STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 3, randomized, double-blind, active controlled study to compare the efficacy and safety of ridinilazole (200 mg, bid) for 10 days with vancomycin (125 mg, qid) for 10 days in the treatment of *Clostridium difficile* infection (CDI)

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VERSION HISTORY

Version	Approval Date	Description
1.0	12Feb2019	Original version
2.0	19Nov2021	Summary: The previous version of SAP was based on Protocol Amendment 3. This version is based on the most recent Protocol Amendment 8. To align with the protocol, major changes include the following: • Combine SMT19969/C004 and SMT19969/C005 into one study for analyses • Modify the definition of Sustained Clinical Response (SCR) • Update secondary and exploratory endpoints including microbiome, bile acid, and antibiotic susceptibility endpoints Other major changes include: • Add recurrence as one of the secondary endpoints • Clinical Cure is removed from the list of secondary endpoints and will be considered as sensitivity analysis for Clinical Response. SCR over 60 days post EOT is removed from the list of secondary endpoints and considered as an exploratory endpoint. • Update the ordering of secondary endpoints for testing • Add analyses for bile acids, ribotype and antibiotic susceptibility, medical resource utilization, patient reported outcomes, and CDI signs and symptoms • Update the analysis visit window for efficacy assessments • Update the analysis populations and variables for subgroup analyses This version also applies the latest template with updated structure and sections (e.g. removal of the sections for exploratory objectives and responsibilities).

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of combined efficacy and safety data as described in both SMT19969/C004 and SMT19969/C005 Protocol Amendment 8 dated August 9, 2021. Per Protocol Amendment 8, to minimize the potential, unknown impact of the coronavirus disease 2019 (COVID-19) pandemic on the trial and because of a much slower enrollment rate than anticipated due to the ongoing pandemic, Summit has decided to combine its ongoing, Phase 3 studies, SMT19969/C004 and SMT19969/C005, into one study with a pre-specified SAP when these blinded, identical studies are at least half enrolled. As a result, both studies will be closed and will proceed with database lock and statistical analysis. The combined analysis will comprise a minimum of 680 randomized subjects. The SAP will be finalized and approved prior to the unblinding for the final analysis.

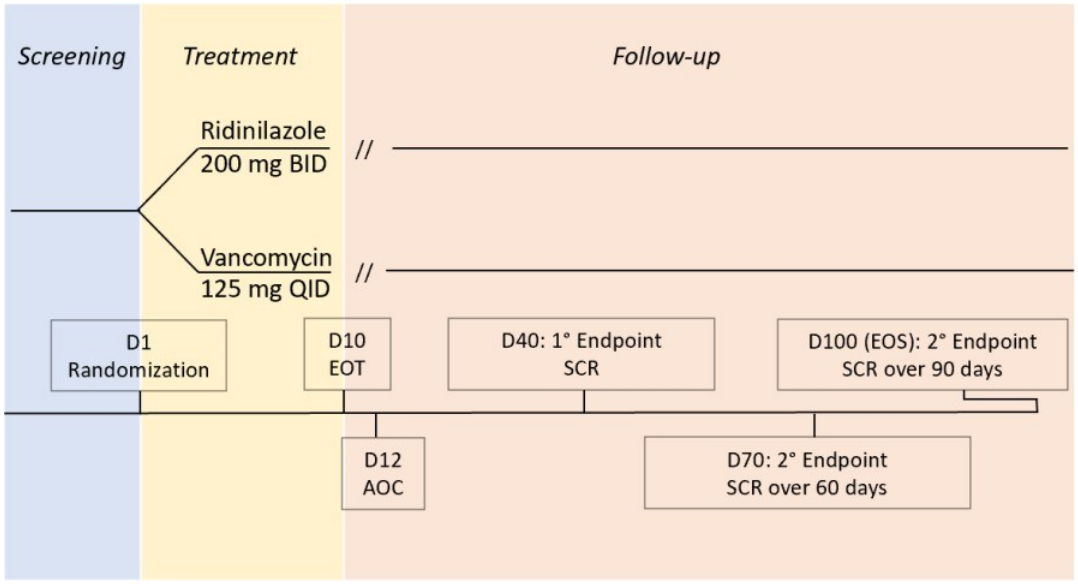
All analyses/outputs will be prepared by combining these two studies for reporting. Analysis methods specified in this document supersede those described in the study protocol should there be any difference.

1.1. Study Design

Each study is a Phase 3, randomized, double-blind, active controlled, parallel group, multi-center study to compare the efficacy of 10 days' dosing of ridinilazole 200 mg *bid* with vancomycin 125 mg *qid* in the treatment of subjects with *Clostridioides difficile (C. difficile)* infection (CDI). Approximately 680 subjects (340 per arm) with a confirmed diagnosis of CDI will be enrolled in the study.

It comprises a screening visit, a 10-day treatment period (beginning on the day of screening or the following day) and a 90-day follow-up period. The Schedule of Activities can be found in Section 5.1.

Figure 1: Study Schema



AOC: Assessment of Cure; EOS: End of study; EOT: End of Treatment; SCR: Sustained Clinical Response

1.2. Study Objectives

Primary Objective

- To compare the efficacy of 10 days' dosing of ridinilazole (200 mg *bid*) with vancomycin (125 mg *qid*) in the treatment of patients with CDI

Secondary Objectives

- To compare the safety and tolerability of 10 days' dosing of ridinilazole (200 mg *bid*) with vancomycin (125 mg *qid*) in the treatment of patients with CDI
- To characterize the systemic exposure of ridinilazole in a subset of patients treated with ridinilazole (200 mg *bid*) tablets
- To compare the effect of 10 days' dosing of ridinilazole (200 mg *bid*) with vancomycin (125 mg *qid*) on the gut bile acid composition and on the gut microbiome diversity at the end of treatment (EOT)

1.3. Endpoints

Primary Endpoint

The primary endpoint is Sustained Clinical Response (SCR) defined as Clinical Response and no recurrence of CDI through 30 days post EOT.

A sensitivity analysis for SCR will be conducted using the definition (i.e. Clinical Cure and no recurrence of CDI through 30 days post EOT) as stated in the Protocol Amendment 6 and earlier versions.

Secondary Endpoints

- Clinical Response is defined as
  - less than 3 unformed bowel movements (UBMs) for 2 consecutive days and maintained through the EOT without further CDI antimicrobial treatment at EOT+ 2 days or
  - the investigator's assessment that the subject is cured and no longer needs specific CDI antimicrobial treatment after completion of the course of study medication.

