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).

Protocol Number: SMT19969/C004

Protocol Amendment Number: 8

Version: 9

Compound Number: SMT19969

Short Title: Comparison of ridinilazole versus vancomycin treatment for *Clostridium difficile* infection

Sponsor Approval Date: 09 August 2021

Regulatory Agency Identifying Number(s): IND No: 119626

EudraCT: 2017-001641-27

Sponsor Name and Legal Registered Address:

Summit Therapeutics Inc.
One Broadway
14th Floor
Cambridge, MA 02142
USA

Summit (Oxford) Limited
136A Eastern Avenue
Milton Park
Abingdon
OX14 4SB
United Kingdom

Sponsor Signatory

Priyanka Mandava
Priyanka Mandava (Aug 9, 2021 14:29 PDT)

Priyanka Mandava
Vice President, Global Clinical Operations
Head of Clinical Operations

Date

Annie Hung (Aug 9, 2021 15:41 PDT)

Annie Hung, MA
Executive Director, Biostatistics
Study Statistician

Date

Camilla Graham (Aug 9, 2021 20:07 EDT)

Camilla Graham, MD, MPH
Head of Clinical Affairs
Interim Global Head of Clinical Development

Date

Medical Monitor Contact Information can be found in the Investigator Trial Site File.

Investigator Signature Page

I agree to conduct this Study in accordance with the requirements of this document (the Clinical Study Protocol), the Study Reference Manual and in accordance with the following:

- Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000, Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002).
- INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH): Guideline for GCP E6 (R2)
- Any amendments to these regulations
- Local laws and regulations.

Investigator Name and Qualifications: _____

Investigator Signature	Date

[Investigator Affiliation]

Protocol Amendment Summary of Changes Table

Note: Please refer to separate rationale of changes document for full explanation of and justification for protocol updates.

DOCUMENT HISTORY	
Document	**Date**
Original Protocol Version 1.0 (not submitted to any Competent Authority or EC/IRB)	28 SEP 2017
Amendment 1; Protocol Version 2.0 • Removal of a blinded data review • Exclusion of patients with a colostomy or ileostomy or likely requirement of an ostomy during the study • Various clarifications and minor amendments	26 OCT 2017
Amendment 2; Protocol Version 3.0 • Allowance of sites to use a regulatory approved, Sponsor agreed, local free toxin test as an alternative to a Sponsor provided specific test • Requirement for the free toxin test to be conducted as soon as possible and no later than 48 h after a suspected recurrence is identified • Clarification that in the event of a suspected recurrence, the result of a free toxin test should be available to determine whether CDI treatment is required • Removal of the requirement for a routine urinalysis at baseline • Extension of collection of concomitant medications throughout the study (rather than just up to D40) • Addition of IVIG as a potentially confounding medication • Allowance low dose and topical steroids during the study • Inclusion of the requirement of >3 UBMs for the mITT population • Signs and symptoms of CDI: use of the term “loose stools” rather than “diarrhea” to distinguish from the protocol definition of diarrhea • Clarification that the PP populations will have a hierarchical order • Update of pharmacovigilance vendor name from Quintiles to IQVIA • Numerous minor administrative clarifications and minor administrative amendments to aid clarity and consistency	29 Mar 2018
Amendment 3; Protocol Version 4.0 • Revision of the protocol definition of diarrhea (number of UBMs) and recurrence (added the requirement for CDI treatment) • Revision of the exploratory endpoint definition for time to resolution of diarrhea • Clarification of the exclusion criterion of >24h antimicrobial therapy • Revision and clarification of requirements for contraception, pregnancy testing and avoidance of sperm donation	04 Jul 2018

DOCUMENT HISTORY	
Document	**Date**
• Probiotics and prebiotics exclusion extended from Day 12 (AOC) to end of study • Addition of permitted and non-permittable changes for eDiary data • Other clarifications for eDiary management • Addition of a blinded sample size assessment • Change of the primary analysis population for the important secondary endpoint from PP to mITT population • Updates to the statistical analysis section to align with protocol changes made • Minor clarifications and administrative amendments to aid clarity and consistency	
Amendment 4; Protocol Version 5.0 • Sponsor company logo updated • Investigator Signature Page statement amended • Addition of a microbiome secondary objective and endpoint • Investigator assessment of clinical cure and sustained clinical response moved from exploratory to secondary endpoints • Day 40 visit window amended from ±3 days to +5 days • Allowance of a negative Free Toxin Test (FTT) to be repeated once at baseline and for suspected recurrence • Addition of an instruction that invalid FTT results should be repeated at baseline and for suspected recurrence • Addition of a CCNA for patients with a negative FTT for suspected recurrence • Clarification of Legally Authorized Representatives (LAR) for patients if IRB/EC permit and addition of an impartial witness if required • Revision of exclusion criteria 6 (immunosuppressed patients) • Additional section to further clarify exclusion criteria 6 (immunosuppressed patients) • Clarification of exclusion criteria 7 (prior antimicrobial treatment) • Revision of exclusion criteria 8 (antitoxin antibodies) • Revision of exclusion criterion 9 in line with changes made to the potentially confounding medication section • Additional instructions for administration of study treatment • Revisions and reorganization of potential confounding medications for clarity and to reflect clinical practice • Allowance for telephone consent to conduct a Free Toxin Test where the test is not standard of care • Revision of the requirement for an eDiary from up to Day 100 to up to Day 40	19 Dec 2019

DOCUMENT HISTORY	
Document	**Date**
• Allowance of the Investigator, or a 3rd party vendor where available, to call the patient daily as an alternative to the eDiary • Addition of weekly calls to the patient post Day 40 to check for diarrhea/suspected recurrence • Stool sampling instructions added • Medical history requirements were updated and clarified • Disease Related Events (DREs) definition was revised and further guidance added • Allowance for a FTT to be conducted without patient consent on a stool sample collected per standard of care for diagnostic purposes • Addition of end of treatment blood sampling for PK analysis • Increase from 60 to 100 patients in the PK sub-group • Additional instruction to collect PK samples after specific doses • Adverse event assessment of causality revised from 4 possible grades (probable, possible, unlikely, not related) to 2 possible grades (related, not related) • Guidance on how to assess adverse event causality has been added • Male contraception language was clarified. • A list of current Sponsor agreed FTT has been added as an appendix • Updates to the statistical analysis section to align with protocol changes made • Addition of the EQ-5D-5L and Cdiff32 as appendices • Addition of references for the EQ-5D-5L and Cdiff32 • Minor clarifications and administrative amendments to aid clarity and consistency	
Amendment 5; Protocol Version 6.0 • Reformatted front page, logo placement, headers, and footers in line with sponsor SOP. • Clarified the position and role of the Global Medical Lead and rearranged the ordering of the sponsor signatories • Indented Declaration of Helsinki language on Investigator signature page • Updated Summary of Changes section to specify that full rationale for changes associated with the amendment is available via separate document. • Added allowance for screening and Day 100 visits to be completed over the phone. • Added the option to conduct the physical exam at screening or baseline. If conducted at screening, the vital sign assessment must still be repeated at baseline. • Added the option to complete the 12-lead ECG assessment at screening or baseline	3 Sept 2020

