusion Criteria 9.2.2 – Daily Diary	Specified that watery diarrhea corresponds to Bristol Stool Scale types 6 or 7.	Revised for clarity.

Section # and Name	Description of Change	Brief Rationale
7.6.1 – Compliance With Antibacterial Drug Treatment for CDI	Clarified that any interruptions (ie, not just those >1 calendar day) in the prescribed antibacterial drug treatment plan require documentation on the eCRF.	Revised for clarity.
9.1.11 – Calibration of Equipment	Revised text and removed list of critical equipment.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of study equipment.
9.2.1.1 – Assessment of Disease Severity	Revised definition of hypoalbuminemia from <20 mg to <2 g/dL.	Revision made to correct an inaccuracy.
12.2 – Appendix 2: Clinical Laboratory Tests	Removed % reticulocytes and phosphorous from the list of laboratory parameters.	These parameters are not needed for assessment of bezlotoxumab safety and tolerability or for assessment of CDI.

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1. Synopsis

Protocol Title:

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of a Single Infusion of Bezlotoxumab (MK-6072, Human Monoclonal Antibody to C. difficile Toxin B) in Children Aged 1 to <18 Years Receiving Antibacterial Drug Treatment for C. difficile Infection (MODIFY III)

Short Title:

Bezlotoxumab (MK-6072) versus placebo in children with CDI: MODIFY III

Objectives/Hypotheses and Endpoints:

The following objectives and endpoints will be evaluated in pediatric participants aged 1 year to <18 years who are receiving antibacterial drug treatment for *Clostridium difficile* infection (CDI):

Objective/Hypothesis	Endpoint
Primary	
1) Objective: To characterize bezlotoxumab pharmacokinetics (PK) in 2 age cohorts (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) of pediatric participants to support dose selection in this population. • Hypothesis: The area under the concentration-time curve from 0 to infinity (AUC_{0-inf}) of bezlotoxumab after treatment of 2 age cohorts of pediatric participants (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) with a single infusion of bezlotoxumab is similar when compared to the AUC_{0-inf} of bezlotoxumab after treatment of adult participants with a single infusion of 10 mg/kg bezlotoxumab, a dose demonstrated to be safe and efficacious in adults. That is, the true geometric mean ratios (GMRs, pediatric participants/adults) for AUC_{0-inf} of bezlotoxumab are contained in the clinical comparability bounds of (0.6, 1.6) in each of the age cohorts.	• The AUC_{0-inf} will be determined for each age cohort from bezlotoxumab serum concentration data.

2) Objective: To evaluate the safety and tolerability of a single infusion of bezlotoxumab as compared with a single infusion of placebo through 12 weeks following infusion.	• Proportion of participants experiencing adverse events (AEs) • Proportion of participants discontinuing study medication due to AEs
Secondary	
3) Objective: To estimate the proportion of participants who have a CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	• Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. CDI recurrence is assessed by the investigator using the criteria defined in Section 9.2.5.2.
4) Objective: To estimate the proportion of participants with sustained clinical response over a period of 12 weeks in participants who received a single infusion of bezlotoxumab or placebo.	• Proportion of participants with sustained clinical response over a period of 12 weeks. Sustained clinical response is defined as initial clinical response of the baseline CDI episode (assessed by the investigator using the criteria defined in Section 9.2.5.1) AND no CDI recurrence (Section 9.2.5.2) through Week 12.
5) Objective: To estimate efficacy (CDI recurrence and sustained clinical response) in the subset of participants at high risk of CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	• Proportion of participants who have a CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study medication infusion in the subset of participants at high risk of CDI recurrence. High risk is defined as meeting 1 or more of the following criteria **at or before randomization**: o Was immunocompromised (as defined in Section 9.1.4) o Had one or more episodes of CDI at any point prior to the baseline episode o Had a baseline CDI episode that met criteria for severe CDI (as defined in Section 9.2.1.1)

	○ Had *C. difficile* ribotype 027 isolated from a stool sample collected during the baseline CDI episode ○ Had received treatment with 1 or more systemic antibacterials known to increase the risk of CDI (during treatment of the baseline CDI episode). Systemic antibacterial agents are defined in Section 7.7.
6) Objective: To assess the incidence of infusion-related reactions in participants who received a single infusion of bezlotoxumab or placebo.	• Proportion of participants experiencing 1 or more infusion-related reactions within 24 hours following the start of the infusion. The definition of infusion-related reactions can be found in Section 9.3.7.1.
7) Objective: To assess the potential for bezlotoxumab to induce immunogenicity within 12 weeks following administration of a single infusion of bezlotoxumab.	• Proportion of participants with treatment-emergent positive antibodies to bezlotoxumab in serum through 12 weeks following a single dose of bezlotoxumab.

Overall Design:

Trial Phase	Phase 3
Clinical Indication	Prevention of recurrent CDI
Population	Male and female participants aged 1 year to <18 years with CDI will be enrolled in this trial.
Trial Type	Interventional
Type of design	Randomized (3:1 bezlotoxumab:placebo), placebo-controlled, parallel-group, multi-site, double-blind trial stratified by age cohort (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) and with sequential enrollment starting with Age Cohort 1
Type of control	Placebo control

Trial Blinding	Double-blind
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 36 months from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 192 (144 bezlotoxumab, 48 placebo) participants will be enrolled.

A list of abbreviations used in this document can be found in Appendix 1.

2. Schedule of Activities (SoA)

Trial Period:	Screening	Treatment[a]	Post-Treatment[a]						
Visit Number/Title	1 Screening	2	EOT[b]	3	4	5	6	Unscheduled 1[c]	Unscheduled 2[d]
Scheduled Day/Week and Window:	Variable[e]	Day 1	~48 hours after last dose of antibacterial drug treatment	Day 10 (±3 days)	Week 4 (Day 29 ±3 days)	Week 8 (Day 57 ±5 days)	Week 12 (Day 85 ±5 days)	Day 1 to Week 12 (Day 85 ±5 days)	Day 1 to Week 12 (Day 85 ±5 days)
Administrative Procedures									
Informed Consent/Assent	X								
Informed Consent/Assent for Future Biomedical Research	X								
Participant Identification Card	X								
Inclusion/Exclusion Criteria	X	X							
Medical History	X	X							
Prior/Concomitant Medication Review[f]	X[g]	X	X	X	X	X	X	X	X
Randomization		X[h]							
Bezlotoxumab/Placebo Infusion		X							
Efficacy Procedures									
Collect Stool Sample(s)[i]	X[j]							X[k]	
Investigator Assessment of Clinical Outcome			X[l]	X[m]	X[m]	X[m]	X[m]	X[m]	
Participant or Participant's Parent or Caregiver Complete Daily Diary		→	→	→	→	→	→		
Phone/Visit Contact[n]	→	→	→	→	→	→	→		
Safety Procedures									
Full Physical Examination	X[o]	X[o,p]					X		
Directed Physical Examination[q]				X	X	X		X	X
Height		X							
Weight	X	X[p]							
Vital Signs[r]	X	X[s]		X	X	X	X	X	X
Urine Pregnancy Test	X[t]	X[t]							
Hematology and Chemistry		X[p,u]		X[v]	X[v]			X[w]	X[v]
AE/SAE Review	X	X	X	X	X	X	X	X	X
Infusion-Related Reaction Monitoring		X[x]							

Trial Period:	Screening	Treatment[a]	Post-Treatment[a]						
Visit Number/Title	1 Screening	2	EOT[b]	3	4	5	6	Unscheduled 1[c]	Unscheduled 2[d]
Scheduled Day/Week and Window:	Variable[e]	Day 1	~48 hours after last dose of antibacterial drug treatment	Day 10 (±3 days)	Week 4 (Day 29 ±3 days)	Week 8 (Day 57 ±5 days)	Week 12 (Day 85 ±5 days)	Day 1 to Week 12 (Day 85 ±5 days)	Day 1 to Week 12 (Day 85 ±5 days)
Pharmacokinetics/Pharmacodynamics/Future Biomedical Research/Biomarkers									
Blood for Anti-Drug Antibody Levels and Neutralizing Antibody for Bezlotoxumab[i]	X				X		X		
Blood Sample for Bezlotoxumab Serum Concentration Assay for Pharmacokinetics[i]		X[y]		X	X	X	X		
Blood for Genetic Analysis[z]		X							

Abbreviations: AE = adverse event; CDI = *Clostridium difficile* infection; DNA = deoxyribonucleic acid; EOT = end of treatment with antibacterial drug for baseline episode of CDI; FBR = future biomedical research; SAE = serious adverse event; UBM = unformed bowel movement.

a. Timing of each trial period and of all visits except the EOT Visit is relative to the infusion of study medication (bezlotoxumab or placebo) on Day 1. Timing of the EOT Visit is relative to the end of antibacterial drug treatment for the baseline episode of CDI.

b. The EOT assessment can be conducted in person or via telephone.

c. Unscheduled Visit 1 to be conducted if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period after completion of antibacterial drug treatment for the baseline episode of CDI. The unscheduled visit should preferably occur within 2 days of the onset of diarrhea or UBMs.

d. Unscheduled Visit 2 to be conducted for any reason other than the onset of a new diarrhea episode (eg, AE assessment, premature withdrawal from the trial, if warranted).

e. Screening period can start as early as the first day of antibacterial drug treatment for the baseline episode of CDI and can extend as long as the last day of antibacterial drug treatment for the baseline episode of CDI.

f. For breast-fed participants, the mothers' prior and concomitant medications should also be recorded.

g. Prior medication use should be recorded for the 28 days prior to the onset of the baseline episode of CDI. Treatment(s) given for the most recent prior episode of CDI should be recorded even if the treatment ended more than 28 days prior to the onset of the baseline episode of CDI.

h. Screening and randomization may occur on the same day, as long as all trial entry criteria have been met. Randomization and study infusion must occur while the participant is receiving antibacterial drug treatment for the baseline episode of CDI. Study infusion is to be given on the day of randomization or as close as possible to the date on which the participant is randomized.

i. Leftover main study stool and serum will be stored for FBR if the participant consents to FBR.

j. Before screening, a stool sample must have tested positive by the local laboratory for toxigenic *C. difficile*. During screening, a new stool sample may need to be collected for study-specific testing. A new sample is not needed if aliquots of the same stool sample that was used for the pre-screening diagnosis are available. If the pre-screening diagnosis was based on a method that does not test for the presence of *C. difficile* toxin, a new test will need to be performed at the local laboratory prior to randomization to confirm the diagnosis. A list of acceptable tests is described in Appendix 7. An aliquot of the pre-screening stool sample or a sample obtained during screening will also be sent to the central laboratory.

k. After completion of antibacterial drug treatment for the baseline episode of CDI, if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period, a stool sample is to be collected and aliquots sent to both a local laboratory and the central laboratory (see Section 9.2.4).

l. The investigator will assess whether the participant has achieved initial clinical response (as defined in Section 9.2.5.1) approximately 48 hours after the last dose of antibacterial drug treatment for the baseline episode of CDI. This assessment can be performed via telephone contact or in person.

[m.] After completion of antibacterial drug treatment for the baseline episode of CDI, if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period, a clinical assessment will be performed to determine whether the criteria are met for a diarrhea recurrence or a CDI recurrence (as defined in Section 9.2.5.2).

[n.] Trial personnel will contact the participant or the participant's parent or caregiver at least 3 times per week during antibacterial drug treatment for the baseline episode of CDI for assessment of antibacterial drug treatment compliance. Trial personnel will also contact the participant or the participant's parent or caregiver approximately 24 hours after the end of the infusion to assess for infusion-related reactions. Trial personnel will contact the participant or the parent or caregiver twice weekly after the EOT Visit through Week 12 to ensure that the daily diary is maintained by the participant or the parent or caregiver. The information communicated by the participant or the parent or caregiver during the contact is to be recorded in the source documents.

[o.] If a full physical examination was previously performed as part of routine clinical management within 72 hours of screening or Day 1, those results can be used for the corresponding visit and a new physical examination for the trial is not required.

[p.] Must be collected before the start of study infusion.

[q.] Targeted to the participant's illness and complaints.

[r.] Heart rate, blood pressure, respiratory rate, body temperature, and, on Day 1 only, pulse oximetry.

[s.] To be collected within 30 minutes before the start of the infusion, 30 (±10) minutes into the infusion, and 30 (±10) minutes after the end of the infusion.

[t.] Required before study infusion for female participants for child-bearing potential (defined in Appendix 5). If results are positive, the participant should be excluded from trial participation.

[u.] If the site has hematology and serum chemistry results for the participant from a blood sample that was collected as part of non-trial-related, routine clinical management up to 72 hours pre-infusion, these results can be used in lieu of collecting a new sample on Day 1.

[v.] Laboratory assessments at discretion of investigator per presenting symptoms.

[w.] Directed hematology and directed chemistry parameters will be assessed at this visit (Appendix 2).

[x.] Monitoring for approximately 24 hours after the end of the study infusion (Section 9.3.7.1). This monitoring should include at least 1 hour of in-clinic monitoring.

[y.] A sample should be collected 2 hours (±15 minutes) after the end of the infusion.

[z.] This sample should be collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

3. Introduction

3.1 Study Rationale

This trial is intended to determine a dosing recommendation for bezlotoxumab in the pediatric population and will evaluate bezlotoxumab pharmacokinetics (PK), safety, tolerability, and efficacy in children with *Clostridium difficile* infection (CDI). The proposed trial will randomize children aged 1 to <18 years of age with a confirmed diagnosis of CDI who are receiving antibacterial drug treatment for CDI. Infants less than 1 year of age will not be evaluated due to challenges with accurate CDI diagnoses; during the first year of life, up to 70% of children have detectable levels of *C. difficile* in their stool yet are asymptomatic, and there is no evidence of an epidemiologic association between colonization and disease during this timeframe [Bryant, K. 2009].

The primary objectives of this trial are to evaluate the PK, safety, and tolerability of bezlotoxumab, and secondary objectives are to estimate the rates of CDI recurrence and sustained clinical response through 12 weeks following a single-dose infusion in participants with CDI aged 1 year to <18 years.

3.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on bezlotoxumab.

