STATISTICAL ANALYSIS PLAN

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, COMPARATOR-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CRS3123 COMPARED WITH ORAL VANCOMYCIN IN ADULTS WITH *CLOSTRIDIOIDES DIFFICILE* INFECTION

Study: 19-0021

1.1 Table 1. Definitions of Terms

Term	Definition
Dose	Study intervention administered, where 4 doses a day are expected over a period of a treatment period of 10 days for a total number of 40 expected doses in the course of the study.
EOT	End of treatment visit (last day of study drug)
Follow-up Period	There will be a total of 3 Follow-up Visits (FUVs) after EOT and up to 60 days after EOT. FUV1 will be at least 2 days after the last dose of study drug and FUV2 will occur at Day 40 (± 3 days). FUV3 is a telephone contact on Day 70 (± 3 days).
Normalization of bowel movement / Resolution of diarrhea	Is defined as the resolution of diarrhea, which is less than 3 unformed bowel movements [UBM] [Bristol Stool Scale score of 5, 6, or 7] per day for 2 consecutive days.
Recurrence	Is defined as a return of diarrhea (≥ 3 UBM per day)
TOC	Test of Cure visit which coincides with FUV1
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Treatment Period	Day 1 through Day 10 (+2 window allowed)
Unformed bowel movements (UBM) / Diarrheal stools	Stool with a Bristol Stool Scale score of 5, 6, or 7

2 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the Crestone protocol 19-0021, "A Phase 2, Randomized, Double-Blind, Comparator-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of CRS3123 Compared with Oral Vancomycin in Adults with *Clostridioides Difficile* Infection." The statistical plan described is an a priori plan and no analyses have been conducted prior to the preparation of this plan. This SAP summarizes the study design and objectives and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol 19-0021. Changes made to the SAP after it has been signed but prior to study unblinding will be documented in an amendment. Any important changes made to the analyses will be described in the clinical study report (CSR). This SAP is based on amended protocol version 7.0 dated 23 August 2023.

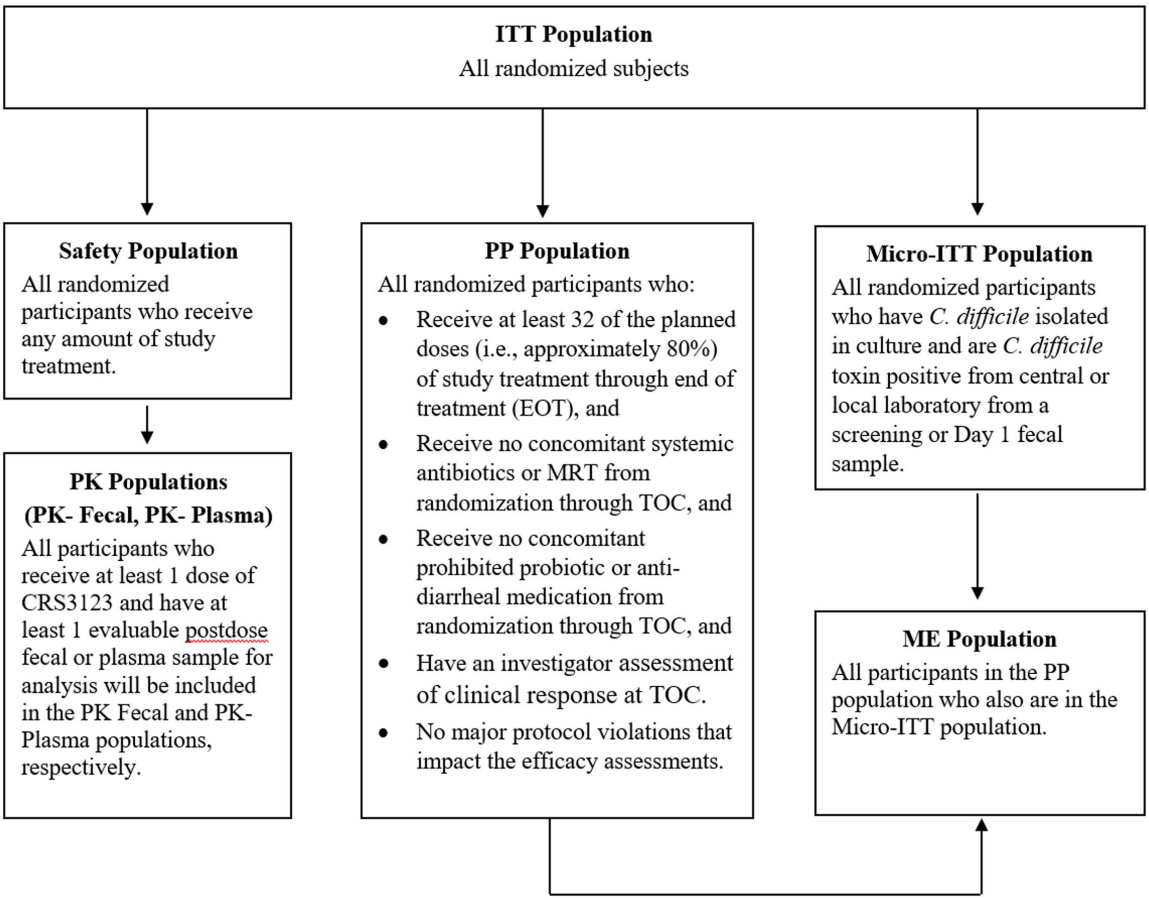
3 DATA MANAGEMENT

Data management procedures, including database design, and coding of medical history, adverse events, and prior and concomitant medications, will be performed by the lead clinical data manager. Data will be entered into an electronic case report form (eCRF) at the study sites. A series of logic and consistency checks will be conducted to ensure accuracy and completeness of the clinical database. Safety laboratory results, microbiology (fecal), bioanalytical, toxin, and pharmacokinetic data will be electronically transmitted from external vendors. After database lock, randomization data will be provided electronically from the IRT vendor. Refer to the Data Management Plan for further Data Management details.

4 DEFINITION OF ANALYSIS POPULATIONS

The relationship between the analysis sets is shown in Figure 1.

Figure 1: Overview of Analysis Populations



EOT = end of treatment; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetic; PP = Per Protocol; MRT= microbiota restoration therapy.

4.1 Enrolled Population

All participants who signed the informed consent form will be included in the enrolled population. Unless otherwise specified, data for subjects who are enrolled but are not randomized will be listed, but not included, in summary tables.

4.2 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized participants regardless of whether study treatment is administered. Participants will be grouped by the treatment to which they were randomized. This will be the population for analysis of the primary efficacy endpoint.