DOCUMENT HISTORY	
Document	**Date**
• Added allowance for baseline visit to be completed at home with assistance from site staff or a home healthcare vendor approved by sponsor with the addition of video conferencing for certain procedures. • Added allowance for Day 12, Day 40, and any recurrence visit(s) to be completed at home synchronously over video conference with site staff and with the addition of a home healthcare vendor where required by the Investigator. • Clarified stool collection requirements for free toxin testing in footnote 6 • Clarified stool sample requirements, including timing and use of a courier, in footnote 8 • Added allowance for consent to be captured electronically (eConsent) or via email, printing, signing, scanning to site as back-up • Added allowance for 'physical exam and vital signs' along with 'signs and symptoms of CDI' procedures to be completed remotely with assistance from site staff or a sponsor provided home healthcare nursing vendor at baseline. Physical exam and vitals must be completed first for safety and need to be completed over synchronous video conference with Investigator. • Added instruction that if a recurrence visit is done remotely, addition of a focused physical exam completed by patient on them self over video conference with the Investigator. • Added allowance for a focused physical exam to be completed remotely by patient over synchronous video conference with Investigator and for patient to take their own vitals at Day 12, Day 40, and recurrence. • Added instruction that the ECG does not need to be completed at baseline if patient's most recent ECG was normal and was completed in the 12 months prior. • Added instruction that the urine and blood samples, including PK, may be collected at patient's home by site staff or home healthcare vendor. Urine and blood samples (except PK sampling) may alternately be completed by other qualified person at alternate location, where needed. • Clarified in footnote 16 that either site or 3rd party vendor may contact patient daily to collect dosing and bowel movement information until Day 40 • Modified risk/benefit assessment section to include COVID-19 pandemic and added risk mitigation language • Added allowance for eDiary and IMP to be shipped or couriered from site to patient's home • Added allowance for used eDiary and IMP wallet to be returned to site via courier or shipping • Added confirmation of no meal, dietary, caffeine, alcohol, tobacco, or activity restrictions. • Updated section 10.1.1 to state that Investigators have a regulatory and ethical obligation to ensure patient safety and medical care is paramount	

DOCUMENT HISTORY	
Document	**Date**
• Clarified in Informed Consent section the telephone consent process for free toxin testing (FTT) where FTT is not SOC • Clarified that consent for retention of samples is captured via separate signature line within the Main ICF • Removed bullet point depicting third-party vendor ICF as a separate ICF document • Removed bolded instruction to "Discuss with the Medical Monitor before unblinding a patient (whenever possible)". • Clarified terminology used in the Population for Analyses table. • Added guidance that a withdrawn patient may request destruction of samples taken and not tested. • Clarified language in footnote 1 of Appendix 2, Table 3 • Added the following abbreviations: Council for International Organizations of Medical Sciences (CIOMS), Coronavirus Disease 2019 (COVID-19), Enzyme Immunoassay (EIA), Food and Drug Administration (FDA), Free Toxin Test (FTT), Home healthcare (HHC), Protected Health Information (PHI), Video Conference (VC), electronic Case Report Form (eCRF), Ethics Committee (EC), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Legally Authorized Representative (LAR), Ribosomal ribonucleic acid (rRNA), and Suspected Unexpected Serious Adverse Reaction (SUSAR). • Updated list of tests in Appendix 6: Sponsor agreed Free Toxin Tests • Minor formatting, clarifications and administrative amendments to aid clarity and consistency, including the removal of duplicate footnotes carried across some rows	
Amendment 6; Protocol Version 7.0 • Updated sponsor signatories. • Revised exclusion criterion 4 to improve clarity and readability, to add pancreatectomy to the examples of prohibited gastrointestinal tract surgery, and to clarify that cholecystectomy is not prohibited. • Deleted exclusion criterion 6 and corresponding Section 5.2.1 (immunosuppressed patients). • Revised exclusion criteria 7, 8, and 9 for clarity and readability (prior/concomitant therapy) • Revised exclusion criterion 12 to provide additional examples of conditions that would make a patient unsuitable for inclusion in the study and to improve clarity and readability.	03 Feb 2021
Amendment 7; Protocol Version 8.0 • Updated sponsor signatories. • Minor formatting, clarifications and administrative edits to add clarity and consistency.	21 Jun 2021

DOCUMENT HISTORY	
Document	**Date**
• Modified the definition of Sustained Clinical Response (Sections 1.1 and 3). • Updated secondary and exploratory endpoints including microbiome, bile acid, and antibiotic susceptibility endpoints (Sections 1.1, 3 and 9). • Clarified the use of Cell Cytotoxicity Neutralization Assay (CCNA) in case of negative free toxin test (Sections 1.1, 3 and 8). • Updated schedule of activities (SoA) and associated footnotes in Section 1.3 to reflect changes made within the COVID-19 section to reflect regulatory requirements and actual operationalization of remote visits; clarified that patients should remain in the study even if they discontinue study treatment early; clarified timing of blood draws for PK samples; and minor wording changes to reduce ambiguity. • Added two stratification factors (number of UBMs and immunocompromised) to ensure balance of the treatment arms with respect to the known prognostic factors for SCR. Note that there is no impact to procedures or data collection as the information required for stratification was covered in the previous version of the protocol (Sections 4.1, 6.3 and 9.1). • Clarified that more than one recurrence may occur and each needs to be assessed (Section 4.1). • Simplified the COVID-19 language in Section 4.1 to reflect regulatory requirements and actual operationalization of remote visits. • Updated instructions for missed dose to reduce risk of underdosing ridinilazole while recognizing the lack of safety concern when doubling a dose of vancomycin; total daily dose is not altered (Section 6.1). • Clarified class and route of administration of potentially confounding medications (Section 6.5.1). Clarified that patients should remain in the study even if they discontinue study treatment early (Section 7.2). • Clarified reporting requirement by the patient through Day 40 and from Day 40 through Day 100 (Sections 8.1.1 and 8.1.4). • Clarified that suspected recurrence applies after the patient is deemed cured (Sections 8.1.1 and 8.1.4). • Added coverage expectations during holiday and vacation and allowed flexibility when adequate supporting documentation is available (Section 8.1.1). • Clarified that a positive free toxin test result is not required to determine the need for treatment (Section 8.1.3). • Clarified the Investigator assessment of cure and sustained clinical response to align with CRF reporting requirements (Section 8.1.4). • Clarified assessments and procedures for stool collection (Section 8.1.5). • Clarified events not meeting the AE/SAE definition and disease-related events not qualifying as AEs/SAEs (Sections 8.3.6 and 8.3.7). • Clarified management of overdose (Section 8.4).	