  The Investigator's assessment is based on the reduction of UBMs since baseline, clinical signs and symptoms and need for further treatment for CDI. A patient will be deemed cured once the Investigator's assessment is that the baseline CDI has resolved such that no further non-study CDI treatment is needed.

  Clinical Cure will be analyzed as a sensitivity analysis for Clinical Response. Clinical Cure is defined as the resolution of diarrhea (<3 UBMs in the 1-day period immediately prior to EOT that is maintained for 2 days after EOT).
- Recurrence is defined as a new episode of diarrhea (≥3 UBMs) in a 1-day period with a positive C. difficile free toxin test or Cell Cytotoxicity Neutralization Assay (CCNA) that requires CDI antimicrobial treatment in subjects who achieved Clinical Response.
- Change from baseline to EOT of the relative abundance of microbiome-derived secondary bile acids.

- SCR over 90 days post EOT is defined as Clinical Response and no recurrence of CDI through 90 days post EOT.

Exploratory Endpoints

- Time to resolution of diarrhea over the first 12 days – defined as the time from starting study treatment to the resolution of diarrhea (<3 UBMs in a 1-day period)
- CDI signs and symptoms
- Change from baseline of the relative abundance of the bile acid components – conjugated primary bile acids and microbiome-derived primary and secondary bile acids in stool samples
- SCR over 60 days post EOT is defined as Clinical Response and no recurrence of CDI through 60 days post EOT.
- Microbiome analysis

Safety Endpoints

- Adverse Events, clinical laboratory values, vital signs

Microbiology Endpoints

- Ribotype and susceptibility to ridinilazole, vancomycin and other antibacterial agents of C. difficile isolates collected in stool samples at baseline, EOT and recurrence

Pharmacokinetics (PK) Endpoints

- Ridinilazole concentrations in plasma

Health Economics and Outcomes Research (HEOR) Endpoints

- Medical resource utilization and health economics endpoints (e.g., hospital readmission rates and length of hospital stay)
- Change from baseline in EQ-5D-5L dimensions and health state visual analog scale (VAS) score

1.4. Statistical Hypotheses

The null (H_0) and alternative (H_1) hypotheses for the primary endpoint, SCR, can be expressed as:

H_0: $\mu_{RID} = \mu_{VAN}$

H_1: $\mu_{RID} \neq \mu_{VAN}$

Where μ_{RID} and μ_{VAN} are the SCR rates for ridinilazole and vancomycin, respectively.

The null (H_0) and alternative (H_1) hypotheses for the secondary endpoint Clinical Response can be expressed as:

H_0: $\mu_{RID} - \mu_{VAN} \leq -10\%$

H_1: $\mu_{RID} - \mu_{VAN} > -10\%$

Where μ_{RID} and μ_{VAN} are the Clinical Response rates for ridinilazole and vancomycin, respectively.

1.5. Sample Size Determination

Approximately 680 subjects (340 subjects per treatment group) will be randomly assigned to study treatment. The Modified Intent-to-Treat (mITT) population will be used for primary and secondary efficacy endpoints.

For the primary endpoint of Sustained Clinical Response, there is approximately 95% power of concluding superiority of ridinilazole over vancomycin using a 2-sided test at the 5% significance level under the assumption of an improvement of 15% with ridinilazole over vancomycin.

For the secondary endpoint of Clinical Response, there is about 90% power of concluding non-inferiority (NI) of ridinilazole compared to vancomycin using a 1-sided test at the 2.5% significance level and an NI margin of 10%.

1.6. Testing Procedures and Level of Significance

Superiority tests will be 2-sided at the 5% significance level. Non-inferiority will be established if the lower limit of the 2-sided 95% confidence interval (CI) for the difference between treatment proportions (ridinilazole - vancomycin) is not more than 10% worse (i.e. > -10%). To preserve the Type 1 error, a fixed sequence testing procedure will be used. The hierarchical testing order will be as follows. Specifically, if superiority is established for the primary endpoint SCR, then a test of non-inferiority in Clinical Response between ridinilazole and vancomycin will be triggered, using the estimated difference and its 95% CIs. Noninferiority will be declared if the lower limit of the 2-sided 95% CI for the estimated difference is > -10%. If the lower limit of the 2-sided 95% CI excludes 0%, superiority of ridinilazole in Clinical Response will be declared. If non-inferiority is established for Clinical Response, then test for the next secondary endpoint will be conducted at the 5% significant level (2-sided).

1. SCR
2. Clinical Response
3. Change from baseline to EOT of the relative abundance of microbiome-derived secondary bile acids
4. Recurrence
5. SCR over 90 days post EOT

1.7. Blinding and Randomization Methods

1.7.1. Blinding Method

The is a double-blind study. The blinding method is described in protocol Section 6.3.

1.7.2. Randomization Method

Central randomization is implemented in this study. Subjects are randomly assigned to one of the two treatment groups in a 1:1 ratio based on a computer-generated randomization schedule. The randomization is to be stratified by age (<65 years and ≥65 years), number of UBMs (<10 or ≥10) in the 24 hours prior to randomization, immunocompromised (Yes/No), and history of CDI (either none or 1 to 3 previous occurrences in the past 12 months). Of note, in Protocol Amendment 7,

number of UBMs and immunocompromised were added as randomization stratification factors but have not been implemented. Therefore, at the time of data cutoff all the subjects are randomized based on the two stratification factors: age and history of CDI.

1.8. Interim Analysis

No interim analysis will be performed.

2. GENERAL ANALYSIS CONSIDERATION

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

In general, baseline value is defined as the last non-missing value collected prior to the administration of the first dose of study treatment.

Study Day is derived as (assessment date - the first dose date +1) if assessment date is on or after the first dose date. Study Day is derived as (assessment date - the first dose date) if assessment date is prior to the first dose date. The first dose date will be identified as Study Day 1.

All statistical analyses will be performed using SAS® (Version 9.4 or higher) except that R packages may be used for data visualization and for specific exploratory analyses on microbiome data as needed.

2.1. Analysis Populations

Intent-to-Treat (ITT) Population

The ITT population includes all randomized subjects, regardless of the actual treatment received.

Safety Population

The safety population includes all subjects who received at least one dose of study treatment (ridinilazole or vancomycin). Subjects in this population will be analyzed based on the actual treatment received. This population will be used for all safety analyses.