3.2.1 Pharmaceutical and Therapeutic Background

C. difficile is an anaerobic, spore-forming gram-positive bacillus that produces toxin A and toxin B [Voth, D. E. and Ballard, J. D. 2005] [Warny, Michel, et al 2005]. CDI occurs when toxigenic strains of *C. difficile*, either endogenous to the colon or exogenously acquired, flourish after disruption of the normal bacterial colonic flora – typically following exposure to antibiotics that alter the endogenous micro-ecology of the gut – and thus lead to clinically significant disease. The laboratory diagnosis of CDI requires the demonstration of toxigenic *C. difficile* or its toxins in stool. A number of different tests are used, including enzyme-linked immunoassays (EIAs) for toxins A and B; cell culture cytotoxicity assay; anaerobic culture followed by toxin detection; nucleic acid amplification tests using polymerase chain reaction (PCR), which detects the gene for toxin B; and EIA for the *C. difficile* common antigen glutamate dehydrogenase, which is typically followed by either a toxin test or a PCR test [Crobach, M. J., et al 2016].

CDI represents an important medical and health care burden. The incidence, severity, rate of complications (eg, ileus, toxic megacolon), and mortality of CDI in adults have increased dramatically in the US, Canada, and Europe over the last 10-15 years [Goorhuis, Abraham, et al 2008] [Gravel, Denise, et al 2009] [Loo, Vivian G., et al 2005] [Loo, Vivian G., et al 2006] [McDonald, L. Clifford, et al 2005] [Pepin, Jacques, et al 2005]. Similarly, CDI incidence rates in pediatric patients have increased over time [Kim, Jason, et al 2008] [Zilberberg, M. D., et al 2010]. Based on the most recent estimates from the Centers for Disease Control and

Prevention for 2011, the incidence of CDI in pediatric patients was 24.2/100,000 population whereas the incidence in those >65 years of age was 627.7/100,000 [Lessa, F. C., et al 2015]. The increased incidence in adult and pediatric patients is attributable in part to the emergence of the NAP1/BI/027 epidemic/hypervirulent strain [Kim, Jason, et al 2008] [Freeman, J., et al 2010].

The risk factors for CDI in pediatric patients appear similar to those for adults (eg, antibiotic use, multiple antibiotics use, and longer duration of hospital stay). In pediatric patients, CDI is also strongly associated with additional factors, namely malignancy, inflammatory bowel disease (IBD), and immune suppression [Pant, Chaitanya, et al 2013] [Hojsak, I., et al 2012] [Banaszkiewicz, Aleksandra, et al 2012] [Enoch, D. A., et al 2011]. The CDI risk appears to be highest in pediatric patients with malignancy [Enoch, D. A., et al 2011] [de Blank, P., et al 2013] [Price, Victoria, et al 2013] [Tai, E., et al 2011]. A case control study identified additional risk factors for pediatric CDI that include solid organ transplant, presence of gastrostomy or jejunostomy tube, receipt of fluoroquinolones, and lack of prior hospitalization; however, the last of these may be a result of control subjects who were hospitalized [Sandora, T. J., et al 2011]. In children, the majority of cases of CDI are community-onset or community-acquired [McFarland, L. V., et al 2016] [Lo Vecchio, A., et al 2016].

Symptoms of pediatric CDI include fever, profuse diarrhea, abdominal tenderness, abdominal distension, leukocytosis, volume depletion, electrolyte imbalance, and occasionally, pseudomembranous colitis. Most cases of pediatric CDI are typically mild in severity and self-limiting in nature. However, moderate to severe CDI does occur in pediatric patients and accumulating evidence indicates that hospital-onset pediatric CDI is associated with increased risk of death, longer length of stay, and higher costs as compared to community-onset CDI in children [Sammons, Julia Shaklee, et al 2013].

Treatment of pediatric patients with moderate to severe CDI typically involves discontinuation of predisposing antibiotics, supportive measures, and initiating antimicrobial therapy directed against *C. difficile* [Cooperstock, M. S., et al 2012]. Both metronidazole and oral vancomycin have been used as standard-of-care regimens to treat pediatric CDI [McFarland, L. V., et al 2016] [American Academy of Pediatrics 2015]. Fidaxomicin is a newer antibiotic, which received approval in 2011 in the US and other countries for treatment of CDI in adults; however, its safety and efficacy have not yet been established in pediatric patients.

One of the key challenges in the clinical management of CDIs in adults and children is to reduce the incidence of recurrent CDI; such recurrences in pediatric patients have been treated with tapered/pulsed administration of oral vancomycin, vancomycin followed by rifaximin, intravenous (IV) immunoglobulin, and therapy with other microorganisms, including fecal microbiota transplantation (FMT) [Kelly, Ciaran P. and LaMont, J. Thomas 2008]. The available limited data for pediatric CDI recurrence rates ranges from 7.5% to 38%, which is similar to that seen in adults [Lo Vecchio, A., et al 2016] [Kelsen, J. R., et al 2011] [Mezoff, E., et al 2011].

Bezlotoxumab (MK-6072) is a fully human monoclonal antibody (mAb) that binds to and neutralizes *C. difficile* toxin B. In Phase 3 trials in adults with CDI, bezlotoxumab significantly reduced CDI recurrence compared to placebo [Wilcox, M. H., et al 2017]. Bezlotoxumab is currently approved for use in adults for the reduction (United States) or prevention (European Union) of CDI recurrence in patients who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. Aside from bezlotoxumab, no other therapeutic or prophylactic biological agents or drugs to prevent CDI recurrences have been licensed to date, and bezlotoxumab is not approved for use in pediatric populations. In the context of the worsening CDI epidemic, there remains an unmet medical need for therapies to prevent CDI recurrence in the pediatric population.

Bezlotoxumab does not have antimicrobial activity and does not take the place of antibiotic therapy for CDI. Moreover, bezlotoxumab does not impact the initial efficacy of the antibiotics that are used to treat CDI because it is administered after the toxins have already caused damage to the gut lining and after antibiotics have already significantly reduced the amount of toxin present in the colon. When administered concurrently with antibacterial drug treatments for CDI (metronidazole, oral vancomycin, or fidaxomicin in adults), bezlotoxumab prevents recurrent infections by providing passive immunity against *C. difficile* toxin B produced by the outgrowth of persistent or newly acquired spores, thereby preventing new or further damage to the gut epithelium.

In order to determine a dosing recommendation for the pediatric population, the current trial was designed to assess the safety, tolerability, and PK of bezlotoxumab, and to estimate the efficacy of bezlotoxumab in participants 1 to <18 years of age.

3.2.2 Pre-clinical and Clinical Trials

Details of pre-clinical studies are described in the bezlotoxumab IB.

Seven adult clinical trials of bezlotoxumab alone or in combination with MK-3415 (actoxumab, mAb directed against *C. difficile* toxin A) have been completed and are described in the bezlotoxumab IB. There are no completed pediatric clinical trials at this time.

3.2.3 Ongoing Clinical Trials

There are no other ongoing adult or pediatric clinical trials involving bezlotoxumab at the time of approval of this protocol.

3.2.4 Information on Other Trial-Related Therapy

Participants will be receiving antibacterial drug treatment for CDI. Please see Section 7.1.1 for further details on antibacterial drug treatment (eg, doses and administration routes for metronidazole, oral vancomycin, or fidaxomicin) for this trial. The investigator should also refer to the local label for information about these antibacterial drug treatments. Please see Section 7.7 for concomitant medication exclusions.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation. In general, bezlotoxumab has a favorable risk-benefit profile and fulfills a significant unmet medical need for therapies to prevent CDI recurrence.

Efficacy data from 2 adult Phase 3 trials demonstrate that a single infusion of bezlotoxumab (10 mg/kg) given in combination with antibacterial drug treatment for CDI is superior to placebo in prevention of CDI recurrence through a 12-week at-risk period for recurrence, addressing an unmet medical need. The low incidence of CDI recurrence in the bezlotoxumab group and the treatment difference in CDI recurrence between the bezlotoxumab and placebo groups were clinically meaningful and highly consistent in each of the Phase 3 trials. The trials included a substantial number of participants (76%) with 1 or more risk factors for CDI recurrence; bezlotoxumab consistently lowered CDI recurrence rates compared with placebo across subgroups at high risk for CDI recurrence. In addition, superior efficacy of bezlotoxumab compared with placebo was demonstrated for the secondary endpoint of sustained cure in the integrated Phase 3 data. In an exploratory analysis of a subset of participants evaluated for up to 12 months following infusion of the trial medication, no bezlotoxumab-treated participants who had achieved sustained cure at the end of the 12-week main trial experienced a CDI recurrence in the subsequent 9 months, thereby providing evidence that the efficacy of bezlotoxumab observed in the main trial was due to prevention of CDI recurrence rather than a delay in onset of a recurrent episode.

In the Phase 3 program, the safety analysis was conducted using integrated data, in which 786 participants received bezlotoxumab, 777 participants received actoxumab + bezlotoxumab, and 781 participants received placebo. The totality of the safety data show that bezlotoxumab, when given with antibacterial drug treatment for CDI, does not increase the risks associated with administration of antibacterial drug treatment for CDI alone. Bezlotoxumab has a very low potential for immunogenicity, and bezlotoxumab administration did not result in the development of treatment-emergent anti-drug antibodies in the Phase 2 and 3 trials; it is therefore unlikely that anti-drug antibodies will compromise efficacy of the product.

The Sponsor considers that 10 mg/kg of bezlotoxumab is an appropriate starting dosage to provide the proper benefit:risk ratio evaluation in this trial based on the efficacy and safety profiles of bezlotoxumab as demonstrated in the Phase 3 trials for adults with CDI. As described elsewhere in the protocol (Section 5.1), provisions are in place to perform PK assessments of the 10 mg/kg dose of bezlotoxumab in Panel A of both age cohorts in the trial.

Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the accompanying IB and informed consent documents.

4. Objectives/Hypotheses and Endpoints

The following objectives and endpoints will be evaluated in pediatric participants aged 1 year to <18 years who are receiving antibacterial drug treatment for CDI:

Objective/Hypothesis	Endpoint
Primary	
1) Objective: To characterize bezlotoxumab PK in 2 age cohorts (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) of pediatric participants to support dose selection in this population. • Hypothesis: The area under the concentration-time curve from 0 to infinity (AUC_{0-inf}) of bezlotoxumab after treatment of 2 age cohorts of pediatric participants (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) with a single infusion of bezlotoxumab is similar when compared to the AUC_{0-inf} of bezlotoxumab after treatment of adult participants with a single infusion of 10 mg/kg bezlotoxumab, a dose demonstrated to be safe and efficacious in adults. That is, the true geometric mean ratios (GMRs, pediatric participants/adults) for AUC_{0-inf} of bezlotoxumab are contained in the clinical comparability bounds of (0.6, 1.6) in each of the age cohorts.	• The AUC_{0-inf} will be determined for each age cohort from bezlotoxumab serum concentration data.
2) Objective: To evaluate the safety and tolerability of a single infusion of bezlotoxumab as compared with a single infusion of placebo through 12 weeks following infusion.	• Proportion of participants experiencing adverse events (AEs) • Proportion of participants discontinuing study medication due to AEs

Objective/Hypothesis	Endpoint
Secondary	
3) Objective: To estimate the proportion of participants who have a CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	• Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. CDI recurrence is assessed by the investigator using the criteria defined in Section 9.2.5.2.
4) Objective: To estimate the proportion of participants with sustained clinical response over a period of 12 weeks in participants who received a single infusion of bezlotoxumab or placebo.	• Proportion of participants with sustained clinical response over a period of 12 weeks. Sustained clinical response is defined as initial clinical response of the baseline CDI episode (assessed by the investigator using the criteria defined in Section 9.2.5.1) AND no CDI recurrence (Section 9.2.5.2) through Week 12.
5) Objective: To estimate efficacy (CDI recurrence and sustained clinical response) in the subset of participants at high risk of CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	• Proportion of participants who have a CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study medication infusion in the subset of participants at high risk of CDI recurrence. High risk is defined as meeting 1 or more of the following criteria **at or before randomization**: o Was immunocompromised (as defined in Section 9.1.4) o Had one or more episodes of CDI at any point prior to the baseline episode o Had a baseline CDI episode that met criteria for severe CDI (as defined in Section 9.2.1.1) o Had *C. difficile* ribotype 027 isolated from a stool sample collected during the baseline CDI episode o Had received treatment with 1 or more systemic antibacterials known to increase the risk of CDI (during treatment of the baseline CDI episode). Systemic antibacterial agents are defined in Section 7.7.

Objective/Hypothesis	Endpoint
6) Objective: To assess the incidence of infusion-related reactions in participants who received a single infusion of bezlotoxumab or placebo.	• Proportion of participants experiencing 1 or more infusion-related reactions within 24 hours following the start of the infusion. The definition of infusion-related reactions can be found in Section 9.3.7.1.
7) Objective: To assess the potential for bezlotoxumab to induce immunogenicity within 12 weeks following administration of a single infusion of bezlotoxumab.	• Proportion of participants with treatment-emergent positive antibodies to bezlotoxumab in serum through 12 weeks following a single dose of bezlotoxumab.
Tertiary/Exploratory	
8) Objective: To estimate the proportion of participants who have a diarrhea recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	• Proportion of participants who have a diarrhea recurrence within 12 weeks of study medication infusion. Diarrhea recurrence is assessed by the investigator as defined in Section 9.2.5.2.
9) Objective: To explore the relationship between genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this trial.	

5. Study Design

5.1 Overall Design

This is a Phase 3, randomized, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the PK, safety, tolerability, and efficacy of a single infusion of bezlotoxumab in pediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for CDI.

Participants will be enrolled into 1 of the following 2 age cohorts:

- Age Cohort 1: 12 to <18 years of age
- Age Cohort 2: 1 to <12 years of age

Enrollment into the trial will begin with Age Cohort 1, and Age Cohort 2 will commence later; the timing for enrollment into each age cohort is described in Section 5.1.2.

At screening, eligible participants must have suspected or confirmed CDI, as described in Section 6.1, and be receiving or planning to receive a 10- to 21-day course of antibacterial drug treatment for CDI (Section 7.1.1).

Prior to randomization, participants' diagnosis of CDI must be confirmed by a positive stool test for *C. difficile* toxin (see Appendix 7 for assay requirements). Once the CDI diagnosis has been confirmed, participants will be randomly assigned to a treatment group in a 3:1 ratio (bezlotoxumab:placebo) and will receive a single IV infusion of either bezlotoxumab or placebo (Day 1). Note that the participant must still be receiving antibacterial drug treatment for CDI on the day of randomization/study infusion. Throughout the protocol, timing of assessments expressed as study day and study week is relative to receipt of study infusion, which is Day 1.