4.3 Microbiological Intent-to-Treat (Micro-ITT) Population

The Micro-ITT population will consist of all participants in the ITT population who have *C. difficile* isolated in culture at the central laboratory and who are *C. difficile* toxin positive (either Toxin A or Toxin B) from the central laboratory or local laboratory from a screening or Day 1 fecal sample. Day 1 fecal samples can include samples collected after the first dose of study drug. Subjects who have culture grown at JMI, have positive spore counts, or have a ribotype identified are considered as having *C. difficile* isolated in culture at the central laboratory. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

4.4 Per-Protocol (PP) Population

The Per-Protocol population will consist of all randomized participants who:

- Receive at least 32 of the planned doses (i.e., approximately 80%) of study treatment through EOT. Note, if vomiting occurs within 15 minutes of dosing, then that dose is considered a missed dose.
- Receive no concomitant systemic antibiotics or MRT from randomization through TOC, and
- Receive no concomitant prohibited probiotic or anti-diarrheal medication from randomization through TOC unless due to failure of study treatment and
- Have an investigator assessment of clinical response at TOC and
- No major protocol violations that impact the efficacy assessments. In particular, subjects who are toxin A or toxin B negative or who violate Inclusion Criteria 2 (More than 3 diarrheal stools per day in the 24 hours prior to randomization) will be excluded from the PP population. Any subjects who take the wrong study drug will also be excluded from the PP population.

Analyses in this population will be grouped by the treatment received.

4.5 Microbiologically Evaluable Population (ME)

The Microbiologically Evaluable population will consist of all participants in the Micro-ITT population who also meet all of the criteria for the PP population.

Analyses in this population will be grouped by the treatment to which they were treated.

4.6 Safety Population

The Safety population will consist of all randomized participants who receive any amount of study drug. All safety analyses will be conducted in this population and will be presented in the summary tables by the treatment the participants actually received. If a participant received both CRS3123 and vancomycin then that participant will be included in the CRS3123 arm for summaries in the Safety population. If the participant received both doses of CRS3123, the participant will be included in the 400 mg group for summaries in the Safety population.

4.7 Pharmacokinetic Population (PK-Plasma and PK-Fecal)

The Plasma Pharmacokinetic Population will consist of all participants who receive at least 1 dose of CRS3123 and have at least 1 evaluable postdose plasma sample for analysis.

The Fecal Pharmacokinetic Population will consist of all participants who receive at least 1 dose of CRS3123 and have at least 1 evaluable postdose fecal sample for analysis.

4.8 Population Determination

Inclusion into the ITT, Micro-ITT, Safety, PP and ME populations will be determined programmatically from the eCRF data. Inclusion into the PK populations will also be determined programmatically based on the presence of at least one evaluable record from the external PK plasma and fecal files.

The Medical Monitor and/or other sponsor designees will review the programmatic population determinations used to confirm inclusion and exclusion of participants into each of the analysis populations. Reviewers will be blinded to treatment assignment and will review the data concurrent with the conduct of the study. All study populations will be identified and finalized after database lock, but prior to study unblinding. The only exception is if subjects are determined to have taken the wrong study drug after study unblinding, they will be excluded from the PP population.

5 DEFINITION OF OUTCOME MEASURES

5.1 Definition of Efficacy Endpoints

A general overview of the efficacy endpoints is defined in Table 2.

Table 1: Clinical Response – Primary and Secondary Endpoints

Endpoints	Definition
Primary	
Rate of clinical cure at TOC in the ITT population[a]	Clinical cure is defined as survival through TOC and resolution of diarrhea (ie, < 3 unformed bowel movements [UBM] [Bristol Stool Scale score of 5, 6, or 7] at EOT with maintenance of resolution through TOC and no further requirement (in the investigator's judgment) for treatment for CDI through TOC. Clinical failure is defined as persistence of diarrhea (≥ 3 UBM per day), or treatment with anti-CDI standard of care at any time through TOC. Return of diarrhea after an initial response, or mortality prior to TOC is also considered a clinical failure. Note that this endpoint is based on Table 6 .
Secondary	
Rate of clinical cure at TOC in the Micro-ITT, PP, and ME populations[a]	Same as for the primary endpoint, above.
Rate of clinical cure at TOC as assessed by the investigator in the ITT, Micro-ITT, PP, and ME populations[b]	Investigator's assessment of clinical response (See Table 4 for more details).
Rate of total relief of symptoms of CDI at TOC in the Micro-ITT, PP, and ME populations[b]	Defined at TOC as resolution (< 3 per day) of UBMs (ie, return to Bristol Stool Scale scores 1-4 recorded on the Participant Daily Diary), an investigator's assessment of clinical cure, and the resolution of signs or symptoms of CDI recorded at baseline (ie, including fever [>37.7 °C], abdominal pain (as assessed by the investigator), and WBC > 15,000 cells/mm^3).
Time to resolution of diarrhea (through TOC) in the Micro-ITT, PP, and ME populations	The time to resolution of diarrhea is defined as the time elapsed from randomization to the last UBM before 2 consecutive days of < 3 UBM (Bristol Stool Scale score of 5, 6, or 7) per day through TOC.

Endpoints	Definition
Rate of early recurrence of CDI through FUV2 in the Micro-ITT and ME populations[c]	Rate of early recurrence of CDI is defined as a new episode of diarrhea (≥ 3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period) with a positive toxin result and requires retreatment for CDI before FUV2. Recurrence will be indicated as clinical failure by the investigator on the eCRF.
Rate of late recurrence of CDI (between FUV2 [Day 40 Visit] and FUV3 [Day 70 Visit]) in the Micro-ITT and ME populations[c]	Rate of late recurrence of CDI is defined as a new episode of diarrhea (≥ 3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period), with a positive toxin result and requires retreatment of CDI between FUV2 (Day 40 Visit) and FUV3 (Day 70 Visit). Recurrence will be indicated as clinical failure by the investigator on the eCRF.
Rate of recurrence of CDI through FUV3 [Day 70 Visit] in the Micro-ITT and ME populations[c]	Rate of recurrence of CDI is defined as a new episode of diarrhea (≥3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period) with a positive toxin result and requires retreatment for CDI at any point between TOC/FUV1 and FUV3 [Day 70 Visit]. Recurrence will be indicated as clinical failure by the investigator on the eCRF.
Time to recurrence of CDI though FUV3 [Day 70 Visit] in the Micro-ITT and ME populations	Time to recurrence of CDI is defined as the number of days from clinical cure at TOC to a new episode of diarrhea (ie, ≥ 3 UBM [Bristol Stool Scale score of 5, 6, or 7] (as evaluated by the clinician at the unscheduled Suspected Recurrence Visit) in a 24-hour period with a positive toxin result and requires retreatment for CDI prior to FUV3 [Day 70 Visit].
Rate of global cure in the Micro-ITT, PP, and ME populations[c]	Global cure is defined as a clinical cure at TOC without recurrence through FUV2.

a. Response will be determined programmatically according to Table 6.
b. Investigator's assessment of response will be determined according to Table 4.
c. Response will be determined programmatically according to Table 6.

5.2 Clinical Response Definitions for Investigator Assessment of Responses

The investigator's assessment of clinical response at EOT, TOC, and post-TOC visits will be classified as defined in the following tables and will be recorded in the eCRF. Once the participant is classified as a failure at TOC or subsequent visits, this assessment is carried forward to subsequent assessments, and investigator assessments of response are no longer needed for this participant at subsequent visits.

Table 2: Clinical Response – Investigator's Assessment at EOT

Assessment	Definition
Clinical Cure	Clinical cure is defined as resolution of diarrhea (i.e., < 3 UBM [Bristol Stool Scale score of 5, 6, or 7]) and no treatment with non-study medication (anti-CDI standard of care) through the EOT visit.