Modified Intent-to-Treat (mITT) Population

The mITT population includes all randomized and treated subjects who have:

- ≥3 UBMs in the 24 hours prior to randomization
- A diagnosis of CDI confirmed by positive result obtained by regulatory approved free toxin tests or CCNA test

This population will be the primary population for the summary/analyses of efficacy endpoints, disposition, demographic and baseline characteristics, patient reported outcomes, bile acids and microbiome measures.

Subjects will be analyzed based on the randomized treatment assignment via IXRS.

Per-Protocol (PP) Population

Analysis for the primary and key secondary efficacy endpoints may be conducted based on the PP population if needed.

Pharmacokinetics (PK) Population

The PK population includes all ridinilazole-treated subjects with at least one ridinilazole concentration, including those below the level of quantification (BLQ).

2.2. Definition Of Subgroups

Subgroup analyses will be performed for the selected variables to assess the internal consistency of the treatment benefit and/or safety. The subgroup variables and the cutoff points are subject to change, if warranted, to better represent the data.

Table 1: Subgroup Definition

Subgroup	Definition of Subgroup
Age	<65, ≥65 years; <75, ≥75 years
Sex	Female, Male
Race	White, Not White
Ethnicity	Hispanic, Non-Hispanic
Geographic region	US/Canada, Europe, Latin America, Other
Number of UBMs at baseline	<10, ≥10
History of CDI in the past 12 months (eCRF)	None, 1-3 previous occurrences
Time since last episode of CDI (eCRF)	None, >0-3 months, >3 months
Baseline IDSA severity[a]	Severe, Non-Severe
Baseline Disease severity (UBM and WBC criteria)[b]	Severe, Moderate, Mild
Hospitalization status at baseline	Inpatient, Outpatient
Non-CDI antimicrobials usage at baseline[c]	Yes, No
Antimicrobial treatment for current CDI at randomization[c]	Yes, No
Proton pump inhibitors usage at baseline	Yes, No
Presence of ribotype 027 strain	Yes, No
Presence of hypervirulent strain	Yes, No
Immunocompromised[c,d]	Yes, No

US: United States; UBM: unformed bowel movement; CDI: *Clostridioides difficile* infection; eCRF: Electronic Case Record Form; IDSA: Infectious Diseases Society of America; WBC: white blood cell

[a] Non-severe: WBC $\leq 15\times10^9$/L and serum creatinine <1.5 mg/dL, Severe: WBC $>15\times10^9$/L or serum creatinine >1.5 mg/dL.

[b] Mild: <6 UBM/day or WBC $\leq 12\times10^9$/L, Moderate: 6-9 UBM/day or WBC >12 – 15×10^9/L, Severe: ≥ 10 UBM/day or WBC > 15×10^9/L.

[c] Grouping will be based on medical review.

[d] Subgroup analysis will be done if at least 5% of subjects are immunocompromised.

2.3. Visit Windows

The study protocol gives the overall study schedule and the permissible intervals for the visits (see Section 5.1). The analysis windows presented in Table 2 below will be used for key efficacy assessments.

Table 2: Analysis Window for Efficacy Assessments

Assessment	Visit/Period	Target Day/Period Per Protocol	Analysis Window
Clinical Response	EOT to EOT+2 or AOC visit	EOT: Study Day 10 (±1) AOC: Study Day 12 (+3)	Study Days 8– 16 (UBM data will be used for derivation if 8 ≤ study day of last dose ≤14. Investigator assessments will be used for derivation if investigator assessment at AOC visit is on or prior to Study Day 16.)
Clinical Cure	EOT to EOT+2	EOT: Study Day 10 (±1)	Study Days 8 – 16 (UBM data will be used for derivation if 8 ≤ study day of last dose ≤14)
SCR	Through 30 days post EOT	Study Day 40 (+5)	Study Days 40 – 45 (Subjects who exit study before Study Day 40 will be considered as failures. Subjects who had other CDI antimicrobial treatment between Study Days 2 and 45 or recurrence on or before Study Day 45 will be considered as failures.)
SCR over 60 days post EOT	Through 60 days post EOT	Study Day 70 (±5)	Study Days 65 – 75 (Subjects who exit study before Study Day 65 will be considered as failures. Subjects who had other CDI antimicrobial treatment between Study Days 2 and 75 or recurrence on or before Study Day 75 will be considered as failures.)
SCR over 90 days post EOT	Through 90 days post EOT	Study Day 100 (±5)	Study Days 95 – 105 (Subjects who exit study before Study Day 95 will be considered as failures. Subjects who had other CDI antimicrobial treatment between Study Days 2 and 105 or recurrence on or before Study Day 105 will be considered as failures.)
Recurrence	Through 90 days post EOT	Up to Study Day 100 (±5)	Study day of recurrence ≤ 105
Bile acids	EOT (or AOC visit)	EOT: Study Day 10 (±1) AOC: Study Day 12 (+3)	8 ≤ study day of stool sample collection ≤ 16
	Study Day 40	Study Day 40 (+5)	35 ≤ study day of stool sample collection ≤45
	Study Day 70	Study Day 70 (±5)	65 ≤ study day of stool sample collection ≤75

Assessment	Visit/Period	Target Day/Period Per Protocol	Analysis Window
	Study Day 100	Study Day 100 (±5)	95 ≤ study day of stool sample collection ≤105
	Recurrence	Date of recurrence	Stool sample collection within 5 days of recurrence date (i.e. ±5 days)
EQ-5D-5L	AOC visit	Study Day 12 (+3)	8 ≤ study day of assessment ≤ 16
	Day 40	Study Day 40 (+5)	35 ≤ study day of assessment ≤ 45
	Recurrence	Date of recurrence	Assessment within 5 days of recurrence date (i.e. ±5 days)

EOT: End of Treatment; AOC: Assessment of Cure; SCR: Sustained Clinical Response; CDI: *Clostridioides difficile* infection

For by-visit analysis of EQ-5D-5L assessments and bile acids, visit windows in Table 2 will be used to associate assessment with a scheduled visit based on assessment date in reference to the date of first dose of study treatment. If there are multiple assessments in the same window for a subject, the one closest to the target day will be used. If two assessments are equally close to the target day, then the later assessment will be used. Similar approach will be applied to microbiology analysis.

For by-visit analysis of safety data, data collected at scheduled visits will be analyzed according to the visit recorded in the eCRF. Assessments will not be reallocated to different visits according to visit window calculations.

2.4. Handling Of Missing Data

Efficacy Data

Subjects who discontinued from study due to any cause prior to Study Day 40 will be considered as failures in the primary analysis for the primary endpoint SCR. A sensitivity analysis for SCR may be conducted by implementing multiple imputation methods for missing outcomes.