After receiving the study infusion, participants will be followed for 12 weeks (ie, 85 ± 5 days) for collection of blood samples for PK and immunogenicity assessments and monitoring of safety and tolerability parameters (clinical and laboratory AEs, vital sign measurements, physical examinations) and signs and symptoms (including clinical laboratory assessments, watery diarrhea or unformed bowel movements [UBMs], abdominal discomfort, and body temperature) to assess efficacy outcomes (including initial clinical response, diarrhea recurrence, and CDI recurrence) (Figure 1).

Each day throughout the 12-week follow-up period, participants or the participants' parents or caregivers will record in a paper diary whether the participant had watery diarrhea or UBMs in the previous 24 hours. If the participant has at least a single episode of watery diarrhea or UBMs, the participant or the participants' parents or caregivers will record the number of episodes, the participant's worst abdominal discomfort score, and the presence or absence of a fever (and the highest body temperature if a fever is present) during the previous 24 hours. The diary will be used as a tool for the investigator to use when performing efficacy outcome assessments and will be maintained as a source document. Daily diary entries will not be entered into the electronic data collection (EDC) system, with the exception of the specific information noted in Section 9.2.5.2.

Trial personnel will contact the participant or the participant's parent or caregiver at the following time points during the study:

- Approximately 24 hours after the end of the infusion to assess for infusion-related reactions.
- At least 3 times per week during antibacterial drug treatment for the baseline episode of CDI for assessment of antibacterial drug treatment compliance.

- Twice weekly after the End of Treatment (EOT) Visit through Week 12 to ensure that the daily diary is maintained by the participant or the parent or caregiver and to remind them to collect a stool sample if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period.

The information communicated by the participant or the parent or caregiver during the contact is to be recorded in the source documents.

Initial clinical response will be assessed by the investigator approximately 48 hours after the last dose of antibacterial drug treatment for the baseline episode of CDI (EOT Visit), as described in Section 9.2.5.1.

Diarrhea recurrence and CDI recurrence will be assessed by the investigator as described in Section 9.2.5.2 at each scheduled visit that occurs after the EOT Visit and at any unscheduled visits due to diarrhea. The investigator will review the diary to assess whether the protocol-specified criteria for diarrhea recurrence were met. If the criteria for diarrhea recurrence were met, a stool sample will be tested for *C. difficile* toxin, and the investigator will record whether the criteria for a CDI recurrence have been met.

Sustained clinical response will be derived from the investigator assessment of initial clinical response and CDI recurrence, as described in Section 10.4.3.

An independent data monitoring committee (DMC) will be appointed and will review the safety and tolerability data. There will be 2 planned reviews by the DMC, as described in Section 5.1.2, with additional information provided in Appendix 3.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Trial Diagram

The trial design is depicted in Figure 1.

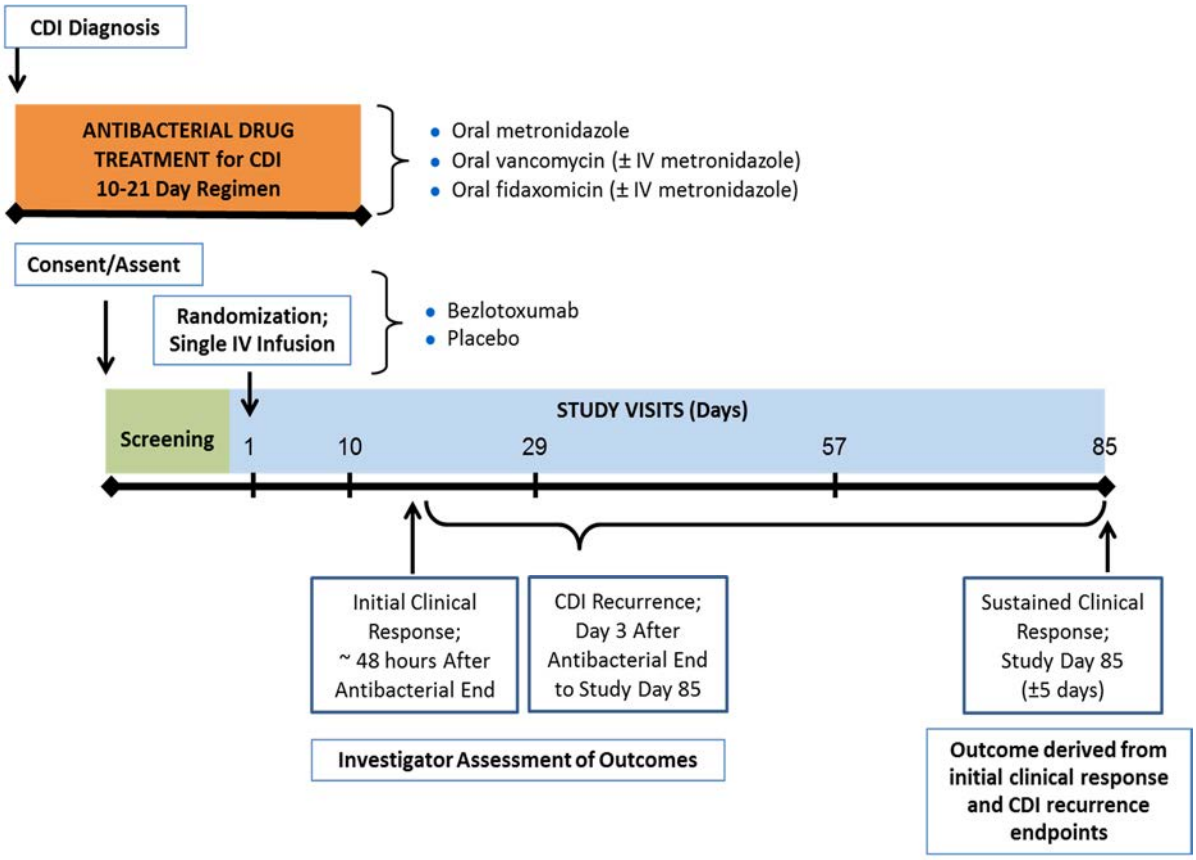

Figure 1 Diagram of Trial Design

5.1.2 Enrollment Strategy

Each age cohort will be enrolled in 2 panels (Panel A and Panel B), as shown in Figure 2. Enrollment will start with Age Cohort 1 participants. Enrollment into Age Cohort 2 Panel A will commence after approximately 12 participants in Age Cohort 1 Panel A complete all study visits.

The starting dose of bezlotoxumab for both age cohorts in Panel A will be 10 mg/kg body weight, which is the dose that has been shown to be effective in reducing recurrent CDI in adults.

When approximately 12 participants from Panel A of each age cohort have complete PK data, their PK data will be evaluated to determine whether dose modification is warranted for subsequent participants in the respective age cohort.

The PK evaluation will determine the following:

- If the criterion described in Section 7.2 is met, then participants enrolled subsequent to the PK evaluation will continue to receive the same dose (10 mg/kg) used in Panel A.

- If the criterion described in Section 7.2 is not met, the bezlotoxumab dose will be modified as needed (see Section 7.2), and participants enrolled subsequent to the PK evaluation will receive the modified bezlotoxumab dose.

Enrollment into Panel A of each age cohort will continue until the PK assessment is complete for that age cohort, at which point enrollment into Panel B of that age cohort will begin.

Safety and tolerability data will be reviewed by a DMC (Appendix 3) as follows:

- Data from Age Cohort 1 Panel A after 12 participants in this panel have completed all study visits through 12 weeks.

- Data from Age Cohort 2 Panel A after 12 participants in this panel have completed all study visits through 12 weeks, plus data from all Age Cohort 1 participants enrolled at that point in time.

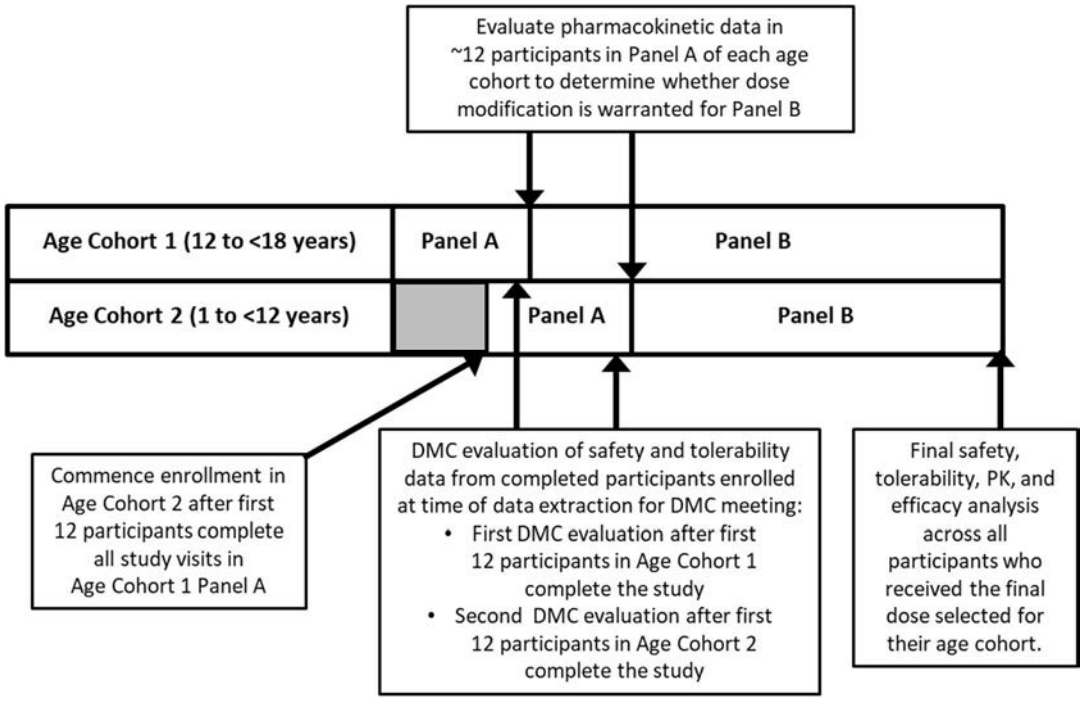

Figure 2 Enrollment Strategy

5.2 Number of Participants

In Panel A, for which the purpose is to determine the dose for each age cohort, a minimum of 24 participants across both age cohorts will be enrolled (Age Cohort 1 Panel A: 12 participants [9 bezlotoxumab, 3 placebo]; Age Cohort 2 Panel A: 12 participants [9 bezlotoxumab, 3 placebo]).

The trial will continue until trial enrollment has reached a total of 192 participants who received the final age-appropriate dose (Table 1). If the dose needs to be modified for either age cohort, then additional participants will be enrolled in Panel B in order to achieve a total of 192 participants who received the final age-appropriate dose.

There is no requirement to enroll an equal number of subjects across the 2 age cohorts. However, a minimum of 24 participants will be required to be enrolled in each age cohort at the final age-appropriate dose as follows:

- Age Cohort 1: 24 participants (18 bezlotoxumab at the final age-appropriate dose, 6 placebo);
- Age Cohort 2: 24 participants (18 bezlotoxumab at the final age-appropriate dose, 6 placebo), with a minimum of 12 participants (9 bezlotoxumab, 3 placebo) aged 1 to <6 years of age, and a minimum of 12 participants (9 bezlotoxumab, 3 placebo) aged 6 to <12 years of age.

If a dose modification is needed, the number of participants may be adjusted in order to ensure 192 participants receive the final age-appropriate dose.

Table 1 Number of Participants, Assuming Dose Modification is Not Required

	Panel A		**Panel B**					
				Minimum in Age Cohort 2				
	Age Cohort 1	**Age Cohort 2**	**Minimum in Age Cohort 1**	**1 to <6 years**	**6 to <12 years**	**Total Across Both Age Cohorts**	**Total Number of Participants**	**Total Number of Participants Who Receive Final Age-Appropriate Dose**
Number of Participants at Final Age-Appropriate Dose	≥12	≥12	24	12	12	168	192	192

5.3 Beginning and End of Study Definition

The overall trial begins when the first participant signs the informed consent/assent form. The overall trial ends when the last participant completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. If the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable.

2. At the recommendation of the DMC based on their evaluation of the ongoing study safety data and the resultant risk/benefit assessment.

3. Further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Pharmacokinetic Endpoints

The $AUC_{0\text{-}inf}$ of bezlotoxumab will be evaluated following a single IV dose from samples collected at time points through 12 weeks after the infusion, as specified in Section 2 – Schedule of Activities (SoA). Based on the shape of the concentration-time profile in adults and experience with this sampling scheme in the Phase 3 trials, the chosen sampling time points are anticipated to provide sufficient data for estimation of $AUC_{0\text{-}inf}$. In addition, maximum concentration (C_{max}), time of maximum concentration (T_{max}), terminal half-life, volume (V_{dss}), and clearance (Cl) will be evaluated for bezlotoxumab. These endpoints will be assessed for Panels A and B.

5.4.1.2 Safety Endpoints

The safety and tolerability of bezlotoxumab will be primarily assessed by clinical and laboratory AEs.

Bezlotoxumab is a mAb, and mAbs have been associated with acute hypersensitivity reactions, referred to hereafter as infusion-related reactions. Although these types of reactions were not observed in participants who received bezlotoxumab alone or in combination with actoxumab in the adult Phase 3 trials, it is important to continue to evaluate the potential for infusion-related reactions in a pediatric population because it is difficult to

detect potentially serious but low-frequency toxic effects. Therefore, the potential for bezlotoxumab to cause infusion-related reactions will be evaluated in the current trial (Section 9.3.7.1).

5.4.1.3 Efficacy Endpoints

The efficacy endpoints in this trial include the proportion of participants who have a CDI recurrence and the proportion of participants who achieve sustained clinical response within 12 weeks (Day 85 ± 5 days) of a single infusion of bezlotoxumab or placebo. CDI recurrence is assessed by the investigator as defined in Section 9.2.5.2, and sustained clinical response is derived from the investigator's assessment of initial clinical response and CDI recurrence, as defined in Section 10.4.3.

In the adult Phase 3 trials of bezlotoxumab, a follow-up period of 12 weeks for CDI recurrence was sufficient to allow for robust demonstration of the efficacy of bezlotoxumab. In these trials, 71% of all recurrences occurred by Week 4 while 29% of recurrences occurred in Weeks 5 through 12. In a subset of participants followed for 12 months, recurrences were rarely observed. Therefore, a minimum of a 12-week follow-up period is necessary to allow for robust assessment of efficacy, but a longer period is not warranted. A 12-week follow-up period will be used in this pediatric trial.