Clinical Failure	Clinical failure is defined as persistence of diarrhea (≥ 3 UBM per day) or treatment with non-study medication (anti-CDI standard of care) through the EOT visit.
Indeterminate	Participants for whom study data are unavailable for evaluation of clinical response at EOT for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment).

Abbreviations: CDI = *C. difficile* infection; EOT = end of treatment; UBM = unformed bowel movements.

Table 3: Clinical Response – Investigator's Assessment at TOC (FUV1)

Assessment	Definition
Clinical Cure	Clinical cure is defined as survival through TOC and resolution of diarrhea (i.e., < 3 UBM [Bristol Stool Scale score of 5, 6, or 7] at EOT with maintenance of resolution through TOC and no further requirement (in the investigator's judgement) for treatment for CDI.
Clinical Failure	Clinical failure is defined as persistence of diarrhea (≥ 3 UBM per day) after initial response, or the treatment with non-study medication (anti-CDI standard of care), or mortality through TOC.
Indeterminate	Participants for whom study data are unavailable for evaluation of clinical response at TOC for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment).

Abbreviations: CDI = *C. difficile* infection; TOC = test of cure (occurring at FUV1); UBM = unformed bowel movements.

Table 4: Clinical Response – Investigator's Assessment post-TOC

Assessment	Definition
Sustained Clinical Cure	Investigator's assessment of clinical cure at TOC (as defined in Table 4, above), no recurrence between TOC and specified visit. Recurrence is defined as the return of diarrhea (≥ 3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period), with a positive toxin result and requires retreatment for CDI through the specified visit.
Clinical Failure	Investigator's assessment of clinical failure at TOC (as defined in Table 4, above), or a recurrence between TOC and the specified visit.
Indeterminate	Participants for whom study data are unavailable at for the specified visit for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment).

Abbreviations: CDI = *C. difficile* infection; FUV = Follow-up Visit; TOC = test of cure (occurring at FUV1).
Note: Recurrence will only be assessed for participants with clinical cure at TOC.

5.3 Programmatic Clinical Response Definitions - Primary Efficacy Endpoint at TOC

The primary efficacy endpoint for the study is clinical cure at TOC in the ITT population. Clinical response for this endpoint will be determined programmatically based on the investigator's assessment at TOC and as outlined in Table 6. Note that once the participant is classified as a failure at TOC or subsequent visits, this assessment is carried forward to subsequent assessments and the participant will be classified as a failure, regardless of whether an investigator's assessment is available at post-TOC visits.

Table 5: Programmatic Clinical Response at TOC

Clinical Cure	Clinical cure is defined as survival through TOC and resolution of diarrhea (i.e., < 3 UBM at EOT with maintenance of resolution through TOC and no treatment with non-study medication (anti-CDI standard of care) through TOC.
Clinical Failure	Clinical failure is defined as persistence of diarrhea (≥ 3 UBM per day) or the need for additional (non-study) medication (anti-CDI standard of care through TOC) or mortality prior to TOC. Recurrence of diarrhea after an initial response at any point through TOC is also considered a clinical failure. Additionally, participants who are classified as clinical cure at TOC on the eCRF but take a potentially effective anti-CDI treatment through TOC (e.g., metronidazole, vancomycin, fidaxomicin, bezlotoxumab, or microbiota restoration therapy [MRT]) will be programmatically classified as clinical failure.
Indeterminate	Participants who meet any of the following criteria will also be programmatically classified as indeterminate: • Participants for whom study data are unavailable for evaluation of clinical response at TOC for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment) • Participants who are classified as clinical failure on the eCRF at TOC, but take medication or receive therapy that can alter normal gastrointestinal (GI) flora (e.g., systemic antibiotics for infections other than CDI) or receive therapy that can cause diarrhea (e.g., laxatives or tube feeds) through TOC • Participants who are classified as clinical cure on the eCRF at TOC, but take medication that can cause constipation or decrease in stool frequency (e.g., Imodium) through TOC

Abbreviations: CDI = *Clostridioides difficile* infection; TOC = test of cure; UBM = unformed bowel movements

5.4 Programmatic Clinical Response Definitions: EOT, FUV2, and FUV3

The protocol also calls for the same programmatic clinical response definitions to be derived for EOT and FUV2; these are provided Table 7 and Table 8.

Table 6: Programmatic Clinical Response at EOT

Clinical Cure	Clinical cure is defined as survival through EOT and resolution of diarrhea (i.e., < 3 UBM [Bristol Stool Scale score of 5, 6, or 7] per day) with maintenance of resolution through EOT and no treatment with non-study medication (anti-CDI standard of care) through EOT.
Clinical Failure	Clinical failure is defined as persistence of diarrhea (≥ 3 UBM per day) or the need for additional (non-study) medication (anti-CDI standard of care through EOT) or mortality through EOT. Recurrence of diarrhea after an initial response at any point through EOT is also considered a clinical failure. Additionally, participants who are classified as clinical cure at EOT on the eCRF but take a potentially effective anti-CDI treatment through EOT (e.g., metronidazole, vancomycin, fidaxomicin, bezlotoxumab, or MRT) will be programmatically classified as clinical failure.
Indeterminate	Participants who meet any of the following criteria will also be programmatically classified as indeterminate: • Participants for whom study data are unavailable for evaluation of clinical response at EOT for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment) • Participants who are classified as clinical failure on the eCRF at EOT, but take medication or receive therapy that can alter normal GI flora (e.g., systemic antibiotics for infections other than CDI) or receive therapy that can cause diarrhea (e.g., laxatives or tube feeds) through EOT • Participants who are classified as clinical cure on the eCRF at EOT, but take medication that can cause constipation or decrease in stool frequency (e.g., Imodium) through EOT

Abbreviations: CDI = *Clostridioides difficile* infection; eCRF = electronic CRF; EOT = end of treatment; MRT= microbiota restoration therapy; GI = gastrointestinal; UBM = unformed bowel movements

Table 7: Programmatic Clinical Response post TOC/FUV1

Sustained Clinical Cure	Clinical cure at TOC, no recurrence between TOC and specified visit, and no further anti-CDI standard of care therapy through specified visit.
Clinical failure	All participants programmatically classified as a clinical failure at TOC, will be automatically classified as failures at the specified visit. Recurrence of diarrhea between the initial response and the specified visit is considered a clinical failure at the specified visit unless diarrhea has a proven cause other than *C. difficile*. Additionally, participants who are classified as clinical cure at the specified visit on the eCRF but take a potentially effective anti-CDI standard of care treatment (e.g., metronidazole, vancomycin, fidaxomicin, bezlotoxumab, or MRT) at any point through the specified visit will be programmatically classified as clinical failure.
Indeterminate	Participants who meet any of the following criteria will be programmatically classified as indeterminate: • Participants for whom study data are unavailable for the specified visit for any reason (e.g., missing data, lost to follow-up, did not attend the clinic appointment) • Participants who are classified as indeterminate at TOC will be classified as indeterminate at the specified visit unless they have previously been classified as a failure, (in which case these subjects will classified as failure) • Participants who are classified as clinical failure on the eCRF at the specified visit, but take medication or receive therapy that can alter normal GI flora (e.g., systemic antibiotics for infections other than CDI) or receive therapy that can cause diarrhea (e.g., laxatives or tube feeds) through the specified follow-up visit • Participants who are classified as sustained clinical cure on the eCRF at the specified visit, but take medication that can cause constipation or decrease in stool frequency (e.g., Imodium) through the specified visit