Subjects who discontinued from study due to any cause prior to Study Day 65 (protocol specified visit window: Day 70 ± 5) will be considered as failures for the SCR over 60 days post EOT, and subjects who discontinued from study due to any cause prior to Study Day 95 (protocol specified visit window: Day 100 ± 5) will be considered as failures for the SCR over 90 days post EOT. Of note, subjects who failed SCR are also failures for SCR over 60 days post EOT and SCR over 90 days post EOT, and subjects who failed SCR over 60 days post EOT are also failures for SCR over 90 days post EOT.

Subjects with missing investigator's assessment at the Assessment of Cure (AOC) visit will be considered as clinical failures for the investigator assessment at AOC. If a subject's UBM is

missing for two days from last dose date through 2 days after last dose of study treatment, then it is considered as failure for the criterion based on UBMs in deriving Clinical Response.

If a subject's UBM is missing at any day from last dose date through 2 days after last dose of study treatment, then it is considered as clinical failure for Clinical Cure.

For time to resolution of diarrhea over the first 12 days, subjects who discontinued study prior to Study Day 12 or received other CDI antimicrobial treatment on or prior to Study Day 12 will be censored.

EQ-5D-5L

If any question is not answered on the five dimensions of the EQ-5D-5L, the health utility score will be missing.

Missing or Partial Dates for Adverse Events (AEs), Medications and Hospitalization

AEs with missing or partial dates will be handled such that in the absence of contradictory information an AE is considered as treatment emergent. For example, if the start date of an AE is missing but the end date is either overlapping into the treatment period or missing, the AE will be considered as treatment emergent. For medications with missing or partial dates, the most conservative case will be considered when assigning medications to categories. For example, if the start date of a medication is missing but the end date is either overlapping into the treatment period or missing, the medication will be considered as both prior and concomitant medications. Similarly, the most conservative case will be considered for hospitalization with missing or partial dates. Imputation of partially missing start or end date for AEs, medications, and hospitalization will be made. The imputation rules will follow Summit's convention and details will be included in the analysis data specifications.

3. SUBJECT INFORMATION

3.1. Subject Disposition

For all the randomized subjects, number of subjects in each of the analysis populations will be presented by treatment group and overall. Reason for exclusion from the mITT population will be presented. The following will be summarized by treatment and overall for the ITT and mITT populations:

- Study treatment disposition and reason for discontinuation
- Study status and reason for study discontinuation
- Subject enrollment by region, country and site

3.2. Protocol Deviation

Subjects with important protocol deviations will be summarized by treatment group.

3.3. Demographic And Baseline Characteristics

Demographic information at baseline and baseline characteristics will be summarized for the ITT and mITT populations by treatment group and overall.

Demographic variables include age, age group (<65 years, ≥65 years, <75 years, ≥75 years), sex, race, ethnicity, body mass index (BMI), and region (US/Canada, Europe, Latin America, Other).

BMI (kg/m^2) = weight in kilogram / (height in meter × height in meter)

Baseline disease characteristics include but not limited to the following:

- History of CDI in the last 12 months per eCRF
- History of CDI in the last 12 months per IXRS
- Time since last episode of CDI: no previous episode, >0-3 months, >3-12 months, and >12 months
- Number of UBMs at baseline: numeric and categorical (3, 4-5, 6-9, ≥10)
- Free toxin test method
- IDSA severity: severe, non-severe
- Disease severity (UBM and WBC criteria): mild, moderate, severe
- WBC: numeric and categorical ($\leq 12 \times 10^9$/L, >12-15 $\times 10^9$/L, >15 $\times 10^9$/L)
- Creatinine: numeric and categorical (<1.5 mg/dL, ≥1.5 mg/dL)
- Hospitalization status: inpatient, outpatient
- Immunocompromised: yes, no
- Non-CDI antimicrobials usage: yes, no
- Proton pump inhibitors usage: yes, no
- Presence of ribotype 027 strain: yes, no
- Presence of hypervirulent strains: yes, no
- CDI signs and symptoms (will be presented separately)

3.4. Prior Treatments for Current CDI Episode

Antimicrobial treatments taken by subjects for the current CDI episode at randomization will be summarized by treatment group for the mITT population. List of treatments collected on the Treatment of Current Episode of CDI eCRF will be provided for medical review and requires finalization at the time of the analyses.

3.5. Prior And Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) drug dictionary version March 2021 or later. Prior medications are defined as those medications started prior to the administration of study treatment on Study Day 1. Concomitant medications are defined as medications taken after the administration of study treatment on Study Day 1 through 30 days after last dose of study treatment. Hence medications started before the first dose of study treatment but continuing after are considered as both prior and concomitant medications.

Concomitant medications will be summarized by therapeutic subgroup and preferred term for each treatment group.

Potential confounding medications (e.g. proton pump inhibitors) will be identified based on clinical review and summarized by treatment group.

3.6. Treatment Exposure

Exposure to study treatment will be summarized by treatment group for the mITT and safety populations. Descriptive statistics will be provided for treatment duration, total number of active doses taken, and relative dose intensity. Treatment duration will be calculated as (last dose date of study treatment - first dose date of study treatment + 1). The relative dose intensity will be calculated as the total number of active doses taken divided by the total number of active doses expected during the treatment period, multiplied by 100.

4. STATISTICAL ANALYSES

4.1. Efficacy Analyses

Analysis of efficacy endpoints will be conducted on the mITT population. Table 3 summarizes the efficacy endpoints and analysis methods to be performed. Additional supportive or exploratory analyses may be performed as needed. The following two randomization stratification factors will be used for all the stratified analysis/test: age (<65 years and ≥65 years) and history of CDI (either none or 1 to 3 previous occurrences in the past 12 months). Of note, all subjects are randomized based on these two stratification factors. All the stratified analyses/tests will be based on the randomization stratification factors as recorded in the IXRS.