5.4.1.4 Planned Exploratory Biomarker Research

5.4.1.5 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

5.4.1.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for The Use of Comparator/Placebo

A placebo control treatment of either 0.9% sodium chloride or 5% dextrose will be included in the trial. These are the approved diluents for the preparation of the bezlotoxumab infusion solution.

Importantly, all participants (regardless of treatment group assignment) enrolled in this trial will receive antibacterial drug treatment for CDI (Section 7.1.1) concurrent with administration of trial infusion. Placebo participants will therefore be receiving current medically acceptable treatment for CDI. Use of a placebo allows for estimation of efficacy of bezlotoxumab and a comparison for safety assessments.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

The initial dose of the single, IV infusion of bezlotoxumab to be administered to Panel A of each age cohort is 10 mg/kg body weight. This dose demonstrated superior efficacy in prevention of CDI recurrence in the adult Phase 3 trials conducted among adults aged >18 years. This dose was also generally safe and well tolerated in adults.

Bezlotoxumab is catabolized through protein degradation processes; thus, metabolism does not contribute to its clearance and it is not eliminated by renal or biliary excretion. Consequently, the clearance of bezlotoxumab is not expected to be different in children compared with adults, except based on weight, which is accounted for by weight-based dosing. Hence, the 10 mg/kg dose is anticipated to be appropriate for children and to provide serum exposures similar to those observed in adults. However, the dose may be modified for Panel B of each age cohort based on PK evaluations performed during this trial (Section 7.2).

5.5.2 Maximum Dose/Exposure for This Trial

The maximum dose and exposure of bezlotoxumab during the trial will not exceed a single, 20 mg/kg IV dose of bezlotoxumab and the exposure associated with this dose previously observed in adults. As described in the bezlotoxumab IB, the maximum known tolerated dose in humans is 20 mg/kg. Based on PK data from children obtained in the initial panels and age cohorts in this trial, the starting dose may be increased to achieve serum exposures similar to those observed in adults receiving 10 mg/kg (Section 7.2).

5.5.3 Rationale for Dose Interval and Trial Design

The dose and trial design are similar to those for the Phase 3 bezlotoxumab clinical trials in adults, MK-3415A Protocol 001 and 002 trials, in which the safety and efficacy of bezlotoxumab was demonstrated, as summarized in the bezlotoxumab IB.

The key trial design differences between the current pediatric trial and the Phase 3 adult trials are as follows:

- Randomization is being stratified on the basis of age cohort instead of being stratified based on antibacterial drug treatment for CDI or hospitalization status,
- Allowed duration of antibacterial drug treatment for the baseline CDI episode has been increased to 21 days to increase the proportion of participants who achieve initial clinical response and are assessable for the CDI recurrence endpoint,
- Characterization of diarrhea recurrence (as defined in Section 9.2.5.2) has been changed,
- The laboratory diagnostic criteria for CDI at study entry and for CDI recurrences has been changed to require a test that detects toxin in the stool, and
- Clinical outcomes will be assessed by the investigator. To be consistent with study inclusion criteria, an outcome of CDI recurrence will require that treatment be given.

6. Study Population

Male and female participants between the ages of 1 and <18 years with CDI will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. At the time of screening, participant

    a. has suspected or confirmed CDI, as evidenced by the following:

        - had a change in normal bowel habits for 2 or more calendar days with either watery diarrhea (for participants using diapers or other type of fecal collection device, Bristol Stool Scale types 6 or 7) or at least 6 UBMs (eg, takes shape of container, or Bristol Stool Scale types 5, 6, or 7) within a 48-hour period, and

        - produced a stool sample that has tested positive for toxigenic *C. difficile* according to local diagnostic criteria.

    b. is receiving or is planning to receive a 10- to 21-day course of antibacterial drug treatment for CDI, which is defined as oral vancomycin, oral metronidazole, or oral fidaxomicin. Additionally, IV metronidazole may be given concurrently with oral vancomycin or oral fidaxomicin (see Section 7.1.1 for further details).

2. At the time of randomization/study infusion, participant:

    a. has a diagnosis of CDI confirmed by a diagnostic assay which detects the presence of *C. difficile* toxin in stool (see Appendix 7 for additional information regarding *C. difficile* assay requirements), and

    b. is still receiving antibacterial drug treatment for CDI.

Demographics

3. Participant is of either sex and of any race, and ≥1 year to <18 years of age at the time of randomization.

Female participants:

4. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
   OR
   b.) A WOCBP who agrees to use any contraceptive method listed in Table 14 in Appendix 5 (including those classified as "acceptable") from Day 1 through at least 12 weeks after the single infusion of study treatment.

Informed Consent/Assent

5. The participant (or legally acceptable representative [LAR] if applicable) provides written informed consent/assent for the trial. The participant or LAR may also provide consent/assent for Future Biomedical Research (FBR). However, the participant may participate in the main trial without participating in FBR.

Adherence to Study Procedures

6. Participant must be able to adhere to the study visit schedules.

7. Participant and/or parent or caregiver must be able to read, understand, and complete the daily diary (Section 9.2.2).

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has an uncontrolled chronic diarrheal illness such as, but not limited to, Crohn's disease, ulcerative colitis, or with a condition such that their normal 24-hour bowel movement habit is 3 or more UBMs. Participants with a history of IBD who are controlled (ie, had no recent active diarrhea/UBMs prior to current CDI episode) may be enrolled if in the opinion of the investigator, the symptoms are more likely due to CDI than a flare of the IBD.

2. Has a known hypersensitivity to bezlotoxumab, its active substance and/or any of its excipients (refer to the Investigator's Brochure for a list of excipients).

Prior/Concomitant Therapy

3. Participant for whom, at the time of randomization, the planned course of antibacterial drug treatment for CDI is longer than 21 days.

4. Participant has received any treatment or procedure listed in Table 2 within the indicated exclusion window.

Table 2 Prohibited Prior and Concomitant Treatments and Procedures at Time of Screening Visit and During Screening Period

Treatment/Procedure	Exclude if Given in the Window Indicated
Treatments	
Rifaximin	Within 14 days prior to receipt of study infusion
Nitazoxanide	Within 14 days prior to receipt of study infusion
Procedures	
Surgery for episode of CDI under treatment at time of randomization	Any time prior to screening or during screening period

Prior/Concurrent Clinical Study Experience

5. Participant has previously participated in this trial, has previously received bezlotoxumab, has received an experimental mAb against *C. difficile* toxin B, or has received a vaccine directed against *C. difficile* or its toxins.

6. Participant has received an investigational trial agent within the previous 30 days, or is currently participating in or scheduled to participate in any other clinical trial with an investigational agent during the 12-week trial period.

Other Exclusions

7. Participant is not expected to survive for 72 hours.

8. Participant has any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of the participant, would make it unlikely for the participant to complete the trial, or would confound the results of the trial.

9. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

6.3 Lifestyle Restrictions

Participant should not donate blood and/or blood products within 3 months following the trial medication infusion.

No other lifestyle restrictions are required in this trial.

6.3.1 Meals and Dietary Restrictions

There are no dietary restrictions for participants in this trial.

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions of caffeine, alcohol, or tobacco for participants in this trial.

6.3.3 Activity

There are no activity restrictions for participants in this trial.

6.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

In general, a participant who discontinues from trial treatment or withdraws from the trial will not be replaced. However, if a Panel A participant discontinues from the trial prior to the last PK blood sampling or had incomplete PK sampling and the collected PK data were determined to be insufficient to allow PK assessments, a replacement participant may be enrolled to replace the original participant. The replacement participant will receive the same treatment that the original participant was randomized to receive.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment(s) to be used in this trial are outlined below in Table 3.

Table 3 Study Treatment(s)

Study Treatment Name:	Bezlotoxumab (MK-6072)	Placebo
Dosage Formulation:	Sterile solution for IV infusion in 0.9% sodium chloride or 5% dextrose	0.9% sodium chloride or 5% dextrose
Unit Dose Strength(s):	25 mg/mL	Not applicable
Dosage Level(s):	10 mg/kg Starting dose for Panel A of each age cohort. Dose modification may be made for Panel B of each age cohort (Section 7.2).	Not applicable
Route of Administration:	IV infusion	IV infusion
Sourcing:	Sponsor	Trial site

All supplies indicated in Table 3 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

Bezlotoxumab or placebo (0.9% sodium chloride or 5% dextrose) is to be administered as a single IV infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter over approximately 60 (±10) minutes.

7.1.1 Antibacterial Drug Treatment for CDI

Participants enrolled in this study should be prescribed an antibacterial drug treatment regimen for CDI by the treating physician; acceptable treatments are oral vancomycin, oral metronidazole, or oral fidaxomicin. Additionally, IV metronidazole may be given concurrently with oral vancomycin or oral fidaxomicin.

Antibacterial drug treatment for CDI should be prescribed for a minimum duration of 10 days and a maximum duration of 21 days, including the duration of antibacterial drug treatment prior to the screening visit, during the screening period, and after the infusion of study treatment. If antibacterial drug treatment is switched, participants should still be prescribed a minimum of 10 days and a maximum of 21 days of total antibacterial drug

treatment for CDI (eg, if oral metronidazole is given as the primary agent initially, but then switched to oral vancomycin, the total antibacterial drug treatment duration with both therapies administered sequentially should total no more than 21 days).

Participants receiving IV metronidazole concurrently with oral vancomycin or oral fidaxomicin may be switched to the respective oral treatment alone when clinically warranted.

The first through the last day of each antibacterial drug treatment for CDI will be recorded in source documents and via the appropriate electronic case report form (eCRF). Also, all changes in antibacterial drug treatment (including changes in dosages) should be recorded.

Permitted antibacterial agents, routes, and dosages for the baseline episode of CDI are specified in Table 4. The choice of agent, dosing regimen, and treatment duration can be per institutional guidelines; however, any regimen not in accordance with those specified in Table 4 must be discussed with the Sponsor's Clinical Director; if this discussion does not result in the use of a protocol-specified regimen, then a valid clinical reason for deviating from the protocol-specified regimen must be documented.

The choice of agents, dosages, and treatment durations to treat a CDI recurrence during the 12-week follow-up period is at the discretion of the investigator; see Section 7.7 for additional details.

Table 4 Antibacterial Drug Treatment for Baseline Episode of CDI

Study Treatment Name:	Metronidazole	Vancomycin	Fidaxomicin
Dosage Level(s):	• 30 mg/kg body weight per day given as 3 or 4 divided doses, or 1.2 g to 1.5 g per day given as 3 or 4 divided doses. Total daily dose not to exceed 1.5 g per day.[a]	• 40 mg/kg body weight per day given as 3 or 4 divided doses, or 500 mg to 2 g per day given as 3 or 4 divided doses. Total daily dose not to exceed 2 g per day.[a]	• For participants ≤12.5 kg: 32 mg/kg body weight per day given as 2 divided doses[b] • For participants >12.5 kg: 400 mg per day given as 2 divided doses[b]
Route of Administration:	Oral[c] or IV infusion[d]	Oral[c,e]	Oral[c]
Sourcing:	Trial site	Trial site	Trial site

a. Sources: [American Academy of Pediatrics 2015] [Schutze, G. E. and Willoughby, R. E. 2013] [Cohen, S. H., et al 2010]; UpToDate [Internet].
b. Source: Optimer Pharmaceuticals LLC. In: ClinicalTrials.gov [Internet]. Safety, tolerability, and pharmacokinetics of fidaxomicin in pediatric subjects with *Clostridium difficile*-associated diarrhea (CDAD). Bethesda (MD): National Library of Medicine (US). 2000- [cited date 2017 Apr 05]. Available from: https://clinicaltrials.gov/ct2/show/NCT01591863?term=fidaxomicin&rank=7 NLM Identifier: NCT01591863.
c. May be administered via gastrostomy tube.
d. IV metronidazole may be administered concurrently with oral vancomycin or oral fidaxomicin.
e. May not be administered intravenously for CDI treatment.

7.2 Dose Modification (Escalation/Titration/Other)

As indicated in Section 7.1, the starting dose of bezlotoxumab for Panel A of each age cohort will be 10 mg/kg. As described in Section 5.1.2, data from approximately 12 participants in Panel A of each age cohort who have complete PK data will be reviewed and evaluated against the following criterion:

- Bezlotoxumab exposure in the relevant panel and age cohort is similar to that observed in adults, as determined by a 90% CI for the pediatric/adult $AUC_{0\text{-}inf}$ comparison within the clinical comparability bounds of (0.6, 1.6). These bounds have been established based on the clinical experience in the Phase 3 trials as reflecting the range of relative change in $AUC_{0\text{-}inf}$ that is expected to be clinically comparable to a 10 mg/kg dose in adult participants with respect to safety and efficacy. Differences in ratios of bezlotoxumab exposures that fall within this range are not considered clinically meaningful and do not warrant dose modification. It is important to note that the upper bound of 1.6 for bezlotoxumab reflects the limit of current clinical exposure.

As shown in Figure 3, if this criterion is met, then participants in Panel B of that age cohort will commence without dose modification. Alternatively, if this criterion is not met, then the dose will be modified to either a higher or a lower dose for participants enrolled subsequent to the PK evaluation based on results of modeling and simulation analyses (see Section 10.6.1).