Abbreviations: CDI = *Clostridioides difficile* infection; eCRF = electronic CRF; MRT= microbiota restoration therapy; FUV1 = Follow-up Visit 1; GI = gastrointestinal; TOC = test of cure

5.5 CDI-DaySyms™

Health-Related Quality of Life will be assessed using the CDI-DaySyms™ instrument which is a valid measure of these patient-reported CDI symptoms (Kleinman et al., 2018 and also Talbot et al., 2019). The CDI-DaySyms™ questionnaire will be included as part of the Participant Daily Diary and will be filled out by the participant daily from screening through

TOC/FUV1. The self-administered questionnaire measures a broad range of CDI symptoms that focus on the burden and/or impact of CDI on patients' lives. The questionnaire consists of a total of 10 CDI symptoms categorized into 3 domains (diarrhea symptoms, abdominal symptoms, and systemic/other symptoms). Each item is scored on a 5-point Likert scale (none = 0, mild = 1, moderate = 2, severe = 3, and very severe = 4), and the scores within each domain are averaged to provide 3 separate domain scores.

The Diarrhea Symptoms domain is calculated by averaging the scores from the first 3 questions (diarrhea, need to empty bowels right away, need to go to the bathroom more than usual). The Abdominal Symptoms domain is calculated by averaging the scores from items 4 through 6 (abdominal cramping, abdominal pain, feeling bloated). The Systemic/Other Symptoms domain is calculated by averaging the scores from items 7-10 (feeling tired, lack of energy, lightheadedness, lack of appetite). For the Diarrhea Symptoms domain, if Item 1 (diarrhea) is available, then a domain score is calculated even if Items 2 and 3 are missing. In all other cases, if greater than 50% of the items are missing, then the Diarrhea Symptoms domain is marked as missing. For the Systemic/Other Symptoms Domain Score, the domain score is only calculated if none of the 4 items are missing. For the Abdominal Symptoms Domain, the domain score will be calculated as long as 2 of the 3 items are available. These missing data calculation rules are based on Talbot et al., 2019 and communication with the FDA.

6 STATISTICAL METHODS AND GENERAL CONSIDERATIONS

6.1 Sample Size

This study is not powered for a hypothesis test. Rather the sample size was chosen in order to provide a reasonable estimate of the rate of clinical cure at TOC to allow for planning of future studies. This study will provide an initial assessment of safety and efficacy data to inform the future development of CRS3123.

If 36 participants are enrolled in each CRS3123 treatment arm and the true rate of clinical cure at TOC is 0.83 in each group, then the exact 95% confidence interval for the treatment of cure rate is (0.67, 0.94). Alternatively, if 30 participants are enrolled in each CRS3123 treatment arm and true rate of clinical cure at TOC is 0.83, then the 95% CI for the rate is (0.65, 0.94). Alternatively, if 12 participants are enrolled in each CRS3123 treatment arm and the true rate of clinical cure at TOC is 0.83, then the 95% exact CI for the rate is (0.52, 0.98).

6.2 Randomization and Masking

Participants will be randomly assigned in a 1:1:1 ratio to one of three treatment arms: CRS3123 200 mg po bid (i.e., 400 mg/day), CRS3123 400 mg po bid (i.e., 800 mg/day), or vancomycin 125 mg po qid (i.e., 500 mg/day). Randomization will be stratified by first episode or by first recurrence of CDI. All participants will be centrally assigned to randomized study treatment with an IRT. Before the study is initiated, login information and

directions for the IRT will be provided to each site. Approximately 30 to 36 participants are planned per treatment arm, for a total of approximately 90 to 108 participants for the study.

After informed consent has been obtained and study eligibility established, the IRT will assign a randomization number to that participant. The IRT will also assign an appropriate blister pack of double-blind study treatment that will be available at the site for that participant and visit. The blinded study site's pharmacist or designee will obtain the randomization number from the IRT. Once the IRT provides the randomization number, the participant is considered randomized regardless of whether the participant ultimately receives the study treatment.

Once a randomization number has been assigned to a participant, the number cannot be reused even if the participant discontinues the study early or withdraws prior to receiving any interventional treatment. Participants who discontinue from the study or who have been previously randomized in the study will not be permitted to re-enter and will not be replaced. Similarly, investigational product dispensed to the participant may not be reused during the study, even if the blister pack is returned unopened.

Those blinded to study treatment assignment throughout the study include the sponsor, CRO, investigator, study monitor, study statistician, study pharmacist and personnel, clinical study personnel participating in direct participant care and those involved in all clinical evaluations. Those unblinded to study treatment assignment include the bioanalytical laboratory, unblinded statistician or programmer, and the designated investigational product distribution team. To minimize the potential for bias, treatment randomization information will be kept confidential by and from the sponsor personnel and will not be released to the investigator, investigational site personnel, CRO, or the study monitor until the conclusion of the study.

If study treatment is determined not to be safe and/or not tolerated, the study treatment assignment for those participants with a significant safety concern may be unblinded. The investigator, Crestone medical monitor, and the InClin medical monitor will review the participant's data, discuss the findings, and jointly decide to unblind the treatment assignment, continue, or terminate enrollment in the study.

The blind may also be broken in the case of a medical emergency that requires the investigator to know the identity of the study treatment to appropriately guide the participant's medical management. Before unblinding the treatment, the investigator is strongly advised to discuss options with the InClin medical monitor or appropriate sponsor study personnel. If the blind is broken for any reason and the investigator is unable to contact the sponsor before unblinding the treatment, the investigator must notify the sponsor as soon as possible, without revealing the participant's study treatment assignment (unless important to the safety of participants remaining in the study). All instances of treatment unblinding will be thoroughly investigated and documented by a designated member of the sponsor team who, if they are unblinded during this process, will thereafter remain unblinded until the conclusion of the study.

In the event of a quality assurance audit, the auditor will be allowed access to unblinded study treatment records at the investigational product distribution sites to verify that randomization/dispensing has been done accurately.

After the database is locked and the SAP is final, and all analysis populations have been determined, the study will be unblinded.

6.3 Interim Analysis

There is no planned interim analysis of efficacy or safety for this study.

As per the protocol, a Data Safety Monitoring Board (DSMB) will be established and managed in this study by the National Institute of Allergy and Infectious Diseases (NIAID); the DSMB will review all AEs and other safety information, as detailed in the DSMB charter.

6.4 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Baseline – A baseline value is the last non-missing value recorded prior to the first dose of study drug. For subjects who never get dosed, the screening measurements will be the baseline. If an assessment has both a date and time that exactly match the date and time of first dose of study drug, this assessment will be counted as baseline.

- Change from baseline – Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus that subject's baseline value.

- Study day – For a given date (date), the study day is calculated as days since the date of first dose of study drug (firstdose).