Table 3: Summary of Efficacy Analyses to be Performed

Endpoint	Definition	Analysis Method
Primary Endpoint		
SCR	SCR is defined as Clinical Response and no recurrence of CDI through 30 days post EOT. Specifically, subjects who had Clinical Response (see definition below) and no recurrence (see definition below) of CDI on or before Study Day 45 are considered as responders. Subjects who exited study prior to Study Day 40 or received other CDI antimicrobial treatment[a] between Study Days 2 and 45 are considered as failures.	Primary Analysis: SCR rate will be compared between the two treatment groups (ridinilazole vs. vancomycin) using Cochran Mantel Haenszel (CMH) chi-squared test, adjusted for the two randomization stratification factors. The treatment difference and 95% confidence interval (CI) will be calculated based on the stratified Miettinen and Nurminen method. The reasons for subjects who failed SCR will be summarized. Sensitivity Analysis: • Based on subjects who achieved Clinical Cure and had no recurrence of CDI through 30 days post EOT: analyzed using the same methods stated above. • Multiple imputation methods (see Section 5.4 for details) may be used for dealing with missing outcomes. The estimate of the treatment effect as well as the

Endpoint	Definition	Analysis Method
		confidence interval will be derived from the imputed datasets. Subgroup Analysis: The results of treatment differences (ridinilazole vs. vancomycin) and 95% CI for each subgroup of selected variables will be presented in a forest plot.
Secondary Endpoints		
Clinical Response	Clinical Response is defined as • less than 3 UBMs for 2 consecutive days and maintained through the EOT without further CDI antimicrobial treatment at EOT+ 2 days **OR** • the investigator's assessment that the subject is cured and no longer needs specific CDI antimicrobial treatment after completion of the course of study medication. Specifically, if the UBM criterion above is met or the investigator's assessment at the Assessment of Cure visit is "Cured", then the subject is considered as having clinical response as long as he/she did not receive other CDI antimicrobial treatment[a] between Study Day 2 and 2 days post treatment.	The treatment difference (ridinilazole vs. vancomycin) and 95% CI for clinical response rate will be calculated based on the stratified Miettinen and Nurminen method. Non-inferiority will be established if the lower limit of the 2-sided 95% CI for the treatment difference is greater than -10%. If non-inferiority is established and the lower limit of the 2-sided 95% CI is greater than 0%, superiority of ridinilazole in Clinical Response will be declared. Sensitivity Analysis: Clinical Cure will be analyzed using the same methods stated above for Clinical Response. Clinical cure is defined as the resolution of diarrhea (<3 UBMs in the 1-day period immediately prior to EOT, that is maintained for 2 days after EOT). Specifically, if a subject's UBMs meet the criterion above, then the subject is considered as "Cured" as long as he/she did not receive other CDI antimicrobial treatment[a] between Study Day 2 and 2 days post treatment.
Change from baseline to EOT of the relative abundance of microbiome-derived secondary bile acids	Relative abundance of microbiome-derived secondary bile acids is defined as proportion of microbiome-derived secondary bile acids concentration against total bile acids concentration reported for each subject.	Wilcoxon rank-sum test will be used to compare treatment groups. Descriptive summary statistics will be provided by treatment group.
Recurrence	Recurrence is defined as a new episode of diarrhea (≥3 UBMs) in a 1-day period with a positive *C. difficile* free toxin test or CCNA that requires CDI antimicrobial treatment in subjects who achieved clinical response.	Recurrence rate will be compared between the two treatment groups using a chi-squared test. The treatment difference (ridinilazole vs. vancomycin) and 95% CI will be calculated based on the Miettinen and Nurminen method without stratification factors.
SCR over 90 days post EOT[b]	Defined as Clinical Response and no recurrence of CDI through 90 days post EOT. Specifically, subjects who had Clinical Response and no recurrence of CDI on or before Study Day 105 are considered as responders. Subjects who exited study prior to Study Day 95 or received other CDI antimicrobial	Same as those for the primary analysis for SCR.

Endpoint	Definition	Analysis Method
	treatment[a] between Study Days 2 and 105 are considered as failures.	
Exploratory Endpoints		
Time to resolution of diarrhea over the first 12 days	Defined as the time from starting study treatment to the resolution of diarrhea (<3 UBMs in a 1-day period). Specifically, it is calculated as days from first dose to the first day of two consecutive days with <3 UBMs that are sustained through Study Day 12. Subjects who reached Study Day 12 without resolution of diarrhea will be censored at Study Day 12. Subjects who exited study prior to Study Day 12 will be censored at the date of last bowel movement. Subjects who received other CDI antimicrobial treatment[a] on or prior to Study Day 12 will be censored on the CDI treatment start date.	Time to resolution of diarrhea over the first 12 days will be compared between the two treatment groups using a stratified log rank test adjusting for the two randomization stratification factors. The hazard ratio and its 95% CI based on a Cox regression model stratified by the two randomization stratification factors will be calculated. Kaplan-Meier (KM) curves will be plotted for the treatment groups. The KM estimated median and 95% CI for each treatment group will be presented. The number and percentage of subjects who have resolution of diarrhea or are censored will be summarized.
CDI signs and symptoms	Individual CDI signs and symptoms, total number of CDI signs and symptoms for each subject and visit	Descriptive summary statistics by treatment group at each visit. Shift table from baseline will be generated.
Relative abundance of microbiome-derived secondary and primary bile acids, conjugated primary bile acids	Value and change from baseline. Relative abundance is defined as proportion of the specific bile acid group (e.g. microbiome-derived secondary bile acids) against total bile acids concentration reported for each subject.	Wilcoxon rank-sum test will be used to compare treatment groups. Descriptive summary statistics will be provided by treatment group at each visit. Descriptive summary statistics will also be provided for the bile acids concentrations. For microbiome-derived secondary bile acids concentration and relative abundance of microbiome-derived secondary bile acids at EOT, descriptive summary statistics may be presented by clinical outcome (e.g. SCR, recurrence).
SCR over 60 days post EOT[b]	Defined as Clinical Response and no recurrence of CDI through 60 days post EOT. Specifically, subjects who had Clinical Response and no recurrence of CDI on or before Study Day 75 are considered as responders. Subjects who exited study prior to Study Day 65 or received other CDI antimicrobial treatment[a] between Study Days 2 and 75 are considered as failures.	Same as those for the primary analysis for SCR.
Health Economics and Outcomes Research (HEOR) Endpoints		
Medical resource utilization: hospital admission, inpatient days, readmission	A subject will be counted as a hospital admission if he/she was admitted to hospital for any reason. If subject moves from one area of a hospital to another (e.g. ICU to general hospital ward), it is only counted as one hospital admission. Total inpatient days is defined as total number of	Hospital admission rate after first dose of treatment and reasons for admission will be summarized by treatment group. Planned admissions for a scheduled procedure will be excluded from the calculation of admission rate. Hospital readmission rate and reasons for readmission will be summarized by treatment