DOCUMENT HISTORY	
Document	**Date**
• Updated the estimate of SCR rate for vancomycin in sample size determination to align with the vancomycin rate in the fidaxomicin label. Removed the testing order for secondary endpoints, which will be specified in the statistical analysis plan. Updated the analysis population for efficacy endpoints, aligned efficacy endpoint analyses, and clarified safety analyses. Amended protocol to allow for an interim analysis to be conducted (Section 9). • Rectified improper use of witness and legally authorized representative (LAR) for the informed consent process and clarified that telephone means verbal consent (Section 10.1). • Clarified data protection laws governing the trial (Section 10.1). • Included additional free toxin tests (Section 10.6).	
Amendment 8; Protocol Version 9.0 • Updated sponsor signatories. • Modified protocol to combine the ongoing Phase 3 studies, SMT19969/C004 and SMT19969/C005, into one study with a pre-specified Statistical Analysis Plan when these blinded, identical studies are at least half enrolled (Sections 1.1, 4.3, and 9.4).	09 Aug 2021

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1. PROTOCOL SUMMARY

1.1. Synopsis

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).

Short Title: Comparison of ridinilazole versus vancomycin treatment for CDI

Rationale:

Clostridioides difficile (formerly *Clostridium difficile*) infection (CDI) is an infection of the colon that invariably develops following prior antibiotic use. The disease is associated with significant morbidity and mortality and primarily affects the hospitalized elderly (>65 years of age) although CDI is becoming increasingly associated with the community setting and younger age groups. Of concern is recurrent infection with up to 30% of patients experiencing a subsequent episode following initial infection with rates increasing to 65% after a third episode [1, 2]. Recurrent disease remains a central unmet medical need in CDI. It is difficult to treat, associated with increased morbidity and poorer clinical outcomes, and further increased risk of mortality. Summit is developing ridinilazole as a novel antimicrobial for CDI with the goal of achieving comparable cure rates to standard of care and reducing rates of recurrent disease. A Phase 2 proof of concept study, with vancomycin as the standard of care, demonstrated these attributes.

The rationale for this Phase 3 study is to demonstrate the improvement in sustained clinical response of ridinilazole over vancomycin and compare the safety of ridinilazole to that of vancomycin. A second Phase 3 study of identical design will be run in parallel.

Primary Objective
• To compare the efficacy of 10 days' dosing with 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 with 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 with ridinilazole (200 mg *bid*) and vancomycin (125 mg *qid*) on the gut bile acid composition and on the gut microbiome diversity at the end of treatment (EOT)

Exploratory Objectives
• To compare the effects of ridinilazole (200 mg *bid*) and vancomycin (125 mg *qid*) on the gut bile acid composition, microbiome, and antibiotic resistance gene profile at EOT and during the follow-up period • To assess the antibiotic susceptibility and ribotype of *C. difficile* isolates in patients receiving ridinilazole (200 mg *bid*) and vancomycin (125 mg *qid*) • To assess the impact of ridinilazole treatment on patient reported quality of life, resource utilization and health economics
Primary Endpoint
• Sustained Clinical Response (SCR) is defined as Clinical Response and no recurrence of CDI through 30 days post EOT.
Secondary Endpoints
• Clinical Response • Clinical Cure • Sustained Clinical Response over 60 days – defined as Clinical Response and no recurrence of CDI through 60 days post EOT • Sustained Clinical Response over 90 days – defined as Clinical Response and no recurrence of CDI through 90 days post EOT • Change from baseline to EOT of the relative abundance of the 3 main bile acid groups (conjugated primary, primary and secondary bile acids) • Change from baseline to EOT of the gut microbiota α-diversity (Shannon) index • Change from baseline to EOT of the gut microbiota β-diversity (Bray-Curtis) index in stool samples

Definitions for the Primary and 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 treatment at EOT+ 2 days or
- the investigator's assessment that the subject no longer needs specific CDI antimicrobial treatment after completion of the course of study medication.

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 treatment.

A UBM is defined as a Type 5, 6 or 7 bowel movement on the Bristol Stool Chart.

Safety Endpoints
• Safety and tolerability as determined by adverse event (AE) and serious adverse event (SAE) reporting
PK Endpoints
• Ridinilazole plasma concentrations in a subset of patients

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 VAS score • Change from baseline in Cdiff32 domains (US sites)
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) • Change from baseline to Day 40, Day 70, Day 100 and day of recurrence (if applicable) of the relative abundance of the bile acid components, conjugated primary, primary, and secondary bile acids in stool samples • Change from baseline to Day 40, Day 70, Day 100 and day of recurrence (if applicable) of the microbiota α-diversity (Shannon) and β-diversity (Bray-Curtis) indices in stool samples • Change from baseline to EOT, Day 40, Day 70, Day 100 and day of recurrence (if applicable) of the relative abundance of bacterial taxa, microbiome gene functions, and microbiome antibiotic-resistance genes in stool samples • Determination of the ribotype and susceptibility to ridinilazole, vancomycin and other antibacterial agents of *C. difficile* isolates in stool samples collected at baseline, EOT and recurrence

Overall Design:

A multicenter, randomized, double blind, active controlled, parallel group pivotal Phase 3 study designed to investigate the use of ridinilazole 200 mg *bis in die* (*bid*), in comparison to vancomycin 125 mg *quarter in die* (*qid*), both administered for 10 days for the treatment of CDI.

Patients must be aged 18 years or over, have the presence of toxin A and/or B of *C. difficile* in the stool as confirmed by a positive free toxin test and not have had more than one prior episode of CDI in the previous 3 months or more than 3 episodes in the past 12 months.

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). Refer to Section 10.6 for a list of known approved free toxin tests. Newly approved free toxin tests that become available during the conduct of the

study will also be suitable for use with Sponsor approval. Free toxin tests will be provided for the site/site laboratory use if a suitable test is not available locally. In case of a negative free toxin test result at a suspected recurrence, detection of *C. difficile* toxin in samples will be performed by the more sensitive Cell Cytotoxicity Neutralization Assay at a central laboratory.

The study will evaluate the efficacy and safety of ridinilazole compared with vancomycin. Ridinilazole systemic exposure will be evaluated in a subset of patients at selected sites. The effect of the two treatments on the gut microbiome and bile acid composition will be evaluated in patients across all sites. The study will also investigate the antibiotic susceptibility and ribotype of *C. difficile* isolates collected at different time points and assess the impact of ridinilazole on quality of life and health economic measures.

Number of Patients:

The original planned sample size was approximately 680 patients (340 patients per arm) to be randomly assigned to study treatment. 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 Statistical Analysis Plan 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.