    - Study day = date – firstdose + 1, where date ≥ firstdose

    - Study day = date – firstdose, where date < firstdose

- Days – Durations, expressed in days, between one date (date1) and another later date (date2) are calculated using the following formula: duration in days = (date2-date1+1).

- Body Mass Index – BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2].

- Age, in years, will be computed from the date of informed consent and the date of birth.

6.5 Handling of Missing Dates / Times and Data:

All missing data and missing and partial dates for events occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained missing data will be handled as outlined below.

- All AEs with partial or missing dates and times will be considered treatment emergent unless a partial start date and/or time indicates the AE began prior to the start of study medication or a stop date indicates the AE ended prior to the start of study medication.

- The severity and causality assessment for adverse events should not be missing and will be queried for a value. Should there be missing data, adverse events with missing severity will be considered severe and adverse events with missing relationship to study drug will be considered related to study drug.

- All medications with partial or missing dates and times recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the first dose of study treatment.

- For the Investigator's assessment of clinical response, subjects will be defined as indeterminate if the Investigator cannot determine whether the subject is a clinical cure/improvement or failure or if any data is missing to make a determination.

- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.

- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only subjects with available data will be included in the denominators).

6.6 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

- All listings will be presented by treatment assigned and sorted by ascending subject number within these. All relevant data captured on the eCRFs and external data sources, including specific descriptions of 'other' and comments fields will be included on the listings.

- All summary tables will be presented by treatment arm. Summary tables presenting results by study visit will include all scheduled study visits using informative visit labels. For baseline tables (excluding MIC tables) and safety tables, results will also be presented for both CRS3123 groups combined.

- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of PK plasma concentrations will also include the geometric mean (GM) and coefficient of variation (CV).

- Frequency counts and percentages will be reported for all categorical data.

- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.

- For all "by visit" safety tables (e.g., laboratory values, vital signs, ECGs), nominal visits will be summarized. In addition, within tables that summarize changes from baseline, the minimum and maximum post-baseline values will be summarized to take unscheduled visits into account.

- Version 9.4 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

- Exact confidence intervals around proportions will use the Clopper-Pearson method.

- Confidence intervals around differences of proportions will use the Miettinen & Nurminen method.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to this will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

7 STATISTICAL ANALYSES

7.1 Screening, Analysis Populations, and Subject Disposition

The number and percentage of subjects included in each of the analysis populations (ITT, PP, Safety, Micro-ITT, ME, PK-Plasma, PK-Fecal) will be summarized by treatment group in the Enrolled Analysis Set. The number of subjects screened and the reasons for screen failures will also be summarized. A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion/exclusion from the analysis population and the reason for exclusion from each analysis population.

The number and percentage of subjects completing the study, prematurely discontinuing from study drug, and prematurely withdrawing from the study will be presented for each treatment group for the ITT, Safety, and ME populations. Reasons for premature discontinuation of study drug, and/or premature withdrawal from the study, as recorded on the eCRF will be summarized (number and percentage) by treatment group.

A listing of all subjects who prematurely discontinued from study drug or prematurely withdrew from the study will be presented, and the primary reason for discontinuation of study drug or withdrawal from the study will be provided. In addition, a listing will be provided for all subjects that shows inclusion into each of the analysis populations, as well as a listing of inclusion and exclusion findings.

7.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group in the ITT, Safety, Micro-ITT, and ME analysis populations. A table will present the subject demographics (e.g., gender, age, age category [18- <65, ≥65) ethnicity, and race) and baseline characteristics (height, weight, BMI, C-Reactive protein, and number of subjects with WBC >15,000 cells/mm^3) collected before the start of study drug as well as the subject's type of CDI episode (Primary versus First Recurrence), and the randomized "CDI episode" stratum (Primary versus First Recurrence).

A demographic data listing, which includes the date the informed consent was signed, will also be provided.

7.3 Medical and Surgical History

Medical history will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) classification, version 23.1. Medical and surgical history will be summarized for the ITT Population and Safety population by system organ class, preferred term, and treatment group. Subjects reporting the same system organ class or preferred term more than once will be counted only once for that system organ class and preferred term.

A listing of medical and surgical history will be provided.

7.4 Prior and Concomitant Medications

All other prescription medications and over-the-counter medications, including herbal, nutritional, and dietary supplements (e.g., any antacid, iron supplement, or multivitamin) or vaccines administered between randomization and the end of the study will be documented in the eCRF. All prior antibiotic therapies taken within 30 days prior to screening, and systemic corticosteroids taken within 2 weeks prior to screening will also be recorded.

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHO Drug– WHO GLOBAL B3 2020-09-01) dictionary.

Prior medications are those medications taken before the first dose of study drug. Concomitant medications are those medications taken at the start of study drug or initiated after the initial dose of study drug, or medications that were initiated prior to the start of study drug and continue to be taken after study drug is administered.

The proportion of subjects who receive the following prior and concomitant medications will be summarized by ATC level 3 class, preferred term, and treatment group in the Safety and ITT populations:

- Prior medications taken amongst All Subjects (ITT, Safety populations)
- Prior CDI medications taken amongst All Subjects (ITT, mITT)
- Concomitant medications taken amongst All Subjects (ITT, Safety Population)

Subjects will be counted only once for an ATC class and preferred term.

A listing will be provided of all prior and concomitant medications received, and will include the reason for receiving, dose, frequency, and route. A separate CDI history listing will be provided including the type of CDI episode, when the primary episode occurred, and the CDI medications.

7.5 Randomization, Study Drug Exposure and Compliance

Subjects are randomly assigned to treatment in one of three treatment arms in a 1:1:1 ratio as per the following table. On the Participant Daily Diary, the subjects should record any missing doses. If vomiting occurs within 15 minutes of dosing, then that dose is considered a missed dose.

Table 8: Treatment Arms and Subject Dosing Regimen

Arm	Study Treatment, Dose, Duration	Study Treatment Administration
A	CRS3123, 200 mg po bid (i.e., 400 mg/day) (daily doses 1 and 3) and placebo bid (daily doses 1 to 4) given approximately q6h (± 1.5 h) for 10 days	CRS3123 (1 capsule of 200 mg + 1 capsule of placebo) at daily doses 1 and 3 1 capsule of placebo at daily doses 2 and 4
B	CRS3123, 400 mg po bid (i.e., 800 mg/day) (daily doses 1 and 3) and placebo bid (daily doses 2 and 4) given approximately q6h (± 1.5 h) for 10 days	CRS3123 (2 capsules of 200 mg) at daily doses 1 and 3 1 capsule of placebo at daily doses 2 and 4
C	Vancomycin, 125 mg po qid (i.e., 500 mg/day) given approximately q6h (± 1.5 h) for 10 days	Vancomycin (1 capsule of 125 mg + 1 capsule of placebo) at daily doses 1 and 3 Vancomycin (1 capsule of 125 mg) at daily doses 2 and 4

Abbreviations: bid = twice daily; po = Oral; h = hours; qid = 4 times daily, q6h = every 6 hours.

A listing of all randomized participants will be provided. The listing will include the randomized CDI episode (Primary versus First Recurrence) as well as the participant's actual type of CDI episode. The randomized and actual CDI episode should be identical unless there are errors in the randomization stratum.