Endpoint	Definition	Analysis Method
	days in hospital from Study Day 1 to study exit. For inpatients at baseline: a subject will be counted as a hospital readmission if he/she was readmitted to hospital for any reason after discharge.	group in inpatients at randomization. Planned readmissions for a scheduled procedure will be excluded from the calculation of readmission rate. Descriptive summary statistics for number of admissions or readmissions, and total inpatient days. Summaries will also be provided for CDI-related and Non-CDI related admissions/readmissions, and for admissions/readmissions to ICU.
EQ-5D-5L dimensions and VAS score	Clinically meaningful improvement is defined as an increase of ≥7 points for VAS score or ≥0.08 points for utility score.	The proportion of subjects achieving clinically meaningful improvement will be compared between the two treatments using the CMH test stratified by the two randomization stratification factors. 95% CI for the difference will be calculated.
	Value and change from baseline	For VAS score and utility score, change from baseline will be analyzed using the Mixed-Effects Model Repeated Measure (MMRM). The model includes the baseline score, age group, history of CDI, and disease severity at baseline as covariates; treatment, time point and treatment-by-time point interaction as fixed effects; and subjects as random effect. An unstructured (co)variance structure will be used to model the within-subject error. Kenward-Roger's approximation will be used to estimate denominator degrees of freedom. 95% CIs will be calculated for the difference of least square means. Descriptive summary statistics for the observed value and change from baseline will be provided by treatment at each visit including recurrence visit.

[a] A subject is considered as "received other CDI antimicrobial treatment" if he/she took CDI antimicrobial medication(s) other than study treatment for >2 days.

[b] Subjects will report bowel movement information daily up to Day 40 to support the primary endpoint analyses. Weekly contact with the subject will occur after Day 40 until study completion to check for diarrhea/suspected recurrence.

EOT: End of Treatment; SCR: Sustained Clinical Response; CDI: *Clostridioides difficile* infection; CMH: Cochran Mantel Haenszel; CI: confidence interval; UBM: unformed bowel movement; KM: Kaplan-Meier; VAS: visual analog scale; MMRM: Mixed-Effects Model Repeated Measure

4.2. Safety Analyses

Safety data will be summarized by treatment group. Table 4 summarizes the safety analyses to be performed. All safety evaluation will be performed on the safety population.

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24 or later. A Treatment-Emergent Adverse Event (TEAE) is defined as an AE that occurs or worsens after the first dose of study treatment through 7 days after the last dose date or that is related to study treatment. Summary tables will be provided for TEAEs as well for

AEs that occur or worsen after the first dose date through 30 days after the last dose date. Serious AEs reported up to the end of study visit may be summarized as needed.

Adverse event of special interest (AESI) is defined as an adverse event (serious or nonserious) of scientific and medical concern specific to the product, for which ongoing monitoring and further investigation is necessary to characterize and understand it. It is expected that additional aggressive follow up efforts are directed at these AESIs.

All laboratory values will be converted to and reported as international standard (SI) units.

Table 4: Summary of Safety Analyses to be Performed

Assessment	Analysis Method
Adverse Events (TEAEs and AEs through 30 days after the last dose)	
AEs, serious adverse events (SAEs), related AEs, related SAEs, AEs leading to treatment discontinuation, AEs resulting in death, AESIs (if applicable), infectious AEs	Frequency and percent of subjects by treatment group and severity; listings for all serious AEs, TEAEs leading to treatment discontinuation, and all deaths. An exploratory analysis of clinical events including infections and glucose which could reflect the balance of the gut microbiome will also be performed.
Clinical Laboratory	
Hematological parameters: hematocrit, hemoglobin, leukocytes, neutrophils, platelets Clinical chemistry parameters: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, creatinine, glucose, potassium, sodium, urea nitrogen	Descriptive summary for observed value, change, and percent change from baseline by treatment group at each scheduled visit; shift table from baseline by treatment group based on CTCAE criteria; summary tables for subjects meeting the Hy's law
Vital Signs	
Blood pressure, pulse, temperature, weight	Descriptive summary for the observed value and change from baseline by treatment group at each scheduled visit

4.3. Microbiology Analysis

Number of subjects with positive, negative, or undetermined culture result will be summarized by treatment group at each visit. Ribotype classification of baseline isolates will be summarized by region, country and site for each treatment group and overall. For subject who had CDI recurrence, relapse (i.e. same ribotype at recurrence and baseline) rate and reinfection (i.e. difference ribotypes at recurrence and baseline) rate will be summarized by ribotype for each treatment group.

Clinical outcomes (e.g. SCR) will be summarized by baseline ribotype for each treatment group.

Descriptive summary statistics (including geometric mean, range, MIC50, MIC90) for minimum inhibitory concentrations (MICs) and percent of resistant by CLSI/EUCAST interpretative criteria will be calculated by treatment group, and will be presented by ribotype, and by region and country.

Descriptive summary statistics for MICs by clinical outcome (e.g. SCR) will be calculated for each treatment group, and will be presented by ribotype, and by region and country. Clinical outcomes (e.g. SCR) will also be summarized by MIC and ribotype at baseline for each treatment group, and

summaries will be presented by region and country. Change from baseline MIC to highest post-baseline MIC result recorded in the study will be summarized by treatment group and baseline ribotype. This will include only those subjects who had the same ribotype at baseline and the post-baseline visit.

4.4. Pharmacokinetic Analysis

Summary statistics will be reported by sampling timepoints over all patients in the PK population for ridinilazole plasma concentrations. A count of the number of samples below the level of quantification (BLQ) will be provided for each time point.

4.5. Microbiome Analysis

All the analyses for microbiome data including microbiota α-diversity (Shannon) and β-diversity (Bray-Curtis) measures will be included in a separate document to support the microbiome report.

4.6. Listings

Patient profiles and key primary or secondary efficacy parameters listings along with individual components in the definitions might be generated to facilitate data review. Additional listings may be generated as needed.

4.7. Covid-19 Impact

The impact of COVID-19 will be reported following FDA's guidance documents, 'Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, Guidance for Industry, Investigators, and Institutional Review Boards' and 'Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, Guidance for Industry'. Summary and/or listing will be considered for the following: COVID-19 AEs including death, subjects with diagnosed COVID-19 prior to randomization, protocol deviations related to COVID-19, study treatment discontinuation or study discontinuation due to COVID-19.

Subgroup analysis for the primary endpoint SCR in subjects with diagnosed COVID-19 prior to randomization will be performed.