To ensure optimal data quality and integrity, it is critical that

- **Inclusion and exclusion criteria are rigorously adhered to.**
- **Diagnosis of CDI is always determined by a positive, Sponsor approved, free toxin test prior to randomization.**
- **A free toxin test must be completed if recurrence of CDI is suspected. Refer to the result of the free toxin test to determine whether CDI treatment is required.**
- **For all suspected recurrences associated with a negative free toxin test result obtained locally by the site, a stool sample aliquot should be prepared for testing by CCNA at a central laboratory.**
- **Patients take all study treatment as directed and complete the 10 days of treatment.**
- **Patients report all study medication doses for the 10 days of treatment.**
- **Patients report all bowel movements every day up to Day 12/AOC and all UBMs to Day 40.**

Potentially confounding medications (i.e., those affecting disease progression) are avoided wherever possible.

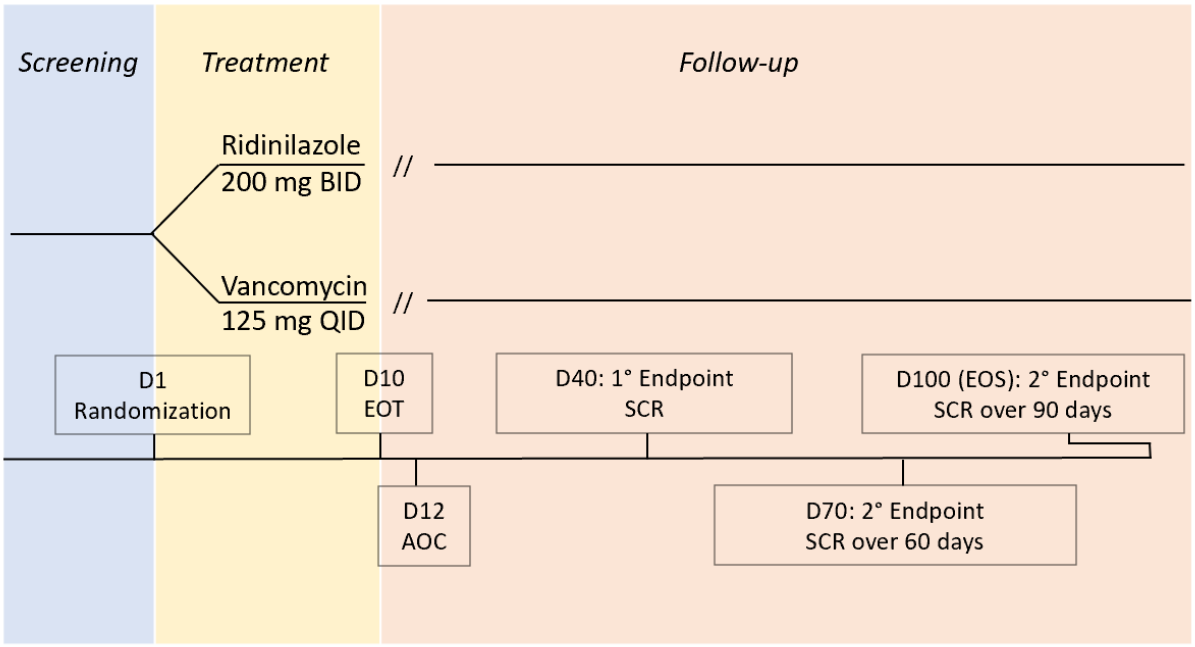
Treatment Groups and Duration:

Each patient will be enrolled in this study for approximately 100 days. This consists of a 0 to 3-day screening period, a 10-day treatment period and a 90-day follow-up period (including an assessment of cure at Day 12).

Patients will be randomized (1:1) to receive either a 10-day course of ridinilazole (200 mg, *bid*) or a 10-day course of vancomycin (125 mg, *qid*).

Data Monitoring Committee: No

1.2. Schema



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

SCR is defined as Clinical Response and no recurrence of CDI through 30 days post EOT.

1.3. Schedule of Activities (SoA)

Phase	Screening	Treatment Period			Follow-Up Period				Recurrence
Day(D)	D-3 to D11[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			

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]
IMP Dosing *qid (10 days)*		←	―	→					
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 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 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.

2. RATIONALE FOR STUDY

2.1. Introduction

Ridinilazole is a novel antimicrobial that is being developed for treating *C. difficile* infection (CDI) and reducing the recurrence of CDI [3]. Ridinilazole is associated with a highly targeted spectrum of activity that has been shown to result in minimal collateral impact on the gut microbiota during therapy and it is expected that this property will lead to reduced rates of CDI recurrence and improved sustained clinical response. This was demonstrated in a Phase 2 proof of concept study where treatment with ridinilazole demonstrated superior efficacy compared with vancomycin, demonstrated by a marked reduction in rates of CDI recurrence and hence improved sustained cure rates [4].

Nonclinical and prior clinical studies have shown that ridinilazole is retained in the gastrointestinal (GI) tract following oral dosing, therefore maximizing exposure of ridinilazole at the site of infection and minimizing systemic exposure. A detailed description of the chemistry, pharmacology, efficacy, and safety of ridinilazole is provided in the Investigator's Brochure.

C. difficile is an anaerobic Gram-positive spore-forming species of bacteria which is responsible for epidemics and individual cases of CDI, with symptoms ranging from mild, self-limiting diarrhea to more severe and potentially life-threatening manifestations such as pseudomembranous colitis and toxic megacolon [5].

C. difficile can often be a harmless resident of the gastrointestinal (GI) tract with levels typically kept in check by the complex community of microorganisms that make up the indigenous gut microbiota. However, disruption to the healthy ecological balance of the gut microbiota, typically by prior antibiotic use, diminishes the ability of the host to resist colonization by *C. difficile* spores that can undergo germination, leading to toxin production and disease symptoms [6, 7].

Recurrence of CDI occurs in up to 30% of patients following initial therapy, hence the prevention of recurrent disease remains a key unmet medical need in the management of CDI [1]. Each episode of recurrent disease is associated with an increased risk of further recurrent episodes placing a significant burden on patients through increased morbidity and diminished quality of life. In a study of 163 patients who had had at least one recurrent episode, the risk of subsequent episodes was 45% [8]. Recurrence rates may be > 65% following a 3rd episode of CDI [2, 9]. Treatment of recurrent CDI is challenging and there is no uniformly effective therapeutic approach.

While administration of standard CDI antibiotics (vancomycin or metronidazole) may result in a reduction in *C. difficile* and subsequent relief of symptoms, they have been shown to have ongoing and deleterious effects to the gut microbiota [10-12]. As such, repeated courses of treatment for CDI may exacerbate the situation with the ongoing suppression of the microbiota leaving patients prone to further episodes of CDI. Therefore, therapeutic approaches that allow natural restoration of a healthy gut microbiome and resistance to *C. difficile* colonization, especially with narrow spectrum *C. difficile*-targeted antibiotics, are expected to reduce rates of recurrent disease and improve sustained clinical response [5, 6].