- The duration of treatment and study drug compliance will be summarized in the ITT and Safety populations. The number of Oral Doses (i.e., capsules) taken over each 24-hour dosing period (maximum of 4 doses a day) for a total potential number of 60 capsules per subject will be summarized as well.

- Duration of Treatment: 'Defined as the number of calendar days from when the subject first received study treatment until the last data study treatment was received and is calculated as (date of last dose – date of first dose +1).
- Compliance to Study Drug: 'Calculated based on the total number of capsules taken for a subject, divided by the total number of expected capsules (60). Compliance is calculated as follows:

$$\text{Compliance (\%)} = 100 \text{ x } \frac{\text{(Number of capsules taken)}}{60}.$$

- Number of Subjects ≥80 % compliance
- Number of Subjects < 80 % compliance

All exposure and dosing data will also be provided in by-subject listings. Drug accountability information will be listed.

7.6 Efficacy Analyses

The primary and secondary efficacy endpoints are identified in Table 10.

Table 9: Efficacy Endpoints

	Efficacy Populations			
	ITT	**micro-ITT**	**PP**	**ME**
Primary:				
Rate of clinical cure at TOC	√			
Secondary and Exploratory:				
Rate of clinical cure at TOC		√	√	√
Rate of clinical cure at TOC as assessed by the investigator	√	√	√	√
Rate of total relief of symptoms of CDI at TOC		√	√	√
Time to resolution of diarrhea through TOC		√	√	√
Rate of early recurrence of CDI through FUV2 (Day 40)		√		√
Rate of late recurrence of CDI between FUV2 (Day 40) and FUV3 (Day 70)		√		√
Rate of recurrence of CDI through FUV3 (Day 70)		√		√
Time to recurrence of CDI though FUV3 (Day 70)		√		√
Rate of global cure (clinical cure at TOC and no recurrence through FUV2 [Day 40])		√	√	√

CDI= *Clostridioides difficile* infection; EOT = end of treatment; FUV=follow-up visit; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent to treat; PP=per-protocol; TOC=test of cure

7.6.1 Primary Efficacy Analysis

The primary efficacy analysis is an examination of the (programmatic) rate of clinical cure (Table 6) in the CRS3123 groups versus the rate of clinical cure in the vancomycin group at TOC in the ITT population. The number and percentage of clinical cure, clinical failure and indeterminate responses will be summarized by treatment group and an exact 95% CI and will be provided for the clinical cure rates in each treatment group. For each of the CRS3123 dosing groups, 95% CIs for the difference between the clinical cure rates versus the vancomycin group will be calculated using the Miettinen & Nurminen method. A summary

of reasons for programmatic clinical failure and indeterminate response at the TOC Visit will also be provided in the ITT population.

7.6.1.1 Additional Analyses for Clinical Cure at TOC

In addition, the rates of clinical cure at TOC will be summarized by randomization stratum in the ITT population.

The following two sensitivity analyses will also be conducted in the ITT population.

- Sensitivity analysis #1: The primary efficacy analysis will be repeated but subjects whose TOC visit occurs less than 2 days from the last dose of study drug will categorized as indeterminate.

- Sensitivity analysis #2: The primary efficacy analysis will be repeated but subjects who have ≥3 UBM as reported in the subject diary in any 24-hour period from the last dose of study drug date to the TOC visit date will be categorized as indeterminate.

7.6.2 Secondary Efficacy Analyses

For all secondary endpoints that are rates, these will be summarized by treatment arm in the relevant populations and exact 95% CI will be provided for the rates in each treatment group. Additionally, for each of the CRS3123 dosing groups, 95% CIs for the difference between the clinical cure rates versus the vancomycin group, will be calculated using the Miettinen & Nurminen method.

Additionally, all primary and secondary efficacy endpoints will be accompanied by subject listings.

7.6.2.1 Rate of (programmatic) clinical cure at TOC

The rate of (programmatic) clinical cure will also be summarized in a similar manner as outlined in Section 7.6.1 for the micro-ITT, PP and ME populations.

The rate of programmatic clinical cure will also be summarized in a similar manner by CDI Episode (Primary or First Recurrence) in the ITT population.

7.6.2.2 Investigator's assessment of clinical cure at TOC

The Investigator's assessment of clinical cure will be as described in Table 4. The number of subjects with an Investigator's assessment of clinical cure, clinical failure, and indeterminate at TOC will be summarized at TOC for both treatment groups in the ITT, micro-ITT, PP and ME populations. Note subjects with an indeterminate response at TOC will be excluded from summaries in the ME populations.

7.6.2.3 Rate of total relief of symptoms of CDI at TOC

The total relief of symptoms of CDI at TOC is achieved when all the following criteria are met:

- the resolution of UBMs (< 3 per day with Bristol Stool Scale scores 1-4 recorded on the Participant Daily Diary on the calendar day of the TOC visit)
- an investigator's assessment of clinical cure,
- resolution of signs or symptoms of CDI recorded at baseline of:
  - no fever [>37.7 °C]
  - no abdominal pain
  - WBC <15,000 cells/mm^3.

The resolution of abdominal pain as assessed by the investigator will be used. If the investigator's assessment of abdominal pain is missing, then the abdominal pain assessment from the patient diary will be used. Persistence of any parameter will be classified as non-total relief. If the Bristol stool score reported on the patient diary is missing or is different from the Investigator's assessment then only the Investigator's assessment will be used to determine total relief of symptoms. If any of the other criteria listed above are missing, then these participants will be classified as indeterminate.

The percentage of subjects with total relief of symptoms of CDI at TOC will be summarized by treatment group in the micro-ITT, PP, and ME populations.

7.6.2.4 Time to resolution of diarrhea through TOC

The time to resolution of diarrhea is defined as, the time elapsed in (decimal) days, from the randomization to the last UBM before 2 consecutive days of < 3 UBM (Bristol Stool Scale score of 5, 6, or 7) per day through TOC. As an example: if a subject was randomized on Day 1 at 10 AM and has their first 2 days of < 3 UBMs on Day 8 and Day 9, and if the last UBM on Day 8 was at 10 pm, then this subject would have a time to resolution of diarrhea of 180.0 hours or 7.5 days. If a subject never has resolution of diarrhea trough TOC, then the time to resolution of diarrhea is censored as the time of the last bowel movement on or prior to TOC.

Kaplan-Meier, time to event analysis will be used to compare the treatment groups. When the event is not observed, the last date and time the subject reported 'no resolution' (i.e.≥ 3 UBM with a Bristol Stool Scale score of 5, 6, 7) will be used as the censored time measurement. The "no resolution" date and time will coincide with the last reported UBM date and time. The Investigator Assessment form and the Participant Daily Diary form will be used to assess the last available date without resolution through the TOC visit. Kapan-

Meier Survival figures will be produced displaying the survival (step-down) curves for the 3 treatment groups. These KM figures and summaries will be completed for the micro-ITT, PP and ME populations.