5. SUPPORTING DOCUMENTATION

5.1. Appendix 1: List of Abbreviations

Abbreviation	Description
AE	Adverse Event
AOC	Assessment of Cure
BID	Twice a day
BMI	Body Mass Index
CCNA	Cell Cytotoxicity Neutralization Assay
CDI	*Clostridioides difficile* Infection
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
eCRF	Electronic Case Record Form
EOS	End of Study
EOT	End of Treatment
HEOR	Health Economics and Outcomes Research
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IDSA	Infectious Disease Society of America
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NI	Non-Inferiority
PK	Pharmacokinetics
PP	Per-Protocol
QID	Four times a day
SAP	Statistical Analysis Plan
SCR	Sustained Clinical Response
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
UBM	Unformed Bowel Movement
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization

5.2. Appendix 2: Changes to Protocol-planned Analyses

Below are the major changes made from the protocol:

- Recurrence is added as one of the secondary endpoints.

- Clinical Cure is removed from the list of secondary endpoints and will be considered as sensitivity analysis for Clinical Response. SCR over 60 days post EOT is removed from the list of secondary endpoints and considered as an exploratory endpoint.
- Change from baseline to EOT of the relative abundance of the bile acid components – conjugated primary and microbiome-derived primary bile acids, and the microbiota α-diversity (Shannon) and β-diversity (Bray-Curtis) indices in stool samples are removed from the list of secondary endpoints and considered as exploratory endpoints in the SAP.

- The following two randomization stratification factors will be used for all the stratified analysis/test: age (<65 years and ≥65 years) and history of CDI (either none or 1 to 3 previous occurrences in the past 12 months). In Protocol Amendment 7 (dated 21 June 2021), number of UBMs and immunocompromised were added as randomization stratification factors but have not been implemented. Therefore, at the time of data cutoff all the subjects are randomized based on the two stratification factors: age and history of CDI.

In addition, CDI signs and symptoms are added as exploratory endpoints. Change from baseline in Cdiff32 domains (US sites) is excluded.

All the analyses for microbiome data including microbiota α-diversity (Shannon) and β-diversity (Bray-Curtis) measures will be included in a separate document to support the microbiome report.

5.3. Appendix 3: Schedule of Activities

Phase	Screening	Treatment Period			Follow-Up Period				Recurrence
Day(D)	D-3 to D1[1,2]	D1[1,3]	D5[2]	D10[2]	D12[4]	D40 ≥30 days from last dose or early term pre-D40[5]	D70[2] 60 days from last dose	D100[2] 90 days from last dose or early term post-D40	Day 12/AOC to D100[4]
Assessment	Screening Visit	Baseline	Check-in	End of Treatment	Assessment of Cure	Primary Sustained Clinical Response Assessment	Sustained Clinical Response Assessment	Sustained Clinical Response Assessment	Suspected Recurrence
Visit window			±1 day	±1 day	+ 3 days	+ 5 days	±5 days	± 5 days	≤48h of identification
Visit format	Clinic/ Tel[1,2]	Clinic/ HHC with VC[1,3]	Tel[2]	Clinic/Tel[2]	Clinic/ VC/ HHC[4]	Clinic/ VC/ HHC[4]	Clinic/Tel[2]	Clinic/ Tel[2]	Clinic/ VC/ HHC[4]
Written informed consent[6]	X								
Inclusion and exclusion criteria	X	X							
Demographics	X								
Free toxin test[7]	X								X
Medical/CDI history[8]	X	X							
Stool sample for microbiology / microbiome/metabolome/future research[9]	X	X		X	X	X	X	X	X
Physical exam and vital signs[10]	X ⟷	X			X	X			X
12-lead ECG[11]	X ⟷	X							
Blood samples (hematology and clinical chemistry)[12]		X			X	X			
Urine pregnancy test (dipstick) for WOCBP[13]		X			X	X			
Randomization		X							
EDiary training and review		X	X	X	X	X			
IMP Dosing *qid (10 days)*		⟷							

Phase	Screening	Treatment Period			Follow-Up Period				Recurrence
Day(D)	D-3 to D1[1,2]	D1[1,3]	D5[2]	D10[2]	D12[4]	D40 ≥30 days from last dose or early term pre-D40[5]	D70[2] 60 days from last dose	D100[2] 90 days from last dose or early term post-D40	Day 12/AOC to D100[4]
Assessment	Screening Visit	Baseline	Check-in	End of Treatment	Assessment of Cure	Primary Sustained Clinical Response Assessment	Sustained Clinical Response Assessment	Sustained Clinical Response Assessment	Suspected Recurrence
Visit window			±1 day	±1 day	+ 3 days	+ 5 days	±5 days	± 5 days	≤48h of identification
Visit format	Clinic/ Tel[1,2]	Clinic/ HHC with VC[1,3]	Tel[2]	Clinic/Tel[2]	Clinic/ VC/ HHC[4]	Clinic/ VC/ HHC[4]	Clinic/Tel[2]	Clinic/ Tel[2]	Clinic/ VC/ HHC[4]
Dosing instruction, compliance + accountability		X	X	X	X				
Signs and symptoms of CDI[10]		X			X				X
EQ-5D-5L		X			X	X			X
Cdiff32 (US sites)		X			X	X			X
Medical resource utilization questions		X			X	X	X	X	X
Investigator assessment of cure/sustained clinical response[14]					X	X	X	X	X
PK Sample (2 & 4 hours post dose in subset of patients/sites)[15]		X		X					
Concomitant medications	←	—	—	—	—	—	—	—	→
Potential confounding medications[16]	←	—	—	—	—	—	—	—	→
Patient daily eDiary completion[17]		←	—	—	→				
Weekly contact to check for diarrhea/suspected recurrence[17]							←	→	
AE reporting[18]		←	—	—	→				X
SAE reporting	←	—	—	—	—	—	—	—	→

Notes: Unscheduled telephone calls and/or visits may be conducted if necessary, for the patient's safety and to ensure dosing and diary completion per protocol.