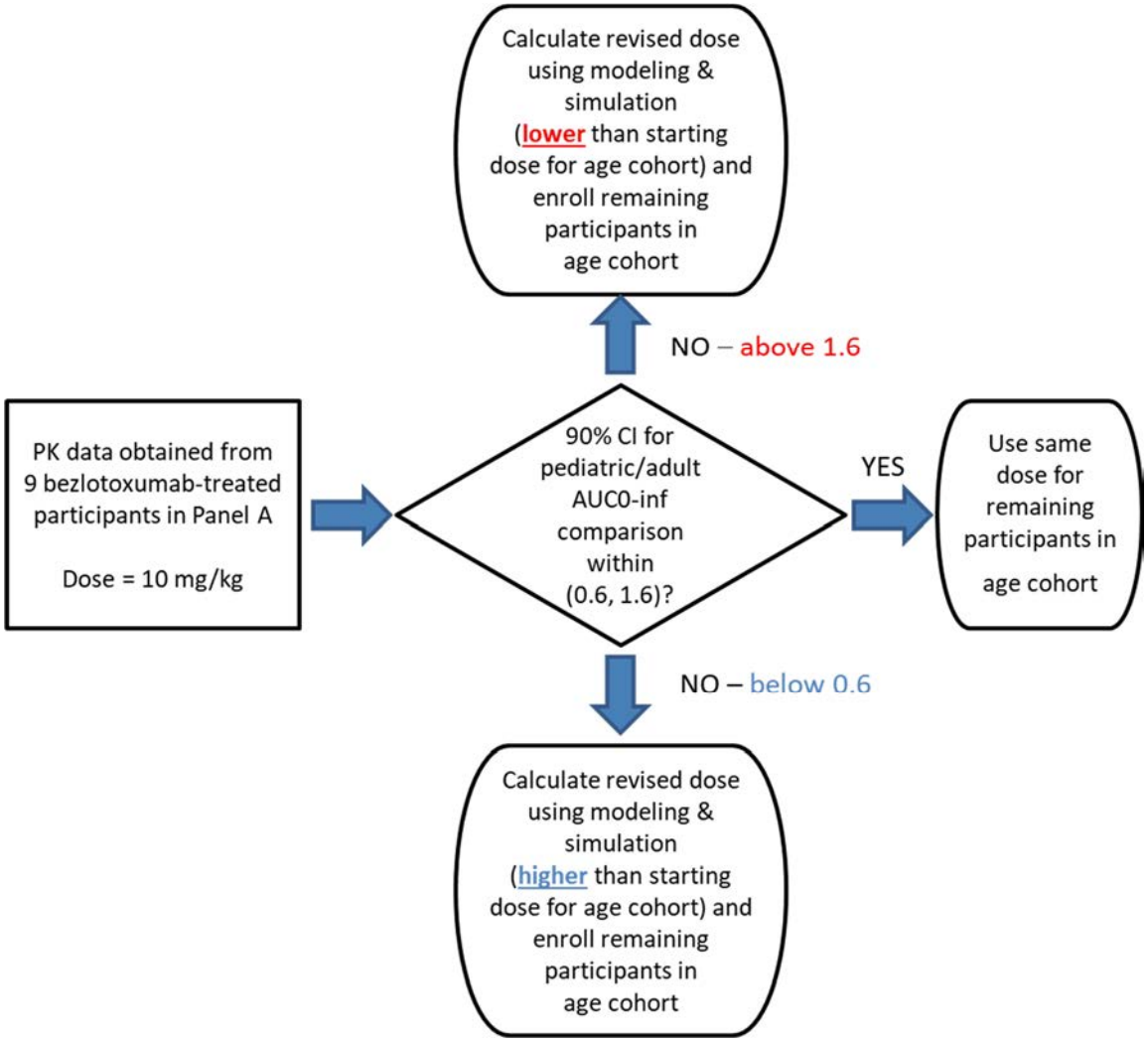

Figure 3 Bezlotoxumab Dose Modification

7.3 Method of Treatment Assignment

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 3:1 ratio to bezlotoxumab or placebo, respectively.

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Participant's age at the time of randomization:

    a. Age Cohort 1 (12 to <18 years of age)

    b. Age Cohort 2 (1 to <12 years of age).

7.4 Blinding

A double-blinding technique will be used. Bezlotoxumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.
See Section 9.1.10 for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The quantity of bezlotoxumab administered is based on the participant's actual body weight. The initial dose will be 10 mg/kg bezlotoxumab for participants in Panel A of each age cohort, and potential dose modifications are described in Section 7.2.

The required dose of bezlotoxumab will be diluted directly in 0.9% sodium chloride or 5% dextrose to comprise a total infusion volume such that the final concentration is between the range of 1 mg/mL and 10 mg/mL. For the preparation of placebo infusions, a weight-appropriate volume of 0.9% sodium chloride or 5% dextrose solution will be given as an IV infusion. Additional details will be provided in the Operational Manual.

In order to maintain the blind, the unblinded pharmacist (or qualified study site personnel designated to prepare the IV supplies) will be responsible solely for the preparation of the IV study therapy. He/She will not be involved in evaluating participants for efficacy or safety. Due to a slight difference in appearance of the bezlotoxumab diluted solution compared with 0.9% sodium chloride and 5% dextrose, an opaque sleeve will be placed over the infusion bag or syringe to maintain the blind.

The product does not contain preservative. The diluted solution of bezlotoxumab may be stored either at room temperature for up to 16 hours or under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 24 hours. If refrigerated, allow the diluted solution to come to room temperature prior to use. These time limits include storage of the infusion solution through the duration of infusion. Do not freeze the diluted solution.

7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

For all participants, the blinded trial staff will be responsible for administration of trial medication, which will be recorded in the participant's eCRF.

7.6.1 Compliance With Antibacterial Drug Treatment for CDI

From the signing of the ICF through the last scheduled day of antibacterial drug treatment for the baseline episode of CDI, the study personnel will have contact by phone or in person with the participant or the participant's parent or caregiver to obtain the compliance with the antibacterial drug treatment for CDI at least 3 times per week. If the antibacterial drug

treatment is being administered in an inpatient or other institutional settings in which medication administration records are routinely kept, then study personnel will transfer the administration records from the participant's chart into the corresponding telephone contact source document worksheet of the participant for the purposes of this trial.

Any interruptions from the prescribed antibacterial drug treatment plan require documentation on the eCRF.

7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the timeperiods specified by this protocol for that medication or vaccination, unless administered to treat a CDI recurrence, as noted below. The investigator should discuss any intended use of these medications as prophylactic or pre-emptive therapy or use for another indication (e.g., metronidazole for intra-abdominal infection) with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

The medications in Table 5 are prohibited during the timeframes specified in the table, unless administered to treat a CDI recurrence (as defined in Section 9.2.5.2), or if the participant is considered a clinical failure (as defined in Section 9.2.5.1).

Table 5 Prohibited Concomitant Treatments and Procedures During the Trial (Day 1 through Day 85 ± 5 days)

Prohibited Timing of Treatment or Procedure	Treatment/Procedure
From study infusion through 12-week trial period	• Cholestimide (>24-hour regimen) • Cholestyramine (>24-hour regimen) • Experimental monoclonal antibody against *C. difficile* toxin B or vaccine directed against *C. difficile* • Fecal microbiota transplantation (FMT)[b] • Nitazoxanide • Rifaximin • *Saccharomyces boulardii* (probiotic) • Teicoplanin (oral or rectal)[a] • Tigecycline[b] • Any other treatments not currently specified in the protocol that have been shown to decrease CDI recurrence

Prohibited Timing of Treatment or Procedure	Treatment/Procedure
From end of antibacterial drug treatment for the baseline CDI episode through 12 week trial period	• Fidaxomicin[a] • Metronidazole[b] • Vancomycin (oral or rectal)[a]

[a.] Discuss prophylactic or pre-emptive use for CDI with Sponsor Clinical Director.
[b.] Discuss prophylactic or pre-emptive use for CDI or use for another indication (eg, intra-abdominal infection) with Sponsor Clinical Director.

Medications given to decrease gastrointestinal peristalsis, such as loperamide (Imodium™) or diphenoxylate hydrochloride/atropine sulfate (Lomotil™), are prohibited as treatments for CDI recurrences throughout the 12-week trial period.

The use of investigational study agents during the 12-week trial period is prohibited.

The use of systemic antibacterial agents, defined as an antibiotic given via a route that results in therapeutic concentrations in the systemic circulation, is permitted before and after randomization.

Refer to Section 9.1.5 for recording of relevant prior and concomitant medications in the eCRF.

7.7.1 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

This trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Study treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 9.1.10). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the single infusion (ie, participants who receive a partial dose) will still continue to participate in the study as specified in Section 2 - SoA and Section 9.1.9 – Withdrawal/Discontinuation.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.

For participants who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Participants may be allowed to begin study treatment again if deemed medically appropriate; that is, if there is an interruption in the 1-hour infusion for any reason, the infusion can be re-started if medically acceptable.

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study including the procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation.

8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit.. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (e.g. phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The approximate total blood volume to be drawn over the 12 weeks of the trial is 29 mL. The maximum volume of blood drawn on any 1 day is 7 mL; this is within approximately 1% of total blood volume (0.8 mL blood per kg of body weight) for the majority of eligible subjects

in this study (ie, starting with 1-year-old girls in the 50th percentile of growth according to World Health Organization growth charts).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The maximum blood volume collected from each participant should be based on weight and should generally not exceed 1% of total blood volume on any 1 day or 3% of total blood volume (2.4 mL blood per kg of body weight) during a given 4-week trial period, unless appropriate justification is documented by the investigator [EMEA/CPMP 2008] [Food and Drug Administration (CDER) 2014].

9.1 Administrative and General Procedures

9.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

9.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the Future Biomedical Research consent/assent to the participant, answer all of his/her questions, and obtain written informed consent/assent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent/assent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the trial.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. In addition to the evaluation of a participant's medical history in terms of trial eligibility, all medical conditions since birth will be documented on the appropriate eCRF.

The number of prior episodes of CDI will be documented separately on the appropriate eCRF, along with additional relevant information, including timing and treatment(s) given for the most recent prior episode.

Whether or not each participant is immunocompromised will be assessed by the investigator and will be based on the participants' status at or before randomization. Compromised immunity is defined as meeting 1 or more of the following criteria:

- Active hematological malignancy (including, but not limited to, leukemia, lymphoma, multiple myeloma)
- Receiving cytotoxic chemotherapy (or received within the 28 days prior to onset of the baseline CDI episode) for an active malignancy

- Receiving immunosuppressive therapy following hematopoietic stem cell transplant or a solid organ transplant
- Asplenia
- Neutropenia (≤500 counts/mm^3)
- Congenital or acquired immunodeficiency disorder
- Receiving other medications known to suppress the immune system (including, but not limited to, antineoplastic and immunomodulating agents, immunosuppressive dose of systemic corticosteroids of at least 7 days' duration) or received within the 28 days prior to onset of the baseline CDI episode.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant from 28 days prior to the onset of the baseline episode of CDI through signing of informed consent. This will include but is not limited to all antibacterial medications, anti-diarrheal medications, treatments for dehydration (including fluids), and any therapies given and procedures performed for treatment of CDI (eg, colectomy, endoscopy, FMT). For breast-fed participants, the mothers' prior medications should also be recorded.

Treatment(s) given for the most recent prior episode of CDI should be recorded even if the treatment ended more than 28 days prior to the onset of the baseline episode of CDI.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant at any point from the signing of informed consent through Week 12 (85 ± 5 days). This will include but is not limited to all antibacterial medications, anti-diarrheal medications, treatments for dehydration (including fluids), any therapies given and procedures performed for treatment of CDI (eg, colectomy, endoscopy, FMT), and any medications used to treat AEs. For breast-fed participants, the mothers' concomitant medications should also be recorded.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

9.1.8 Treatment Administration

Blinded trial staff will be responsible for administration of trial medication.

Study treatment is to be given on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

9.1.8.1 Timing of Dose Administration

Bezlotoxumab or placebo will be administered as a single IV infusion over approximately 60 (±10) minutes on the day of randomization (Day 1) or as close as possible to the date of randomization. All participants must still be receiving antibacterial drug treatment for CDI on the day of the infusion (that is, participants will receive their last antibacterial dose on the day of study infusion or after).

It is important to record the details of the infusion, including start and stop times and date as well as any interruptions, on the appropriate eCRF. If a participant does not receive the entire infusion, the volume administered and reason the infusion was stopped must be recorded.

9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the single infusion (ie, participants who receive a partial dose) should be encouraged to continue to be followed for all remaining study visits.

When a participant discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Unscheduled Visit 2 in the Schedule of Assessments should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.9.1 Withdrawal From Future Biomedical Research

A Participant's consent for Future Biomedical Research may be withdrawn by the participant or the participant's legally acceptable representative (as appropriate) and have their specimens and all derivatives destroyed. A participant's consent may be withdrawn at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Participant Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the drug used by a participant and/or the dosage administered he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or non-study treating physician should continue to be monitored in the trial.

Additionally, the investigator or medically qualified designee must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS

should be used for emergency unblinding in the event that this is required for participant safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

9.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

9.2 Efficacy Assessments

9.2.1 Details of Baseline and Recurrent CDI Episodes

Details of the baseline episode of CDI and any recurrent episodes with an onset during the 12-week follow-up period should be documented separately in the source documents and on the appropriate eCRFs (including documentation of the local stool test for toxigenic *C. difficile*, as per Appendix 7). The investigator site personnel will also need to record on the appropriate eCRF the onset date and the highest number of UBMs in a 24-hour period for the baseline and recurrent CDI episodes.

Additionally, the following information of relevance to the baseline and each recurrent CDI episode will be collected on the appropriate eCRF:

- Presence of pseudomembranous colitis;
- Presence of bloody diarrhea;
- Highest body temperature;
- Highest white blood cell count;
- Lowest serum albumin concentration;
- Highest serum creatinine concentration;

- Signs and symptoms consistent with dehydration;
- Whether the participant had signs and symptoms consistent with toxic megacolon, bowel perforation, or ileus.

9.2.1.1 Assessment of Disease Severity

The baseline episode of CDI and any recurrent episodes with an onset during the 12-week follow-up period will be characterized by severity (mild to moderate versus severe) and severe-complicated course.

Severity will be assessed by the investigator. Participants who meet at least one of the following criteria during the CDI episode will be characterized as having severe CDI [van Dorp, S. M., et al 2017]:

- the presence of bloody diarrhea; and/or
- pseudomembranous colitis; and/or
- diarrhea accompanied by dehydration (as judged by the treating physician); and/or
- hypoalbuminemia (<2 g/dL); and/or
- fever (≥38.0°C) with leukocytosis (>15.0 × 10^9/L).

Participants will be characterized as having severe-complicated CDI if they meet at least one of the following criteria associated with the CDI episode within 30 days after diagnosis of the episode [Na, X., et al 2015], as assessed by the investigator:

- Intensive care unit admission
- Death
- Toxic megacolon
- Colectomy

9.2.2 Daily Diary

The participant or the participant's parent or caregiver will complete a daily diary to record the following information from randomization/study infusion through Week 12 (85 ± 5 days):

- Whether the participant had watery diarrhea (for participants using diapers or other type of fecal collection device, Bristol Stool Scale types 6 or 7) or any UBMs (takes shape of container, or Bristol Stool Scale type 5, 6, or 7) in the previous 24-hour period.