2.2. Background

CDI is an infection of the colon that typically develops following prior antibiotic use. The disease is associated with significant morbidity and mortality and primarily affects the hospitalized elderly (>65 years of age), although CDI is becoming increasingly associated with the community setting.

Of particular concern is recurrent infection with up to 30% of patients experiencing a subsequent episode following initial infection, with rates increasing to 65% after a third episode. Prevention of recurrent disease remains a central unmet medical need in CDI as it is difficult to treat, associated with increased morbidity and poorer clinical outcomes, and further increased risk of mortality.

A recent EU wide survey of 1,047 healthcare professionals involved in the management of CDI, [13] revealed a high level of agreement (97.3% and 90.7%, respectively) with the statements that *"*recurrent CDI is a strong contributor to poor clinical outcomes, increased length of hospital stay and increased costs" and that "treatment decisions for both initial infection and recurrent CDI should take into account the impact on resource utilization and wider societal costs.".

Therefore, the optimal strategy in CDI therapy is to achieve high levels of clinical response at the end of therapy and to minimize rates of recurrent disease such that the initial clinical response at the end of dosing is sustained for a period of time following the EOT.

Current treatment options are limited and of sub-optimal efficacy. Oral vancomycin and metronidazole are the current mainstay antibiotics and both are associated with high rates of recurrent disease [14]. The most recent Infectious Diseases Society of America (IDSA) guidelines state metronidazole is only recommended in settings where access to vancomycin or fidaxomicin is limited, and then only for initial cases of non-severe CDI. Vancomycin and fidaxomicin are recommended for initial CDI. [15-17]. There is evidence that metronidazole is associated with inferior clinical response at end of therapy compared to vancomycin across all disease severities [18, 19] and may be associated with higher 30 day all –cause mortality rates in subjects with severe CDI [20]. Response to metronidazole treatment in the frail and elderly is generally slow, with patients prone to recurrence; 30-day-mortality of 21% has been reported after treatment with metronidazole [21]. Oral vancomycin remains the currently recognized standard of care and, based on recent clinical trial experience, is typically associated with initial cure rates of 80-90% based on recent Phase 3 clinical trials [22-24]. Given vancomycin may be used in both severe and non-severe CDI, is associated with higher clinical response rates and faster symptomatic resolution when compared with metronidazole and is generally considered the standard of care in CDI it will be the active comparator for this study. A description of oral vancomycin's efficacy, safety and pharmacology can be found in the Prescribing Information (FDA Reference ID: 3058238).

Fidaxomicin is approved in the US and EU for the treatment of CDI and has seen limited routine use in clinical practice. Fidaxomicin has been shown in Phase 3 clinical studies to be non-inferior on clinical response to vancomycin at the end of treatment and in a secondary analysis to be superior to vancomycin on SCR to 25 days post end of therapy, although fidaxomicin was not shown to be superior to vancomycin for SCR for the subgroup of patients infected with BI/NAP 1/027 strains of *C. difficile* [22, 23]. ESCMID treatment guidelines give equal recommendation (Quality of Evidence = II; Strength of Recommendation = B) on the use of fidaxomicin and vancomycin in the treatment of a first episode of CDI and they note that there is no evidence for use of fidaxomicin in severe life-threatening disease. In treatment of first recurrence, both

vancomycin and fidaxomicin receive an equal recommendation strength (B-I). Only in the treatment of multiple recurrences do ESCMID recommend fidaxomicin or taper/pulsed vancomycin regimens over a standard regimen of vancomycin (B-II vs. C-II respectively).

New antibiotic treatments, such as ridinilazole, that can treat the initial infection and minimize the subsequent risk of recurrent infection are needed.

A Phase 2 randomized, double-blind study (SMT19969/C002) conducted in 100 patients with CDI comparing the safety and efficacy of ridinilazole 200 mg bis in die (*bid)* for 10 days versus the approved dose of vancomycin 125 mg *quarter in die (qid)* in the treatment of CDI has been completed [4]. The primary endpoint used was sustained clinical response, defined as clinical cure at test of cure (TOC) and no recurrence of CDI within 30 days post end of therapy. The important secondary endpoint was Investigator-assessed clinical response at test of cure (TOC). The primary analysis population was a modified Intent to Treat (ITT) population comprising patients (36 ridinilazole; 33 vancomycin) whose diagnosis was confirmed by the presence of free toxin in stool. In the mITT population, SCR rates were 24/36 (66.7%) and 14/33 (42.4%) for patients on ridinilazole and vancomycin, respectively. The difference between treatment proportions was 21.1% with a 90% CI (3.1%, 39.1%), which showed ridinilazole was non-inferior to vancomycin (15% non-inferiority margin; p = 0.0004). Furthermore, as the 90% confidence interval lies entirely above zero it was concluded ridinilazole was superior to vancomycin at the pre-specified 10% level of significance (2-sided test). Clinical response at TOC was 28/36 (77.8%) and 23/33 (69.7%) for patients on ridinilazole and vancomycin, respectively (mITT population). The difference between treatment proportions was 8.3% (90% CI −9·3, 25·8), demonstrating non-inferiority (pre-specified 15% margin) on initial cure. In addition, the study showed that ridinilazole was well tolerated, with an adverse event profile comparable to that of vancomycin. In the safety population (all treated patients), 82% (41/50) and 80% (40/50) in the ridinilazole and vancomycin groups, respectively, reported adverse events, while 16% (8/50) and 18% (9/50) of patients in the respective groups reported serious adverse events. There were no study drug-related adverse events that led to discontinuation in the ridinilazole group. Full details of the study results are provided in the Investigators Brochure.

An exploratory Phase 2, multi-centre, open-label, randomised, active-controlled, parallel-group study (SMT19969/C003) was conducted to evaluate the safety and tolerability of 10 days of dosing with ridinilazole (200 mg BID) compared with fidaxomicin (200 mg BID). Secondary objectives included efficacy of ridinilazole compared with fidaxomicin as determined by sustained clinical response to 30 days post EOT and the assessment of the qualitative and quantitative effect of ridinilazole and fidaxomicin on the gut microbiota of patients. The study was not designed to demonstrate efficacy differences and the primary aim was to assess the relative impact of the two agents on the gut microbiota. A total of 27 patients (14 ridinilazole: 13 fidaxomicin) were randomised to study treatment and all were included in the safety and primary efficacy analysis populations. Overall, ridinilazole was considered safe and generally well tolerated. All patients in the safety population, except two patients in the fidaxomicin group, experienced TEAEs. The majority of TEAEs were mild in severity and resolved without treatment and there were no discontinuations due to TEAEs. Sustained clinical response was comparable between the ridinilazole group (50.0%) and the fidaxomicin group (46.2%) with an overall treatment difference of 2.9% (95% CI: -30.8%, 36.7%). The ridinilazole group had a higher proportion of patients with risk factors for CDI recurrence than fidaxomicin including concomitant antibacterial use, severe disease, and age ≥65 years. Analysis of the microbiome of the patients showed that ridinilazole

was associated with reduced negative impact on the indigenous microbiota as measured through reduced α-diversity and changes in major taxa identified via 16S rRNA sequencing. Full details of the study results are provided in the Investigators Brochure.