7.6.2.5 Rate of early recurrence of CDI through FUV2 (Day 40 visit)

Early recurrence of CDI is defined as the return of diarrhea (≥3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period), a stool sample positive for *C. difficile* Toxin A and/or B, and requires retreatment for CDI before FUV2. Recurrence will be indicated as clinical failure by the investigator on the eCRF. Additionally, subjects who are treated with an anti-CDI medication prior to FUV2 will be programmatically classified as recurrences and failures, even if clinical failure is not indicated on the eCRF.

Only subjects who were a clinical cure at TOC (programmatic clinical cure) and had no recurrence thorough FUV2 will be assessed for early recurrence.

The number and percentage of subjects with early recurrence of CDI through FUV2 will be summarized by treatment groups in the micro-ITT and ME populations.

7.6.2.6 Rate of late recurrence of CDI between FUV2 (Day 40) and FUV3 (Day 70)

Late recurrence of CDI is defined as the return of diarrhea (≥3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period), a stool sample positive for *C. difficile* Toxin A and/or B, and requires retreatment of CDI between FUV2 (Day 40) and FUV3 (Day 70). Recurrence will be indicated as clinical failure by the investigator on the eCRF. Additionally, subjects who are treated with an anti-CDI medication between FUV2 and FUV3 will be programmatically classified as recurrences and failures.

If a subject has an early recurrence, then late recurrence will be undefined. Only subjects who were a clinical cure at TOC (programmatic clinical cure based on the Investigator's assessment) and had no recurrence thorough FUV2 will be assessed for late recurrence.

The number and percentage of subjects with a late recurrence of CDI will be summarized by treatment groups in the micro-ITT and ME populations.

7.6.2.7 Rate of recurrence of CDI through FUV3 (Day 70 Visit)

Recurrence of CDI is defined as the return of diarrhea (≥3 UBM [Bristol Stool Scale score of 5, 6, or 7] in a 24-hour period), a stool sample positive for *C. difficile* Toxin A and/or B, and requires retreatment of CDI through FUV3 (Day 70 Visit). Recurrence will be indicated as clinical failure by the investigator on the eCRF. Additionally, subjects who are treated with an anti-CDI medication through FUV3 (Day 70 Visit) will be programmatically classified as recurrences and failures.

Only subjects who were a clinical cure at TOC (programmatic clinical cure based on the Investigator's assessment) will be assessed for recurrence through FUV3.

The number and percentage of subjects with recurrence of CDI through FUV3 will be summarized by treatment groups in the micro-ITT and ME populations.

7.6.2.8 Time to recurrence of CDI though FUV3 (Day 70 Visit)

Time to recurrence of CDI is defined as the number of days from clinical cure at TOC to recurrence of symptoms (i.e., ≥3 UBM [Bristol Stool Scale score of 5, 6, or 7] per day, as evaluated by the clinician on the unscheduled Suspected Recurrence Visit), AND a stool sample positive for *C. difficile* Toxin A and/or B. Alternatively, the criteria for recurrence will also be met if the subject is treated with anti-CDI standard of care prior to FUV3 (Day 70 Visit). As an example: if a subject has clinical cure at TOC (Day 12) and suspected recurrence occurs at Day 25, then this will trigger a Suspected Recurrence Visit (unscheduled). If the assessment at this visit confirms the presence of ≥3 UBM for 2 or more days, then the time to recurrence would be 13 days (25-12). Only subjects who were a clinical cure at TOC (programmatic clinical cure based on the Investigator's assessment at TOC) will be assessed for time to recurrence of CDI through FUV3. If a subject never has recurrence of CDI through FUV3 then the time to recurrence of CDI is censored as the last available date without recurrence through the FUV3 visit.

Time to recurrence will be assessed in the Micro-ITT and ME analysis sets. Only subjects with clinical cure at TOC will be included in the analysis. The analysis for this time to recurrence of CDI through FUV3 will be similar to the KM analysis proposed for the time to resolution of diarrhea (through TOC), which is detailed in Section 7.6.2.4. The methods of analysis are the same except that, for this secondary outcome, should recurrence of CDI through FUV3 not occur, then the latest date and time the participant reported ≥3 UBM or the Investigator specified no recurrence will be used as the censored value. The date and time of the first of ≥3 UBM or the investigator identified a recurrence will be used as the time of recurrence.

7.6.2.9 Rate of global cure

Global cure (sustained clinical response) is defined as a clinical cure at TOC without recurrence through FUV2 (Day 40 Visit) and will be derived from the combination of the primary endpoint of (programmatic) 'Rate of Clinical Cure' and the secondary endpoint of the 'Recurrence of CDI (between TOC and FUV2)'. Any subject with a 'clinical cure' result for the former and no recurrence on the latter will be defined as a 'global cure'. Additionally, subjects who are treated with an anti-CDI medication through FUV2 (Day 40 Visit) will be included as a subject with recurrence. The rate of global cure will be calculated as follows:

$$= \frac{(\text{subjects with programmatic clinical cure at TOC AND no recurrence through FUV2})}{(\text{All Subjects in Analysis Set})} * 100.$$

The percentage of subjects with global cure will be summarized by treatment group in the micro-ITT, PP, and ME populations.

7.6.2.10 CDI-DaySyms™

The CDI-DaySyms™ domain scores of: Diarrhea symptoms, Abdominal symptoms and Systemic/Other for will be summarized by visit and treatment arm using summary statistics. Changes from baseline in domain scores to each post-baseline visit will also be summarized by visit and treatment arm in the Micro-ITT and ME populations.

All CDI-DaySyms™ question responses and domain scores will also be provided in by-subject listings.

7.7 Microbiology Assessments

For all patients, the central microbiology laboratory will attempt to isolate and quantitate *C. difficile* (from the initial, TOC, and recurrence episode stool samples, including early discontinuation due to clinical failure), and perform antimicrobial susceptibility testing.

The number of subjects with *C. difficile* isolated at baseline via culture and the number who are toxin positive (either local laboratory or central laboratory) at each relevant visit will be summarized in the micro-ITT population.

The minimum inhibitory concentrations (MICs) to CRS3123 and vancomycin will be summarized at baseline and each visit for subjects in the Micro-ITT and ME populations. MICs to CRS3123 and vancomycin will also be summarized separately at baseline and each visit. MIC summary statistics. In addition, the MIC_{50}, MIC_{90} and MIC Range of CRS3123 and vancomycin for *C. difficile* will be summarized by study drug for the mITT and ME populations. MIC_{50} and MIC_{90} are the antibiotic concentration that would inhibit the growth of 50% and 90% of tested isolates, respectively.

The number of isolates with each MIC will be summarized for all collected *C. difficile* isolates for CRS3123, fidaxomicin, metronidazole, moxifloxacin, and vancomycin.

All microbiology data will also be listed. Subjects with an MIC increase ≥4-fold over the baseline MIC for either CRS3123 or vancomycin will be listed.

7.8 Safety Analyses

All safety analyses will be conducted in the Safety population.

7.8.1 Adverse Events

Adverse events will be coded to System Organ Class (SOC) and preferred term using Version 23.1 of MedDRA.

Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or

worsened in severity following initiation of study drug and up through the last study visit (FUV3) or evaluation, or an SAE that occurs during or after the first administration of study drug up through 60 days after the final administration of study drug.