- On any day when the participant has diarrhea, the following will be recorded:
    - Presence of watery diarrhea (if child uses diapers or other type of fecal collection device) or number of UBMs;
    - Intensity of abdominal discomfort; and
    - Elevations in body temperature.

It is recommended to complete the diary nightly (at approximately the same time each day).

If all or a portion of the daily diary is lost or misplaced, the participant or the participant's parent or caregiver should contact study personnel to obtain a replacement.

At the end of the trial, the daily diary will be maintained as a source document. The data recorded on the diary will not be entered into the EDC system, with the exception of the specific information noted in Section 9.2.5.2.

9.2.3 Phone/Visit Contact

Trial personnel will contact the participant or the participant's parent or caregiver at least 3 times per week during antibacterial drug treatment for the baseline episode of CDI for assessment of antibacterial drug treatment compliance.

Trial personnel will also contact the participant or the participant's parent or caregiver either by phone or in person approximately 24 hours after the end of the infusion to assess for infusion-related reactions (see Section 9.3.7.1).

Trial personnel will contact the participant or the parent or caregiver twice weekly from approximately 48 hours after the last dose of antibacterial drug treatment (EOT) through Week 12 to ensure that the daily diary is maintained by the parent or caregiver. These phone calls will help to determine if the participant experienced watery diarrhea (for participants using diapers or other type of fecal collection device) or 3 or more UBMs within a 24-hour period, at which point a stool sample will be collected and an unscheduled study visit will be conducted to assess whether the criteria for a diarrhea recurrence or a CDI recurrence have been met (as defined in Section 9.2.5.2).

Study personnel do not need to contact the participant or the participant's parent or caregiver on weekends or holidays, unless the 24-hour infusion follow-up assessment for infusion-related reactions occurs on one of these days.

The information communicated by the participant or the parent or caregiver during the contact is to be recorded in the source documents. In addition, if any discrepancy is noted between the information obtained via phone contact and the information provided in the daily diary, study personnel must discuss the discrepancy with the participant/caregiver, and the explanation/resolution must be documented.

9.2.4 Stool Sample Collection and Assessments

Before screening, a stool sample collected during the episode of CDI being treated at the time of randomization must have tested positive by the local laboratory for toxigenic *C. difficile*; results of all *C. difficile* tests (positive of negative) performed for this episode are to be recorded in the eCRF. Positive results of any other tests performed at the local laboratory during this CDI episode to detect other pathogens in stool are to be recorded in the eCRF.

During screening, a new stool sample may need to be collected for study-specific testing (see Appendix 7 for assay requirements). A new sample is not needed if aliquots of the same stool sample that was used for the pre-screening diagnosis are available. If the pre-screening diagnosis was based on a method that does not test for the presence of *C. difficile* toxin, a new test will need to be performed at the local laboratory prior to randomization to confirm the diagnosis. Results of the new test are to be recorded in the eCRF.

An aliquot of the pre-screening stool sample or a sample obtained during screening will also be sent to the central laboratory.

After completion of antibacterial drug treatment for the baseline episode of CDI, if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period, a stool sample will be collected that same day, frozen, and brought to the unscheduled visit; if the criteria for a diarrhea recurrence are met (Section 9.2.5.2), the aliquots will be sent to both a local laboratory and the central laboratory for testing. The local laboratory will perform a *C. difficile* toxin test on stool samples (see Appendix 7 for assay requirements).

The central laboratory will perform the following tests on stool samples:

- Anaerobic culture followed by toxin testing for *C. difficile* strains isolated
- Toxigenic strain ribotyping
- Antibacterial susceptibility testing (vancomycin, metronidazole, and fidaxomicin)
- Panel for gastrointestinal pathogens (Section 9.2.4.1)

Stool samples will be collected at the time points indicated in Section 2 – SoA. Stool samples collected at sites will be stored at –70° C or below and shipped frozen to the central laboratory. Results of central laboratory tests are for data analysis purposes only and will not be available during the conduct of the study to inform patient care decisions.

9.2.4.1 Gastrointestinal Panel

The central laboratory will test frozen stool samples using FilmArray® gastrointestinal panel, manufactured by Biofire Diagnostics, Salt Lake City, UT, US. The FilmArray gastrointestinal panel is a sensitive and specific multiplex PCR-based assay capable of detecting 22 different pathogens directly from stool specimens (Table 6).

Table 6 Pathogens Detected by Gastrointestinal Panel

Bacteria	*Campylobacter (jejuni, coli and upsaliensis)* *Clostridium difficile* (toxin A/B) *Plesiomonas shigelloides* *Salmonella* *Yersinia enterocolitica* *Vibrio (parahaemolyticus, vulnificus and cholerae)* *Vibrio cholera* Diarrheagenic *Escherichia coli/Shigella* Enteroaggregative *E. coli* (EAEC) Enteropathogenic *E. coli* (EPEC) Enterotoxigenic *E. coli* (ETEC) *lt/st* Shiga-like toxin-producing *E. coli* (STEC) *stx1/stx2* *E. coli* O157 *Shigella*/Enteroinvasive *E. coli* (EIEC)
Viruses	Adenovirus F 40/41 Astrovirus Norovirus GI/GII Rotavirus A Sapovirus (I, II, IV and V)
Parasites	*Cryptosporidium* *Cyclospora cayetanensis* *Entamoeba histolytica* *Giardia lamblia*

Sources: [Spina, A., et al 2015] [Buss, S. N., et al 2015] [Stockmann, C., et al 2015] [Murphy, C. N,, et al 2017]

9.2.5 Investigator Assessment of Clinical Outcomes

9.2.5.1 Investigator Assessment of Clinical Response

The investigator will assess clinical outcomes of the baseline episode of CDI approximately 48 hours after the last dose of antibacterial drug treatment (EOT) for determination of initial clinical response (Table 7). This assessment can be performed via telephone contact or in person. The outcome of the investigator assessment will be recorded on the appropriate eCRF.

Randomized participants who are deemed clinical failures or have an indeterminate assessment will be medically managed as necessary and continue to be monitored during the trial unless they are discontinued or withdrawn from the trial for other reasons (Section 8).

Table 7 Investigator Assessment of Initial Clinical Response

Clinical Outcome	Response Definition
Initial Clinical Response	Improvement in the number and character of bowel movements AND does not require further CDI therapy within 2 days after completion of up to 21 days of antibacterial drug treatment for CDI.
Clinical Failure	Initial clinical response not achieved.
Indeterminate	Study data are not available for evaluation of clinical outcome for one of the following reasons: a) Participant was withdrawn for any reason or died before sufficient data had been obtained to permit evaluation; OR b) Extenuating circumstances (eg, a protocol violation) preclude classification as "initial clinical response" or "clinical failure."

9.2.5.2 Investigator Assessment of a New Episode of Diarrhea During the 12-Week Follow-Up Period

An investigator assessment will occur at each study visit after the EOT visit. In addition, an unscheduled visit will be conducted if the participant experiences watery diarrhea (if the child is using diapers or other fecal collection device) or 3 or more UBMs within a 24-hour period, and an investigator assessment will determine whether the criteria for a diarrhea recurrence or a CDI recurrence have been met (Table 8). The unscheduled visit should preferably occur within 2 days of the onset of diarrhea or UBMs. The investigator assessment and information to support this assessment (eg, stool test result, treatments given, maximum number of UBMs, maximum temperature, maximum white blood cell count, maximum abdominal discomfort score) will be recorded on the appropriate eCRF.

Every effort will be made to ensure that all diarrhea recurrence episodes are assessed for CDI recurrence.

Sustained clinical response will be derived from the investigator assessment of initial clinical response and CDI recurrence, as described in Section 10.4.3.

Table 8 Investigator Assessment of New Episode of Diarrhea

Diarrhea Recurrence	New episode of diarrhea after initial clinical response as defined by a change in normal bowel habits for 2 or more calendar days with either watery diarrhea (for participants using diapers or other type of fecal collection device) or at least 6 UBMs within a 48-hour period.
CDI Recurrence	Diarrhea recurrence (see above definition) associated with a positive test for the presence of *C. difficile* toxin in stool, and for which the participant, in the investigator's opinion, requires and receives antibacterial drug treatment for CDI.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 9.3.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 12 weeks following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 9.

Table 9 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period		Timeframe to Report Event and Follow-up Information to SPONSOR:
Serious Adverse Event (SAE)		Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome.)		Within 24 hours of learning of event
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Overdose		Report if: - receiving placebo run-in or other run-in medication	Report all	Not required		Within 5 days of learning of event
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required		Within 5 days of learning of event
Cancer		Report if: - due to intervention - causes exclusion	Report all	Not required		Within 5 days of learning of event
Pregnancy/Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event

9.3.2 Method of Detecting AE and SAE

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and the onset of menses occurring at a physiologically appropriate time.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAE, pregnancy and exposure during breastfeeding, Events of Clinical interest (ECI), Cancer, and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

A CDI recurrence is not considered a reportable event and will not be reported to the Sponsor as described in Section 9.3.1 unless it meets one or more SAE criteria.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an elevated AST or ALT postbaseline lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing in a participant with baseline values that did not meet these criteria, or if baseline values were elevated, there is a clinically significant worsening, as determined by the investigator.*

* Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. infusion-related reactions (Section 9.3.7.1).

9.3.7.1 Infusion-Related Reactions

Anaphylaxis is likely when multiple organ systems are adversely affected following exposure to an allergen. A list of symptoms that may be present during anaphylaxis include flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, vomiting, diarrhea and abdominal cramps, wheezing, dyspnea due to laryngeal spasm, lower airway obstruction, pruritus, rashes (such as urticaria), or angioedema. A modification of the Sampson criteria [Sampson, H. A., et al 2006] will be used to identify potential anaphylaxis due to bezlotoxumab (infusion-related reactions). Participants will be monitored during the infusion of study medication and asked to report onset of new symptoms through 24 hours following the end of the infusion; this monitoring

should include at least 1 hour of in-clinic monitoring. Events meeting any of the 3 criteria below will be assessed as potential infusion-related reactions and are to be reported to the Sponsor as an ECI. Infusion-related reactions should be treated supportively, if clinically indicated.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following:

    - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

    - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after onset of the study infusion (minutes to several hours):

    - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

    - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

    - Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

    - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after onset of the study infusion (minutes to several hours):

    - Low systolic blood pressure (age specific)

        - 1 to 10 years: less than (70 mm Hg + [2X age])

        - 11 to 17 years: less than 90 mm Hg

    - OR greater than 30% decrease in systolic blood pressure from participant's baseline

9.4 Treatment of Overdose

In this trial, an overdose is any dose higher than the highest dose studied in man to date (ie, >20 mg/kg body weight of bezlotoxumab).

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

9.5 Safety

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

- A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.
- A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard and will be targeted to the participant's illness and complaints.
- Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Abnormal findings from complete and directed physical examinations will be recorded as AEs.

9.5.2 Vital Signs

Vital signs will be collected at the time points specified in the SoA and include heart rate, blood pressure, respiratory rate, body temperature, and, on Day 1 only, pulse oximetry. Participants should be in a seated or semirecumbent position prior to having vital sign measurements obtained. For those participants who cannot sit up for any reason (eg, infants, intubated participants), vital sign measurements will be taken in a supine or semirecumbent position. When possible, oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary methods are acceptable.

9.5.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

All clinical safety laboratory assessments specified in Appendix 2 will be performed by local laboratories.

Directed Hematology and Chemistry Assessments

As specified in the SoA (Section 2), directed hematology and chemistry assessments will be conducted at specified time points. The parameters for these directed assessments are specified in Appendix 2.

9.6 Pharmacokinetics

Blood samples will be collected at the time points specified in Section 2 – SoA to measure the concentrations of bezlotoxumab for PK assessments. While every effort should be made to schedule visits with PK draws so that they occur within the window specified in Section 2, when this is not possible, the PK samples should still be collected even if out of the collection window, and this will not be considered a major protocol deviation.

9.6.1 Blood Collection for Bezlotoxumab (MK-6072) in Serum

Serum will be separated from blood samples and sent to a central laboratory for testing. Sample collection, storage, and shipment instructions for serum samples will be provided in the operations/laboratory manual.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main study stool samples stored for future research
- Leftover main study serum samples collected for anti-drug antibody levels and neutralizing antibody levels stored for future research
- Leftover main study serum samples collected for bezlotoxumab serum concentration assay for PK stored for future research

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in Section 2 – SoA:

- Blood samples for planned genetic analysis (Section 9.9.1)
- Blood samples for immunogenicity assessments (Section 9.9.2)

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

9.9.2 Immunogenicity Assessments

The potential for bezlotoxumab to induce immunogenicity through 12 weeks in participants aged 1 to <18 years given a single dose will be evaluated as an exploratory endpoint in this trial by detecting treatment-emergent anti-drug and neutralizing antibodies to bezlotoxumab in serum at the time points specified in Section 2 – SoA.

Sample collection, storage, and shipment instructions for immunogenicity samples will be provided in the operations/laboratory manual.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Screening period can start as early as the first day of antibacterial drug treatment for the baseline episode of CDI and can extend as long as the last day of antibacterial drug treatment for the baseline episode of CDI. During this time, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 6.1 and 6.2. Screening and randomization may occur on the same day, as long as all trial entry criteria have been met. The duration of the screening period cannot be longer than the antibacterial drug treatment regimen for the baseline episode of CDI, as the participant must still be receiving antibacterial drug treatment on the day of randomization/study infusion.

Screening procedures may be repeated after consultation with the Sponsor. If the subject is rescreened, screening procedures should be repeated, unless they fall within the window specified.

9.10.2 Treatment Period

The procedures before and after the trial infusion (ie, Day 1 and beyond until Week 12 [Day 85 ± 5 days]) are described in Section 2 and in detail earlier in Section 9.

9.10.3 Unscheduled Visits

From completion of antibacterial drug treatment for the baseline episode of CDI through the end of the 12-week follow-up period, if the participant experiences watery diarrhea (for participants using diapers or other type of fecal collection device) or 3 or more UBMs in a 24-hour period, an unscheduled visit must be conducted and the assessments specified in the "Unscheduled Visit 1" column in Section 2 – SoA will be performed to determine whether the criteria for a diarrhea recurrence or a CDI recurrence have been met (as defined in Section 9.2.5.2).

Unscheduled visits that are conducted for any other reason, including withdrawal from participation in the trial, should follow the assessments specified in the "Unscheduled Visit 2" column in Section 2 – SoA.

9.10.4 Discontinued Participants Continuing to be Monitored in the Study

See Section 9.1.9.