Ridinilazole is being developed specifically with the dual concept of achieving high cure rates of the initial acute episode of CDI and reducing rates of recurrent CDI and improving Sustained Clinical Response. As such, the endpoints proposed for the Phase 3 trials are designed to demonstrate cure of initial disease and improvement of Sustained Clinical Response.

2.3. Study Rationale

The rationale for this Phase 3 study is to demonstrate the improvement in sustained clinical response of ridinilazole over standard of care and compare the safety of ridinilazole to that of standard of care. A second Phase 3 study of identical design will be run in parallel.

This Phase 3 study is a pivotal study designed to investigate the use of ridinilazole 200 mg bid, as a 10-day therapy, in comparison with the approved dose and duration of vancomycin (125 mg [qid] given for 10 days) for the treatment of CDI. The study will evaluate the efficacy of ridinilazole compared with vancomycin in terms of Sustained Clinical Response (SCR) defined as Clinical Response and no recurrence of infection with *C. difficile* through 30 days post end of treatment (EOT). The efficacy of ridinilazole will also be compared with vancomycin with respect to Clinical Response, and SCR through 60- and 90-days post EOT. Safety and tolerability of ridinilazole will be compared with vancomycin, as well as various health economic measures. The study will also investigate the antibiotic susceptibility and ribotype of *C. difficile* isolates collected at different time points and assess the effect of the two treatments on the gut microbiome and bile acid composition. Ridinilazole plasma concentration will be assessed in a subset of patients.

Oral vancomycin has been selected as a comparator as it is the current standard of care for the treatment of CDI and is generally recommended for use in the treatment of moderate to severe CDI, in treatment of a first recurrent episode and in treatment of those at high risk of recurrent disease [16, 21].Vancomycin therapy is associated with increased rates of clinical response, faster resolution of diarrhea [21] and other symptoms and reduced rates of recurrent disease when compared to metronidazole for all disease severities [19]. Although higher doses are routinely used clinically, the recommended clinical dose of oral vancomycin is 125mg four times daily. In addition, recent studies have shown high dose regimens of vancomycin are no more effective that standard dose regimens [25]. Vancomycin remains the standard active comparator used in clinical trials of novel agents. As such, Summit will use 125 mg of vancomycin dosed four times daily as the active comparator in the pivotal Phase 3 trials.

Pharmacokinetic samples will be collected from a subset of the patients to allow characterization of the systemic exposure of ridinilazole with the tablet formulation. In vitro dissolution profiles and a cross-over study in dogs indicate that the tablet formulation behaves similarly to the Phase 2 capsule formulation. These data indicate that the physicochemical characteristics of ridinilazole govern its behavior leading to very poor absorption from the gut. Therefore, the expectation is that systemic exposure will continue to be negligible in CDI patients with the tablet formulation. Prior studies have indicated that most plasma samples are near or below the limit of quantification of the assay, therefore it is not possible to determine PK parameters nor is there evidence of accumulation upon repeat dosing. To further assess systemic exposure of the tablet formulation, two post-dose samples, at 2 and 4 hours, will be collected on Day 1 or 2, and at EOT. As the study

is blinded, samples will be collected from approximately 100 patients to ensure approximately 40 patients have received ridinilazole. Some of these patients are expected to meet the IDSA criteria for severe CDI (white blood cell count ≥15,000 cells/mm^3 or serum creatinine >1.5 mg/dL). In order to assess the systemic exposure of ridinilazole in patients with severe CDI, the number of patients with severe CDI in the PK subgroup will be monitored, and additional PK patients may be enrolled as required.

2.4. Scientific Rationale for Study Design

Ridinilazole is a novel antibiotic being developed for the treatment of CDI and reducing the recurrence of CDI. Ridinilazole has been shown to demonstrate potent growth inhibition with a narrow minimum inhibitory concentration (MIC) range against a broad range of *C. difficile* ribotypes collected from both the US and Europe. This range includes hyper virulent ribotypes such as 027 and isolates showing reduced susceptibility to vancomycin and metronidazole. Importantly, ridinilazole has a narrow spectrum of activity with typically >1,000-fold selectivity for *C. difficile* over Gram-positive and Gram-negative anaerobic and facultative members of the gut microbiota. This feature of ridinilazole has been shown to result in minimal collateral damage to the gut microbiota [26] compared with vancomycin, throughout the course of treatment of CDI during a Phase 2 clinical trial and ultimately led to a marked reduction in rates of recurrent CDI.

Therefore, this study will use a similar design to the Phase 2 study to provide confirmatory evidence of ridinilazole's effect on CDI recurrence of infection. The primary endpoint of SCR is the most appropriate measure of efficacy for comparison to vancomycin since it captures both cure of the initial infection and any onset of CDI recurrence. An important aspect of the design is that the randomized population will have a diagnosis of CDI confirmed by the presence of free toxin in stool to ensure the study population has the most rigorous diagnosis of true infection (and not colonization) in accordance with treatment guidelines [16, 27].

2.5. Justification for Dose

In the Phase 2 clinical trials of ridinilazole a single dose of 200mg bid for 10 days was assessed. The dose was selected based on known effective gut concentrations of drug from animal models and from fecal concentrations established during Phase 1 clinical trials.

As recognized in guidelines the use of PK/pharmacodynamic (PD) analyses do not assist in the prediction of an effective dose for oral agents intended to act locally within the gut lumen and this has been clearly demonstrated for other GI restricted antibiotics where no correlation between baseline MIC values, fecal concentrations and outcome could be demonstrated. Previous CDI antibiotic studies which varied the daily drug exposure generally failed to demonstrate any significant dose response treatment effect [28-30]. In addition, it has recently been shown that there is no significant improvement in rates of clinical improvement at end of therapy with high dose vancomycin regimens when compared to standard dose regimens [25].

In the Phase 2 study, 50 patients were administered ridinilazole 200 mg *bid* for 10 days for treatment of CDI. The dose was shown to be safe and well-tolerated and demonstrated superiority in sustained clinical response over vancomycin at the 10% level of significance (2-sided test). Furthermore, at this dose there was negligible systemic exposure of ridinilazole with mean (SD) plasma concentrations of 0.06 (0.11), 0.16 (0.26), and 0.18 (0.22) ng/mL at nominal 4 hours post-dose on Days 1, 5, and 10, respectively. Furthermore, there was no notable effect on systemic

exposure due to food, gender, concomitant medication, age, or disease severity. Corresponding fecal concentrations of drug (Day 10 mean = 1,373 µg/g) were significantly above the MIC_{90} value of 0.125 µg/mL for *C. difficile.*

Based on these results and the acceptable safety and tolerability profile seen in both the Phase 1 and Phase 2 studies the same dose will be used in this larger Phase 3 study.