The following summaries for TEAEs will be provided by treatment group:

- An overall summary of AEs will include number and percentage of subjects in each treatment group who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE (defined as possibly related and or related to study drug), any severe or life-threatening TEAE, any serious TEAE (SAE), any drug-related SAE, any SAE leading to death, and any TEAE or SAE leading to premature discontinuation of study drug.

- Subject incidence of TEAEs by MedDRA system organ class and preferred term.

- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and worst severity/intensity (grade).

- Subject incidence of TEAEs related to study drug by MedDRA system organ class and preferred term.

- Subject incidence of serious TEAEs (SAEs) by MedDRA system organ class and preferred term

Summary tables will be presented alphabetically by system organ class and preferred term within system organ class. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug.

In addition, all AEs (including non-TEAEs), serious AEs (SAEs), fatal SAEs, SAEs leading to hospitalization, and TEAEs leading to study drug discontinuation or study discontinuation will be provided in listings.

7.8.2 Laboratory Values

Laboratory assessments for hematology, serum chemistry, and/or urinalysis will be performed at each visit indicated in the Schedule of Activities. Coagulation will be performed at screening and EOT. Assessments will be performed by a local laboratory at screening to ensure inclusion/ exclusion criteria are met and at the central laboratory for the remainder of the study. All summaries will be based on the central lab data and local laboratory data will only be listed.

All laboratory parameters will be converted to the conventional units prior to summarization. Descriptive statistics for hematology, coagulation, chemistry, and creatinine clearance results and the change from baseline will be summarized for baseline and post-baseline visits. The

highest and lowest post-baseline values and changes to these values will also be summarized for each parameter to allow for summarization of high and low values collected at unscheduled visits. Change from baseline will be calculated for each subject at the specified visit as the value at the specified visit minus the baseline value.

The grade of a laboratory measurement will be assigned programmatically using the CTCAE V5.0 (NCI-CTCAE version 5.0). Shift tables, from baseline to post-baseline visits will be provided by CTCAE V5.0 toxicity grade for selected chemistry, hematology, and coagulation parameters. The shift to highest grade post-baseline will also be included.

General detailed subject listings for all relevant laboratory data collected during the study will be provided. All CTCAE grades will be included in the listing and laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H).

7.8.3 Vital Signs

Blood pressure (systolic and diastolic), respiration rate, heart rate, and temperature will be summarized using descriptive statistics by treatment group at each time point at which they were measured. Descriptive statistics of the change from baseline to each post-baseline time visit will also be provided as well as the change to the maximum and minimum post-baseline values.

The number and percentage of subjects with abnormal values as identified by the threshold values provided in the table below, will be summarized by treatment group. Only subjects with both baseline and post-baseline values will be summarized for diastolic blood pressure increases.

All vital signs will also be provided in by-subject listings.

7.8.4 Electrocardiogram

12-lead ECG recordings will be obtained at screening and EOT (after resting in a supine position for 10 minutes) and before collection of blood for laboratory and PK assessments. Additional ECGs may be performed for any participant who experienced a cardiovascular-related significant medical event (e.g., tachyarrhythmia) during the course of the study.

Descriptive statistics for central ECG parameters of RR interval, PR interval, QRS duration, QT interval, and QTcF (using the Frederica's formula for correction) interval, as well as the changes from baseline will be presented by treatment group at each scheduled visit.

In cases where QTcF is not available from an ECG machine at the study site, the eCRF value for QTcF will be left blank and QTcF will be calculated programmatically as follows: (QT interval)/$(RR)^{1/3}$.

For QTcF values, a distribution showing counts and percentages for the increase from baseline to EOT will be provided using the following categories: <0, ≥1 - <30 msec, ≥30 - <60 msec, ≥60 - <90 msec, >=90 msec. Actual QTcF visit values will also be summarized using counts and percentages for the following categories: ≤ 450, > 450 - ≤ 480, >480 - ≤ 500, and >500 msec).

A listing of ECG data will also be provided and will include the tracing results of normal, abnormal and clinically significant status for these measurements as well as any linked AE or Medical History event.

7.8.5 Physical Examinations

Abnormal physical examination results in each treatment group will be tabulated by body system for each time point at which they were measured and will be listed.

7.8.6 Pharmacokinetic Analyses

Characterization of the plasma exposure by sparse sampling during the 10-day CRS3123 course of treatment for CDI is secondary objective for this study. Additionally, fecal concentrations of CRS3123 will be assessed as an exploratory endpoint at selected timepoints as described in the Schedule of Activities. Only blood and fecal PK samples collected from participants randomized to CSR3123 will be analyzed.

Plasma concentrations of CRS3123 (parent) and CRS3123-GLU3 (metabolite) will be measured in the collected blood samples at selected timepoints. Fecal concentrations of CRS3123 will also be measured. Plasma concentrations of CRS3123 and CRS3123-GLU3 and fecal concentrations of CRS3123 will be summarized in the PK-Plasma and PK-Fecal populations, respectively. These concentrations will be summarized by treatment arm using descriptive statistics and will be graphically displayed.

If feasible, primary parameters will be estimated from concentration versus time data using a population PK approach. These parameters include C_{max}, t_{max}, $t_{1/2}$, AUC_{0-24}, and CL/F, and accumulation ratio calculated using the estimated AUC_{0-24} on Day 10 vs. Day 1.

Methods and analysis for the population PK analysis will be provided in separate reports.

8 REFERENCE LIST

1. https://www.alere.com/en/home/about/stories/putting_c_diff_to_test-us.html?gclid=EAIaIQobChMIlIe84sOj5QIVQdbACh2RiQVXEAAYASAAEgJn2_D_BwE. Abbott Laboratories, Waukegan, IL. Accessed 17 October 2019.
2. Kleinman, L., Talbot, G. H., Hunsche, E., Schüler, R., & Nord, C. E. (2018). The CDI-DaySyms: Content Development of a New Patient-Reported Outcome Questionnaire for Symptoms of Clostridium difficile Infection. *Value in Health*, *21*(4), 441–448. https://doi.org/10.1016/j.jval.2017.08.3017
3. Talbot, G. H., Kleinman, L., Davies, E., Hunsche, E., Revicki, D., Roberts, L., Rosenberg, D., & Nord, C. E. (2019). Clostridium difficile Infection–Daily Symptoms (CDI-DaySyms™) questionnaire: psychometric characteristics and responder thresholds. *Health and Quality of Life Outcomes*, *17*(1). https://doi.org/10.1186/s12955-019-1142-9
4. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. National Institutes of Health, US Department of Health and Human Services. Published 27 Nov 2017. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
5. Miettinen, O., & Nurminen, M. (1985). Comparative analysis of two rates. *Statistics in Medicine*, *4*(2), 213–226. https://doi.org/10.1002/sim.4780040211
6. Goorhuis, A., Bakker, D., Corver, J., et al (2008). Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis 47, 1162-1170.
7. Merrigan, M., Venugopal, A., Mallozzi, M et al (2010). Human hypervirulent *Clostridium difficile* strains exhibit increased sporulation as well as robust toxin production. J Bacteriol 192, 49
8. Sponsor Responses to FDA Type C Meeting (IND 146348, SN0021, 4 May 2023).