9.10.5 Post-Study

No post-study follow-up is planned for this trial.

10. Statistical Analysis Plan

10.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) will be developed to detail other planned analyses (ie, those specific to the analysis of PK data, and future biomedical research).

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2 - 10.12.

Study Design Overview	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of a Single Infusion of Bezlotoxumab (MK-6072, Human Monoclonal Antibody to C. *difficile* Toxin B) in Children Aged 1 to <18 Years Receiving Antibacterial Drug Treatment for *C. difficile* Infection
Treatment Assignment	There are 2 study treatment arms. Participants will be assigned randomly in a 3:1 ratio to bezlotoxumab or placebo, respectively, and will be stratified into 2 age groups according to the participant's age at the time of randomization (1 to <12 years of age or 12 to <18 years of age).
Analysis Populations	**Pharmacokinetics**: Per-Protocol (PP) **Safety**: All Participants as Treated (APaT) **Efficacy**: modified Intent to Treat (mITT), Efficacy Evaluable (EE)
Primary Endpoint(s)	**Pharmacokinetic**: The $AUC_{0\text{-}inf}$ will be determined for each age cohort from bezlotoxumab serum concentration data. **Safety**: Proportion of participants with any AE and proportion of participants with a discontinuation due to an AE through 12 weeks following infusion.

Key Secondary Endpoints	**Efficacy**: 1) Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. 2) Proportion of participants with sustained clinical response over a period of 12 weeks. 3) Proportion of participants who have a CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study medication infusion in the subset of participants at high risk for CDI recurrence. **Safety**: 4) Proportion of participants experiencing 1 or more infusion-related reactions within 24 hours following the start of the infusion. **Immunogenicity:** 5) Proportion of participants with treatment-emergent positive antibodies to bezlotoxumab in serum through 12 weeks following a single dose of bezlotoxumab.
Statistical Methods for Key Efficacy/ Pharmacokinetic Analyses	**Pharmacokinetic**: In each age cohort, a point estimate as well as its 90% confidence interval (CI) will be generated from an analysis of variance (ANOVA) model containing a factor for cohort (pediatric participants and adults) for the GMR (pediatric participants/adults) of bezlotoxumab $AUC_{0\text{-inf}}$. The 90% CI of the GMR will be compared against the pre-specified bounds (0.6, 1.6). If the 90% CI for the GMR falls within (0.6, 1.6), then it will be claimed that the $AUC_{0\text{-inf}}$ of bezlotoxumab in the pediatric age cohort is similar to adults. **Efficacy**: Miettinen and Nurminen's method for stratified data will be used to compare the proportion of participants with CDI recurrence and the proportion of participants who achieved sustained clinical response between the treatment groups (bezlotoxumab and placebo). The strata will be the participant's age category at time of trial entry (same as the stratification for the randomization). Similar methodology will be used for sustained clinical response.
Statistical Methods for Key Safety Analyses	Miettinen and Nurminen's method (not stratified) will be used for between group comparisons for all Tier 2 endpoints.

Immunogenicity	The Agresti & Coull method will be used to calculate the 95% CI for the bezlotoxumab group for the proportion of participants with treatment-emergent positive antibodies to bezlotoxumab.
Interim Analyses	An independent, unblinded DMC will be appointed and will review the safety and tolerability data. There will be 2 planned reviews by the DMC, which will occur during the pre-specified time points. There are no plans to conduct an interim analysis of unblinded efficacy data in the study.
Multiplicity	No multiplicity adjustment is being made.
Sample Size and Power	**Pharmacokinetic**: The estimated log-scale between-subject standard deviation for $AUC_{0\text{-inf}}$ of bezlotoxumab following single-dose IV administration of 10 mg/kg MK-3415A in adults was 0.402 based on data from two Phase 3 trials (MK-3415A P001 and MK-3415A P002). Assuming the same variability in pediatric participants, if the true GMR (pediatric participants/adults) is 1.00 for $AUC_{0\text{-inf}}$ of bezlotoxumab, then 9 pediatric participants and 1400 adults provides at least 93.6% probability of observing the 90% CIs of $AUC_{0\text{-inf}}$ of bezlotoxumab to be contained within (0.6, 1.6). **Safety:** The fundamental justification for the sample size is to complete the trial in a timely manner while still providing a sufficient number of participants with bezlotoxumab exposure in this population to assess the safety profile. **Efficacy**: The study is not powered for the assessment of efficacy.

10.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. The analyses and summaries described in 10.6.1 are the responsibility of PPDM - Quantitative Pharmacology and Pharmacometrics of the SPONSOR and Early Clinical Development Statistics - Clinical Biostatistics of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Separate functional unblinding for bioanalysis and PK will be conducted in support of PK evaluations. A small team as specified in a separate unblinding memo will be unblinded for the purpose of preparing the PK analyses for Panel A.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

Planned interim analyses are described in Section 10.7. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

Treatment–level results will be provided by an internal, unblinded statistician (with no involvement in the conduct of the study) to the external DMC. Limited additional Sponsor personnel may be unblinded to the treatment level results, if required, in order to act on the recommendations of the DMC. The extent to which individuals are unblinded with respect to results will be documented by the unblinded statistician.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

10.4.1 Pharmacokinetics Endpoints

The primary PK endpoint of interest is $AUC_{0\text{-}inf}$ of bezlotoxumab following single-dose IV administration of 10 mg/kg bezlotoxumab in pediatric participants. Other PK endpoints of interest are C_{max}, T_{max}, terminal half-life, V_{dss}, and Cl.

10.4.2 Safety Endpoints

A description of safety measures is contained in Sections 9.3 and 9.5. The analysis of safety results will follow a tiered approach (see Section 10.6.2 for further detail).

10.4.3 Efficacy Endpoints

CDI Recurrence:

The proportion of participants with CDI recurrence assessed through Week 12 (Day 85 ± 5 days) will be evaluated as a secondary endpoint. The proportion of participants with CDI recurrence will be calculated as follows for each treatment group. The numerator will be the number of participants in the mITT population, as defined in Section 10.5.3, who have CDI recurrence (as assessed by the investigator as defined in Section 9.2.5.2) following initial clinical response. CDI recurrence is defined as the development of diarrhea recurrence associated with a positive test for the presence of *C. difficile* toxin in stool and for which the participant, in the investigator's opinion, requires and receives antibacterial drug treatment

for CDI. The denominator will be the number of participants in the mITT population who achieve initial clinical response of the baseline episode. Every effort will be made to obtain CDI recurrence information for each randomized participant.

As a supportive approach, the proportion of participants with CDI recurrence will be evaluated in the mITT population. For this analysis, participants who do not achieve initial clinical response of the baseline episode will be imputed as not having CDI recurrence. The numerator will be the number of participants in the mITT population who have CDI recurrence following initial clinical response (as in the primary approach detailed above). The denominator will be the number of participants in the mITT population.

As an additional analysis, the proportion of participants who have CDI recurrence in subsets of participants at high risk of CDI recurrence (defined as those with one or more risk factors) will be assessed. The numerator will be the number of participants in the mITT population who have CDI recurrence following initial clinical response among those at high risk for CDI recurrence. The denominator will be the number of participants in the mITT population who achieve initial clinical response of the baseline episode and are at high risk for CDI recurrence.

Participants at high risk for CDI recurrence are those who meet 1 or more of the following criteria **at or before randomization**:

- Was immunocompromised
- Prior history of CDI defined as one or more episodes of CDI at any point prior to the baseline episode
- Had a baseline CDI episode that met criteria for severe CDI (as defined in Section 9.2.1.1)
- *C. difficile* ribotype 027 was isolated from a stool sample collected during the baseline CDI episode
- Had received treatment with 1 or more systemic antibacterials known to increase the risk of CDI (during treatment of the baseline CDI episode), including but not limited to clindamycin, fluoroquinolones, cephalosporins, aztreonam, penicillins, macrolides, and carbapenems. The list of specific antibacterials will be finalized prior to database lock.

As a sensitivity analysis, the proportion of participants who have a CDI recurrence will be calculated in the subset of participants at high risk for CDI recurrence (as defined above) or who received 1 or more systemic antibacterials during the 12-week follow-up period.

As a supportive analysis, time to CDI recurrence will be assessed. Time to CDI recurrence will be measured from the date of infusion. For participants who discontinue prior to a CDI recurrence, time to CDI recurrence will be right censored at the date of discontinuation. Participants who complete the 12-week study period without documented CDI recurrence will be censored at the minimum of the date of study completion or 12 weeks. Participants who fail to achieve initial clinical response will be excluded from this analysis.

Sustained Clinical Response:

The proportion of participants with a sustained clinical response will be assessed as a secondary efficacy endpoint. Sustained clinical response is defined as a composite of initial clinical response of the baseline CDI episode AND no CDI recurrence through Week 12.

The proportion of participants with sustained clinical response will be calculated as follows for each treatment group: The numerator will be the number of participants within the mITT population who achieve sustained clinical response, and the denominator will be the number of participants in the mITT population.

As additional analyses, the proportion of participants who achieved sustained clinical response in subsets of participants at high risk of CDI recurrence (defined as those with one or more risk factors as above) will be assessed. The numerator will be the number of participants in the mITT population who achieve sustained clinical response among those at high risk for CDI recurrence. The denominator will be the number of participants in the mITT population at high risk for CDI recurrence.

As a sensitivity analysis, the proportion of participants who achieved sustained clinical response will be calculated in the subset of participants at high risk for CDI recurrence (as defined above) or who received 1 or more systemic antibacterials during the 12-week follow-up period.

Initial Clinical Response of Baseline CDI Episode:

The proportion of participants with initial clinical response of the baseline CDI episode will be calculated as follows for each treatment group: The numerator will be the number of participants within the mITT population who achieve an initial clinical response, as determined by the investigator. The denominator will be the number of participants in the mITT population.

Diarrhea Recurrence:

The proportion of participants with diarrhea recurrence assessed through Week 12 (Day 85 ± 5 days) will be assessed as an exploratory efficacy endpoint. The proportion of participants with diarrhea recurrence will be calculated as follows for each treatment group. The numerator will be the number of participants in the mITT population who develop diarrhea recurrence (as assessed by the investigator as defined in Section 9.2.5.2). The denominator will be the number of participants in the mITT population who achieve initial clinical response of the baseline episode.

10.5 Analysis Populations

10.5.1 Pharmacokinetic Population

The Per-Protocol (PP) population will be the subset of treated participants who complete PK sampling with at least 4 post-dose evaluable samples and comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. The non-compartmental PK analysis will be conducted for the PP population.

10.5.2 Safety Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who receive infusion of study medication. Participants in Panel A (Cohort 1 and/or 2) will only be included in the APaT population if there is not a dose modification as described in Section 5.1.2; if there is a dose modification in a particular cohort, participants in Panel A of that cohort will be summarized separately. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized.

At least 1 vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

10.5.3 Efficacy Population

The mITT population will serve as basis for the efficacy analyses. The mITT population is a subset of all randomized participants with participants excluded for the following reasons:

- Did not receive any amount of study medication
- Did not have a positive local stool test for *C. difficile* toxin to confirm CDI diagnosis of the baseline episode
- Was not taking a protocol-defined antibacterial drug treatment for CDI on the day of the infusion.

In addition, participants will only be included in the mITT population if they received the final age-appropriate dose; if there is a dose modification in a particular cohort, participants in that cohort will be summarized separately.

A supportive analysis using the Efficacy Evaluable (EE) population will be performed for efficacy endpoints. The EE population is a subset of the mITT population that excludes participants for the following reasons:

- important deviations from the protocol that may affect the efficacy results
- prior or concomitant usage of IV immune globulin (IVIG)

The final determination on protocol deviations, and thereby the composition of the EE population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

Details on the approach to handling missing efficacy data are provided in Sections 9.2.5.1 and 10.4.3.

10.6 Statistical Methods

10.6.1 Statistical Methods for Pharmacokinetics Analyses

During the conduct of the trial, and to inform enrollment of additional participants, initial PK evaluations will include all participants in Panel A who received the infusion of trial medication and who have sufficient data to calculate $AUC_{0\text{-}inf}$. Data will be natural log transformed prior to model fitting. The $AUC_{0\text{-}inf}$ of bezlotoxumab following a single-dose IV administration in Panel A of each pediatric age cohort will be compared to the $AUC_{0\text{-}inf}$ of bezlotoxumab in adults using an analysis of variance (ANOVA) model. The adult PK dataset(s) to be used in this comparison will be based on that obtained from the participants in the 2 adult Phase 3 trials (MK-3415A P001 and MK-3415A P002). The ANOVA model will contain a factor accounting for group (pediatric participants and adults). Least-squares geometric mean (GM) (95% CI) of the $AUC_{0\text{-}inf}$ of bezlotoxumab in pediatric participants will be calculated from the model. A point estimate as well as its 90% CI will also be generated from the model for the GMR (pediatric participants/adults) of bezlotoxumab $AUC_{0\text{-}inf}$. The 90% CI of the GMR will be compared against the pre-specified bounds (0.6, 1.6). If the 90% CI for the GMR falls within (0.6, 1.6), then it will be claimed that the $AUC_{0\text{-}inf}$ of bezlotoxumab in the pediatric age cohort is similar to adults.

At the conclusion of this trial, PK data from all participants who received the trial medication and who have sufficient data to assess PK from both Panels A and B will be used to compile an overall bezlotoxumab PK profile in the pediatric population.

Individual values will be listed for each PK parameter by treatment and age cohort, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt($\exp(s^2) - 1$), where s^2 is the observed variance on the natural log-scale). Descriptive statistics will be provided by gender and race or other covariates of interest as well if needed.

10.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and vital signs.

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 12 participants in the bezlotoxumab treatment group or 2 participants in the placebo treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 12 participants in the bezlotoxumab arm was chosen because the lower limit of 95% CI for the between-group difference (bezlotoxumab – placebo) in percent incidence would not exclude zero when the number of participants in bezlotoxumab was less than 12 and thus would add little to the interpretation of potentially meaningful differences. Similarly, the threshold of at least 2 participants in the placebo arm was chosen because the upper limit of 95% CI for the between-group difference (bezlotoxumab – placebo) in percent incidence would not exclude zero when the number of participants in placebo was less than 2 and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

Continuous measures such as changes from baseline in laboratory and vital signs parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change-from-baseline will be provided by treatment group in table format.