As per IDSA guidelines, vancomycin 125 mg *qid* over 10 days is recommended therapy option for all severities of CDI.

2.6. Benefit/Risk Assessment

In 28-day oral toxicity studies in rats and dogs up to ridinilazole 1000 mg/kg/day no adverse study findings were seen with associated plasma levels below the LLOQ. Assessment of the systemic toxicity of ridinilazole for 28 days by the i.v. route in the rat and the dog identified the liver, lungs (findings possibly caused by particulate deposition of ridinilazole in capillary beds due to plasma saturation), spleen and kidneys (rat only), thymus and gall bladder (dog only) as target organs from a dose-level of ridinilazole 0.5 mg/kg/day. The associated ridinilazole plasma levels were several hundred-fold higher than the plasma levels observed in humans so far.

In a Phase 1 study 42 healthy male patients received single oral doses of up to 2000 mg in the fasted state, a single oral dose of 1000 mg in the fed state or repeated doses at up to 500 mg *bid* for 9 days in the fed state with ridinilazole being considered safe and well tolerated. The most frequent drug-related AEs were classified as GI disorders: diarrhea and abdominal distension/pain.

In Phase 2 studies a total of 64 patients (SMT19969/C002 50 patients; SMT19969/C003 14 patients) received ridinilazole 200 mg *bid* for 10 days with no additional safety signals observed. The most frequent AEs were GI related. The safety profile of ridinilazole in the SMT19969/C002 study was comparable to the comparator, vancomycin, which will be used in this proposed study.

In the SMT19969/C002 Phase 2 study in patients with CDI ridinilazole was shown to be superior at the pre-specified 10% level of significance (2-sided test) over standard of care vancomycin with respect to its primary endpoint of SCR and non-inferior with respect to its key secondary endpoint at AOC. In the SMT19969/C003 study ridinilazole displayed comparable clinical efficacy to fidaxomicin on sustained clinical response (SCR).

In both Phase 2 clinical studies the plasma concentrations of ridinilazole were either below or close to the LLOQ, with a maximum systemic concentration of 1.31 ng/mL across all patients and assessment days. Therefore, GI related local tolerability AEs can be expected to be the main safety risks for ridinilazole.

Together with pre-clinical data showing ridinilazole has a narrow spectrum activity against *C. difficile* and microbiome sparing properties, these clinical data provide a positive risk-benefit profile for patients in this study. Safety procedures during this clinical trial consist of vital signs, physical examinations, and laboratory assessments.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ridinilazole may be found in the Investigator's Brochure including the Reference Safety Information (RSI). A risk assessment for vancomycin can be found in the SPC/package insert.

Summit Therapeutics believes it is important to continue developing ridinilazole for patients with CDI while ensuring the safety of study patients, study personnel, and the public during Coronavirus Disease 2019 (COVID-19) pandemic. We have carefully assessed the Ri-CoDIFy studies in the context of the COVID-19 pandemic. Both CDI and COVID-19 are emerging infections that occur in at-risk populations (e.g., elderly, those with pre-existing medical conditions) and can result in significant morbidity and mortality. Like SARS-COV-2, *C. difficile* is a transmissible pathogen and infection rates may be lower initially with the recent implementation of COVID-19 public health actions. However, antibacterial treatments used empirically when a patient is being assessed with a respiratory infection or complicated by post-COVID-19 bacterial pneumonias could lead to an increase in CDI infections and associated changes to the gut microbiome. New therapies for CDI that are effective, safe and have lower post-treatment recurrences are needed.

To mitigate the risk of exposure to COVID-19 and optimize data integrity, protocol amendment 5 provides guidance for sites, including the allowance of all study visits to be completed remotely.

3. OBJECTIVES AND ENDPOINTS

Primary Objective

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

Exploratory Objectives

- To compare the effect of ridinilazole (200 mg *bid*) and vancomycin (125 mg *qid*) on the gut bile acid composition, microbiome, and antibiotic resistance gene profile at EOT and during the follow-up period
- To assess the antibiotic susceptibility and ribotype of *C. difficile* isolates in patients receiving ridinilazole (200 mg *bid*) and vancomycin (125 mg *qid*)
- To assess the impact of ridinilazole treatment on patient reported quality of life, resource utilization and health economics

Primary Endpoint

- Sustained Clinical Response (SCR) is defined as Clinical Response and no recurrence of CDI through 30 days post End of Treatment (EOT).

Secondary Endpoints

- Clinical Response
- Clinical Cure
- Sustained Clinical Response over 60 days – defined as Clinical Response and no recurrence of CDI through 60 days post EOT
- Sustained Clinical Response over 90 days – defined as Clinical Response and no recurrence of CDI through 90 days post EOT
- Change from baseline to EOT of the relative abundance of the 3 main bile acid groups (conjugated primary, primary and secondary bile acids) in stool samples
- Change from baseline to EOT of the microbiota α-diversity (Shannon) index in stool samples
- Change from baseline to EOT of the gut microbiota β-diversity (Bray-Curtis) index in stool samples

Definitions for the Primary and Secondary Endpoints

Clinical Response is defined as

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

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 treatment.

A UBM is defined as a Type 5, 6 or 7 bowel movement on the Bristol Stool Chart.

Safety Endpoints
• Safety and tolerability as determined by AE and SAE reporting
PK Endpoints
• Ridinilazole plasma concentration in a subset of patients
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 VAS score • Change from baseline in Cdiff 32 domains (US sites)
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) • Change from baseline to Day 40 and up to Day 100 and at time of recurrence (if applicable) of the relative abundance of the bile acid components, conjugated primary, primary, and secondary bile acids in stool samples • Change from baseline to Day 40 and up to Day 100 and at time of recurrence (if applicable) of the microbiota α-diversity (Shannon) and β-diversity (Bray-Curtis) indices in stool samples • Change from baseline to EOT, Day 40 and up to Day 100 and at time of recurrence (if applicable) of the relative abundance of bacterial taxa, microbiome gene functions, and microbiome antibiotic-resistance genes in stool samples • Determination of the ribotype and susceptibility to ridinilazole, vancomycin and other antibacterial agents of *C. difficile* isolates collected in stool samples at baseline, EOT and recurrence

4. STUDY DESIGN

4.1. Patient Enrolment and Overall Design

SMT19969/C004 is a Phase 3 randomized, double-blind, active controlled, parallel group, multi-center study to compare the efficacy of 10 days' dosing with ridinilazole 200 mg *bid* with vancomycin 125 mg *qid* in the treatment of patients with CDI. Approximately 680 patients (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.