1. Screening and D1/baseline assessments may occur on the same day or within a 1- to 3-day window. Patients can be rescreened once for this study.
2. D5 visit will be conducted by telephone. Screening, D10, D70, and D100 assessments may be conducted in-clinic or by telephone.
3. Preferably the Baseline visit should be completed as an in-clinic visit; however, to maximize potential enrollment (e.g., during a pandemic) the visit may be conducted remotely. If so, a sponsor-contracted home healthcare vendor or properly trained and delegated site staff must conduct assessments at the patient's home. All assessments should be completed prior to randomization except for the following, which must still be conducted prior to their 1st dose of study medication: weight, blood samples (hematology and clinical chemistry), stool collection (if required, to collect a sample for microbiology/microbiome/metabolome that is <24h old), eDiary training, EQ-5D-5L, Cdiff32 and medical resource utilization questions.
4. D12, D40 and recurrence visits are preferably in-clinic visits; however, these visits may be conducted remotely.
5. Subjects who have discontinued study drug early should remain in the study and be monitored, e.g., for adverse events.
6. Documented informed consent must be provided by the patient prior to any study procedure being conducted. Informed Consent is allowed in other than face to face method as per site local procedure or local regulations.
7. Current/baseline CDI free toxin test: A free toxin test must be the 1st assessment conducted using a sample produced within 72 hours prior to randomization. Patients with a negative free toxin test will be excluded from the study.
   Suspected recurrence free toxin test: A free toxin test should be conducted as soon as possible – and at a maximum of 48 hours - after identifying a suspected recurrence. Cell Cytotoxicity Neutralization Assay (CCNA) sample is to be collected when free toxin test is negative and sent to a specialized central laboratory.
   Negative or invalid free toxin test results: A negative free toxin test may be repeated once for baseline and suspected recurrence. The same sample may be used if collected within 24 hours, otherwise a fresh sample must be used. Invalid test results should be repeated.

   Free toxin test specification: Sites may use an established local free toxin test laboratory service if it is a suitable test, and it is prospectively agreed with the Sponsor. Suitable tests will have appropriate regulatory approvals (FDA approval, EU CE Mark or equivalent). Please see protocol Appendix 6 for list of approved tests. Free toxin tests will be provided for the site/site laboratory use if a suitable test is not available locally.
8. Record all known historical CDIs along with associated treatment, information on the current/baseline CDI including signs and symptoms, any potential confounding medications taken up to 4 weeks prior to randomization, relevant medical history for 12 months prior to randomization and all prior and current medications taken up to 4 weeks prior to randomization.
9. Stool samples should be aliquoted and frozen within 24 hours of sample being produced. Only one sample is required at either Screening or D1. Only one sample is required at either D10 or D12. Additional stool samples are required at each of the following visits: D40, D70, D100, and each suspected recurrence. If the visit is conducted remotely, stool sample drop off or collection from the patient (e.g., courier) must be arranged.
10. If the visit is conducted remotely physical exam and vital signs if taken by the patient are done through sponsor approved video conferencing between the patient and Investigator.

    The following assessments must be included: temperature, blood pressure, pulse, height (baseline only) and weight. The physical exam may be conducted at the screening or baseline visit; if conducted at screening, the vital sign assessment must still be repeated at baseline.

11. The ECG may be conducted at the screening or baseline visit. It does not need to be completed if most recent ECG was normal and was completed in the 12 months prior.
12. An appropriately qualified person will need to collect blood samples (hematology and clinical chemistry per protocol Appendix 2). For visits conducted remotely, this person will either need to visit the patient at home or the site will need to arrange an alternative location.
13. WOCBP = Women of Child Bearing Potential. Testing in the case of missed menses should also be conducted up to 30 days following the last dose of study treatment. An appropriately qualified person will need to perform this procedure. For visits conducted remotely, this person will either need to visit the patient at home or the patient may perform a home pregnancy test over video conference with the site.
14. Based on the Investigator's assessment of the reduction of UBMs since baseline, clinical signs and symptoms and need for further treatment for CDI.
15. Approximately 100 patients will undergo PK sampling. Blood draws should occur at on Day 1 or 2 **at 2 and 4 hours (±30 minutes) following either Dose 1, 3, 5 or 7** and at EOT **at 2 and 4 hours (±30 minutes) following either Dose 33, 35, 37 or 39**.

    PK sampling must be conducted following administration of study medication. A ±30-minute window is allowable for the sampling times relative to dosing. An accurate date and time of dose and sampling is required. A home healthcare vendor or appropriately trained and delegated site staff may perform this procedure at the patient's home.
16. Potential confounding medications should be avoided where possible except for CDI medications required in the case of recurrence. If antimicrobial therapy is required for infections other than those due to *C. difficile*, antimicrobials without activity/efficacy against *C. difficile* should be prescribed where possible.
17. Patients will report dosing information daily until EOT and bowel movement information daily until D40 in their eDiary. As an alternative the patient may be contacted daily either by site or a 3rd party vendor. After D40 the site will contact the patient weekly to check for new episodes of diarrhea/suspected recurrence. The eDiary needs to be collected/returned (e.g., courier) upon study completion.
18. AEs only need to be reported up to the D40 visit (inclusive). AEs meeting the definition of serious should be reported throughout the study.

5.4. Appendix 4: Sensitivity Analysis for SCR Using Multiple Imputation

The missing outcomes in sensitivity analysis will be imputed using multiple imputations (MI) method. The MI procedure replaces each missing binary SCR value with a set of plausible values that represent the uncertainty about the right value to impute. These multiple imputed data sets are then analyzed by using the same method for the primary analysis for complete data. The results from each set of imputed data sets will then be combined using Rubin's rule. The estimate of the treatment effect as well as the confidence interval will be derived from the imputed datasets.

In the imputation step, missing outcomes will be imputed using a logistic model predicting the probability of SCR with covariates of baseline characteristics. Specifically, the following variables will be considered in the logistic model: treatment group, region, sex, age, prior CDI episodes, UBMs at baseline or baseline disease severity, immunocompromised, antimicrobial treatment for current CDI at randomization.

Subsets	**SCR: Primary Analysis**	**SCR: Sensitivity Analysis**
No Clinical Response	No	No
Subjects with Clinical Response		
Recurrence prior to or on Study Day 45	No	No
Other CDI antimicrobial treatment prior to or on Study Day 45 with diarrhea (i.e. UBM ≥3): negative or missing free toxin test/CCNA	No	No
Other CDI antimicrobial treatment prior to or on Study Day 45 without diarrhea	No	Missing
Exit study prior to Study Day 40	No	Missing if the above criteria are not met
Meet all criteria for SCR and Clinical Response is based on UBM criterion only (i.e. investigator assessment at Assessment of Cure visit is "Failed" or missing; no evidence of recurrence)	Yes	Missing
Meet all criteria for SCR and investigator assessment at Assessment of Cure visit is "Cured"	Yes	Yes

SCR: sustained clinical response; UBM: unformed bowel movement; CDI*: Clostridioides difficile* infection.

C004-C005 Final SAP

Final Audit Report 2021-11-20

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