For this protocol, there are no Tier 1 events given the favorable safety profile demonstrated in the Phase 3 program. The broad clinical and laboratory AE categories (through the 12 week follow up period) consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, a death, an AE which is both drug-related and serious, a discontinuation due to an AE and specific AEs (meeting the thresholds described above) are considered Tier 2 endpoints. Infusion-related reactions, as previously defined in Section 9.3.7.1, will also be considered Tier 2 endpoints. 95% CIs (Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses

will be performed using the Miettinen and Nurminen method (1985) [Miettinen, Olli and Nurminen, Markku 1985], an unconditional, asymptotic method.

For the analyses of safety, participants at the final dose selected for each cohort will be pooled across cohorts. In addition, key summaries of safety will be provided separately by cohort. Limited summaries of safety will be provided in participants in Panel A if there is a dose modification.

Missing laboratory and vital sign measurements will be handled using the Data-As-Observed (DAO) approach.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	X	X	X
Tier 2	Any AE		X	X
	Any drug-related AE		X	X
	Any serious AE		X	X
	A death		X	X
	Any serious and drug-related AE		X	X
	Discontinuation[b] due to AE		X	X
	Infusion-related reactions[c]		X	X
	Specific AEs or system organ classes (incidence ≥12 of participants in bezlotoxumab or ≥2 participants in placebo)		X	X
Tier 3	Specific AEs or system organ classes (incidence <12 of participants in bezlotoxumab and <2 participants in placebo)			X
	Change from Baseline Results (Vital signs)			X

95% CIs will be based on the method of Miettinen and Nurminen [Miettinen, Olli and Nurminen, Markku 1985].

[a] Adverse Events references refer to both clinical and laboratory AEs.

[b] Study medication withdrawn.

[c] Infusion-related reactions are defined in Section 9.3.7.1.

Note: X = results will be provided.

10.6.3 Statistical Methods for Efficacy Analyses

Miettinen and Nurminen's method for stratified data will be used to compare the proportion of participants with CDI recurrence and the proportion of participants who achieve sustained clinical response between the treatment groups (bezlotoxumab and placebo). The strata will be the participant's age category at time of trial entry (same as the stratification for the

randomization). Cochran-Mantel-Haenszel weights will be used. The 95% CI for the differences in proportions will be presented along with nominal 2-sided p-values. As there are no associated hypotheses to be tested, the p-values are not inferential and are only presented as an additional measure of the effect size.

For the proportion of participants who have CDI recurrence in subsets of participants at high risk of CDI recurrence, the bezlotoxumab vs. placebo difference (with a nominal 95% CI) will be estimated using Miettinen and Nurminen's method without stratification. Sustained clinical response in subset of participants at high risk of CDI recurrence will use the same methodology.

The nonparametric Kaplan-Meier method will be used to estimate the time to CDI recurrence distribution for each treatment group. Treatment differences in time to CDI recurrence will be assessed using the stratified log-rank test.

For the analyses of efficacy, participants at the final dose selected for each cohort will be pooled across cohorts. In addition, key summaries of efficacy will be provided separately by cohort as described in Section 10.10. Limited summaries of efficacy will be provided in participants in Panel A if there is a dose modification.

10.6.4 Statistical Methods for Immunogenicity Analyses

The Agresti & Coull method will be used to calculate the 95% CI for the bezlotoxumab group for the proportion of participants with treatment-emergent positive antibodies to bezlotoxumab.

10.6.5 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, sex, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analyses

Initial PK evaluations will be conducted as described in Section 10.6.1.

An independent, unblinded DMC will be appointed to review safety and tolerability data for Panel A of both Age Cohort 1 and Age Cohort 2, as described in Section 5.1.2, with additional information provided in Appendix 3. A description of the structure, function, and guidelines for decision-making by the DMC will be outlined in the DMC charter. There are no plans to conduct an interim analysis of unblinded efficacy data in the study.

10.8 Multiplicity

There are no multiplicity adjustments made.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for Pharmacokinetic Analyses

The estimated log-scale between-subject standard deviation for $AUC_{0\text{-inf}}$ of bezlotoxumab following single-dose IV administration of 10 mg/kg bezlotoxumab in adults was 0.402 based on data from two Phase 3 trials (MK-3415A P001 and MK-3415A P002).

Primary hypothesis: Assuming the same variability in pediatric participants, if the true GMR (pediatric participants/adults) is 1.00 for $AUC_{0\text{-inf}}$ of bezlotoxumab, then 9 pediatric participants and 1400 adults provides at least 93.6% probability of observing the 90% CIs of GMR (pediatric participants/adults) for $AUC_{0\text{-inf}}$ of bezlotoxumab to be contained within (0.6, 1.6).

Precision estimates: 9 pediatric participants who receive bezlotoxumab in each age cohort provides at least 69.7% probability that the 95% CI of the GM is within 60% and 140% of the GM estimates of $AUC_{0\text{-inf}}$ for bezlotoxumab. A minimum of 27 participants who receive bezlotoxumab in each age cohort provides at least 99.9% probability that the 95% CI is within 60% and 140% of the GM estimates of $AUC_{0\text{-inf}}$ for bezlotoxumab.

10.9.2 Sample Size and Power for Efficacy Analyses

This study will randomize approximately 144 participants into the bezlotoxumab group and 48 into the placebo group at the final dose selected for each age cohort. The planned sample size for this study will have limited power to confirm superiority of bezlotoxumab over placebo. Table 11 presents the treatment difference and 95% CI for various possible combinations of CDI recurrence event rates that could be observed in this study. Assumptions about the incidence of CDI recurrence among participants on bezlotoxumab are based on the pooled results from the Phase 3 clinical trials (PN001 and PN002) of a single infusion of this investigational product and expectations about the rates anticipated in this study population. In these studies, CDI recurrence was observed in 16.5% (129/781) of bezlotoxumab participants in the primary analysis population, while the recurrence rate among participants on placebo was 26.6% (206/773). Rates were slightly higher, in both treatment groups, in the subset of participants with initial clinical response: in this subset, CDI recurrence was observed in 20.6% (129/625) of bezlotoxumab participants, while the recurrence rate among participants on placebo was 33.2% (206/621).

Similarly, there is also limited power for this study for sustained clinical response; the pooled response rates observed in the Phase 3 clinical trials (PN001 and PN002) were 63.5% (496/781) in bezlotoxumab participants, while the response rates among participants on placebo were 53.7% (415/773).

Table 11 Variability Around Various Possible Treatment Differences

Bezlotoxumab (n=144)	Placebo (n=48)	Difference (95% CI) (Bezlotoxumab – Placebo)
8% (11/144)	15% (7/48)	-7 (-20, 2)
12% (17/144)	19% (9/48)	-7 (-21, 4)
16% (23/144)	23% (11/48)	-7 (-22, 5)
20% (29/144)	27% (13/48)	-7 (-22, 6)
8% (11/144)	17% (8/48)	-9 (-23, 1)
12% (17/144)	21% (10/48)	-9 (-23, 2)
16% (23/144)	25% (12/48)	-9 (-24, 3)
20% (29/144)	29% (14/48)	-9 (-24, 4)
8% (11/144)	19% (9/48)	-11 (-25, -1)
12% (17/144)	23% (11/48)	-11 (-26, 0)
16% (23/144)	27% (13/48)	-11 (-26, 2)
20% (29/144)	31% (15/48)	-11 (-27, 2)

* Based on the Miettinen and Nurminen method (unstratified)

10.9.3 Sample Size and Power for Safety Analyses

The fundamental justification for the sample size is to complete the trial in a timely manner while still providing a sufficient number of participants with bezlotoxumab exposure in this population to assess the safety profile. A 3:1 randomization was used to maximize the number of participants exposed to bezlotoxumab while still maintaining a control arm of reasonable size.

The probability of observing at least one serious adverse event in this study depends on the number of subjects treated and the underlying percentage of subjects with a serious adverse event in the study population. If the underlying incidence of a serious adverse event is 1% (1 of every 100 subjects receiving bezlotoxumab), there is a 76% chance of observing at least one serious adverse event among 144 subjects in the bezlotoxumab group. If no serious adverse events are observed among the 144 subjects in bezlotoxumab group, this study will provide 95% confidence that the underlying percentage of subjects with a serious adverse event is ≤2.6% (<1 in every 38 subjects) in the bezlotoxumab group.

10.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the CDI recurrence and the sustained clinical response will be estimated within each category of each subgroup. The following subgroups will be examined:

- Age cohort (1 to <12 years, 12 to <18 years)
- Sex (female, male)
- Race (white, non-white)
- Antibiotic used for treatment of CDI episode ongoing at time of infusion (metronidazole, vancomycin, fidaxomicin)

The 95% CI will only be calculated if there are 10 or more participants in each treatment group.

As a secondary objective, the proportion of participants with CDI recurrence and the proportion of participants who achieved sustained clinical response in the subset of participants at high risk for CDI recurrence will be assessed as discussed in Section 10.4.3.

Additionally, the proportion of participants who have a CDI recurrence and the proportion of participants who achieved sustained clinical response will be calculated in the subset of participants meeting the criteria for each risk factor. As above, the 95% CI will only be calculated if there are 10 or more participants in each treatment group.

10.11 Compliance (Medication Adherence)

Compliance assessments are not relevant for a single-dose infusion study.

10.12 Extent of Exposure

Assuming no change in dose following review of exposures in Panel A participants, all participants will receive the same dose (10 mg/kg). Given this, the extent of exposure will be the same for all participants and no summary of this information will be provided. If a dose change is required, the number of participants exposed at each dose level will be summarized using descriptive statistics.

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	*Description*
AE	Adverse events
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APaT	All Participants as Treated
AST	Aspartate aminotransferase
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from 0 to infinity
β hCG	β human chorionic gonadotropin
BUN	Blood urea nitrogen
CDI	*Clostridium difficile* infection
CI	Confidence interval
Cl	Clearance
C_{max}	Maximum concentration
CRF	Case report form
CSR	Clinical study report
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ECI	Event of clinical interest
eCRF	Electronic case report form
EDC	Electronic data collection
EE	Efficacy Evaluable
EIAs	Enzyme-linked immunoassays
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	End of treatment with antibacterial drug for baseline episode of CDI
FBR	Future biomedical research
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	*Description*
FMT	Fecal microbiota transplantation
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GM	Geometric mean
GMR	Geometric mean ratio
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
IV	Intravenous
IVIG	Intravenous immune globulin
IVRS/IWRS	Interactive voice response system/Integrated web response system
mAb	Monoclonal antibody
mITT	Modified intent to treat
LAR	Legally acceptable representative
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PP	Per-Protocol
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SoA	Schedule of Activities
sSAP	Supplemental statistical analysis plan
T_{max}	Time of maximum concentration
UBM	Unformed bowel movements
V_{dss}	Volume
WOCBP	Woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory. Samples for these tests should be collected on Study Day 1, unless otherwise specified in the table. If the tests were performed as part of routine patient care within 72 hours of the scheduled visit, there is no need to repeat the test.

- The tests detailed in Table 13 will be performed by the local laboratory. Samples for these tests should be collected at Unscheduled Visit 1, at the time of a return of diarrhea.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, red blood cell indices (MCV, MCH), platelet count, hemoglobin, hematocrit
Chemistry	Alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, bilirubin (total, and direct bilirubin if total bilirubin is elevated above the upper limit of normal), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose (indicate if fasting or nonfasting on eCRF), potassium, sodium, total protein
Other Screening Tests	Urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential). Samples to be collected at screening and on Day 1. If results are positive, the participant should be excluded from trial participation.

Table 13 Directed Hematology and Chemistry Parameters (Unscheduled Visit 1)

Directed Hematology	White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Directed Chemistry	Albumin (serum), C-reactive protein, creatinine (serum), lactate (plasma)

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of

results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Committees Structure

Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim

Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are participant to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical

Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any

regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported

Additional Events which require reporting

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
  - Is a cancer;
  - Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording
● When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. ● The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination. ● It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. ● There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. ● The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity

● An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
● The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  ● Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric trials, awareness of symptoms, but easily tolerated)
  ● Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric trials, definitely acting like something is wrong)
  ● Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric trials, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
    - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
      - If yes, did the AE resolve or improve?
        - If yes, this is a positive dechallenge.
      - If no, this is a negative dechallenge.

      (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor’s product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use any one of the contraception methods described in Table 14 , including those classified as "acceptable" (ie, failure rate >1% per year when used consistently and correctly), during the protocol-defined time frame in Section 6.1.

Table 14 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide ● Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly).

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

12.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations

with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in the trial flow chart. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for FBR (ie, only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.7 Appendix 7: C. Difficile Diagnostic Test Method Requirements

A diagnosis of CDI is required prior to consent of the participant. A stool sample must have tested positive for toxigenic *C. difficile* according to local diagnostic criteria prior to assigning the participant a screening number.

If the local diagnostic method(s) does not include an assay which detects the presence of *C. difficile* toxin in stool, a confirmatory test that detects *C. difficile* toxin in stool must be performed prior to randomization. The confirmatory test must not detect only toxin A (ie, it must also detect toxin B) and must be one of the following test types:

1. Cell culture cytotoxic assay, OR

2. Commercial stool assays, approved by the local regulatory agency, must detect the presence of *C. difficile* toxin, and the specificity of the assay must be ≥94% as stated in the manufacturers' product insert

The commercial tests shown in Table 15 are allowed per protocol. Use of other commercial tests not included in Table 15 must be discussed with the Sponsor.

Table 15 Permitted Commercial Enzyme Immunoassay Tests for Detecting Presence of *Clostridium difficile* Toxin in Stool

Type	Name of Test	Manufacturer
Well-type EIA toxins A/B	*Clostridium difficile* Tox A/B II	TechLab (may also be distributed by Alere, Inc)
	Premier toxins A/B	Meridian
	Remel ProSpecT	Oxoid/Remel
	Ridascreen toxins A/B	R-Biopharm
Membrane-type EIA toxins A/B	ImmunoCard toxins A/B	Meridian
	Quik Chek Complete-Tox A/B	TechLab (may also be distributed by Alere, Inc)
	Tox A/B Quik Chek	TechLab (may also be distributed by Alere, Inc)
	Xpect	Oxoid/Remel
Automated EIA toxins A/B	*Clostridium difficile* Tox A/B Certest	Biotec
	Clostridium difficile Toxin A+ B	DRG Diagnostics
	GastroTect	Medical Chemical Corp
	VIDAS CDAB	Biomerieux

Abbreviations: EIA = enzyme immunoassay.