Due to the acute nature of CDI and typical requirement for immediate treatment it is expected that the screening and the baseline/D1 assessments will be conducted on the same day but, the screening visit can be conducted within 3 days prior to the baseline/D1 visit if required for practical reasons. In addition, protocol v.6.0 introduces the option for all study visits to be conducted remotely due to the COVID-19 public health emergency. However, patients should continue to attend in-clinic visits whenever possible or as required. All assessments should be completed prior to randomization except for the following:

- May be conducted after randomization but prior to 1st dose: weight, hematology and clinical chemistry samples, stool collection, eDiary training, EQ-5D-5L, Cdiff32 and medical utilization questions.
- In a subset of patients, samples for PK analysis must be obtained (refer to Section 8.5).

Randomization will occur after confirmation of eligibility is established with reference to the protocol inclusion and exclusion criteria. Patients will be randomized to receive ridinilazole or vancomycin in a 1:1 fashion. Randomization will 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 recurrent CDI (either none or 1 to 3 previous occurrences in the past 12 months). Dosing with study treatment starts on Day 1 following randomization. Further visits will be scheduled at Day 10 (EOT), 12 (AOC), 40 (SCR), 70 (SCR) and 100 (SCR). A telephone check will be conducted at Day 5. Day 10 and Day 70 assessments may be conducted by telephone per Investigator judgement/convenience although arrangements will be required for patient drop-off or site collection of a stool sample. The AOC visit will be conducted on Day 13 if the patient's 10 days' dosing is completed on Day 11.

Patients will report dosing information to EOT and bowel movements daily up to Day 40, to support the primary endpoint analyses. Weekly contact with the patient will occur after Day 40 until study completion to check for diarrhea/suspected recurrence. Investigators or designee will take measures to ensure patients are compliant with reporting diarrhea/suspected recurrence during the study.

An *assessment of suspected recurrence* visit will occur for each suspected recurrence (≥ 3UBMs in one day, after assessment of cure or resolution of previous recurrence).

Unscheduled visits may occur at the Investigator's discretion (e.g. in the case of AEs). Additionally, patients should be requested to attend an in-clinic visit in the event of suspected recurrence of CDI. If they have a suspected recurrence and are not able to visit the clinic, this visit

may be completed at home over video conference with the site and with the additional assistance of a home health vendor, where required by the Investigator.

Note: The term "Investigator" refers to the Principal Investigator of a clinical site or delegate as documented on the site Delegation of Authority log.

Details on the timing of treatment and assessments are given in the Schedule of Activities Table (Section 1.3).

COVID-19

All assessment visits may be conducted at the clinic or remotely; however, whenever possible, screening/baseline visits should be conducted in-person at the clinic. Below are modifications to the protocol when remote assessments are necessary to protect patients, site personnel, or community safety, or to respond to COVID-19-related public health measures.

For study visits that must be conducted remotely, and where the patient is not residing at home, investigative site staff or home healthcare vendor with proper delegation and training may see patients at an alternative location(s) where they have the privileges to do so, as permitted by local law and policies. Informed Consent is allowed in other than face to face method as per site local procedure or local regulations. This may include electronic signature or e-Consent if already in place and used at the site. Consent form(s) must be received and acknowledged by the site prior to the commencement of any study procedures. Original, signed consent form(s) must be returned to the site either at the next in-clinic visit, posted to the site, or returned via courier or any other approved alternate method.

The stool sample may be couriered to the site.

A sponsor contracted home healthcare vendor or appropriately trained and delegated site staff may conduct remote visit at the patient's home or alternate agreed on location.

The patient may take their own vital signs using their vital signs machine if they already have one or one that is provided to them (where available). The physical exam and vital signs when taken by the patient, 'signs and symptoms of CDI' assessments must be done via sponsor approved video conferencing between the Investigator and the patient.

Following Investigator assessment of eligibility and randomization, eDiaries C-diff 32 questionnaire (where applicable) and IMP should be provided directly to the patient (shipped by courier, provided by site staff or picked up by the patient or caregiver).

Used IMP wallets and any unused medication should be returned to the site, either during the next in-clinic visit or shipped or couriered to site.

4.2. End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including D100 assessments (EOS).

The end of the study is defined as the date of the last study assessment of the last patient in the study.

4.3. Combination of Databases of Studies SMT19969/004 and SMT19969/005

Measures were taken in Protocol Amendments 5 and subsequent amendments to mitigate the impact of the COVID-19 pandemic on the trial. To minimize the potential, unknown impact of the 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 Statistical Analysis Plan 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 modifications to the statistical handling of the study are described briefly in Section 9 and in detail in the Statistical Analysis Plan.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Patient must be at least 18 years of age, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2. Have signs and symptoms of CDI including diarrhea such that in the Investigator's opinion CDI antimicrobial therapy is required. Diarrhea is defined as a change in bowel habits, with ≥3 UBMs (5, 6 or 7 on the Bristol Stool Chart) in the 24 h prior to randomization.

3. Have the presence of either toxin A and/or B of *C. difficile* in the stool determined by a positive free toxin test (using a Sponsor agreed test). The stool sample must be current (produced within 72 hours prior to randomization).

Sex

4. Male or Female

Male patients:

- A male patient must agree to use contraception as detailed in Section 10.4 of this protocol during the treatment period and for at least 30 days after the last dose of study treatment and refrain from donating sperm during this period.

Female patients:

- A female patient is eligible to participate if she is not pregnant (see Section 10.4), not breastfeeding, and at least one of the following conditions applies:

  i. Not a woman of childbearing potential (WOCBP) as defined in Section 10.4

  OR

  ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 30 days after the last dose of study treatment.

Informed Consent

5. Has provided documented signed informed consent and any authorizations required by local law (e.g. Protected Health Information [PHI]). If unable to read, understand and sign the informed consent form a legally authorized representative (LAR) may provide consent on the patient's behalf if permitted by the Institutional Review Board (IRB)/Ethics Committee (EC).

5.2. Exclusion Criteria

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

Medical Conditions

1. Have had more than one prior episode of CDI in the previous 3 months or more than 3 episodes in the past 12 months prior to randomization.

2. Have a history of chronic diarrheal disease including inflammatory bowel disease (Crohn's disease or ulcerative colitis).

3. Have had a positive diagnostic test for other GI pathogens, considered to be clinically relevant, within 2 weeks of randomization.

4. Have had major gastrointestinal (GI) tract surgery (e.g. significant bowel resection or pancreatectomy) within 3 months of randomization (this does not include appendectomy or cholecystectomy); or the presence of a colostomy or ileostomy or likely requirement of an ostomy during the study.

5. Have life threatening or fulminant CDI with evidence of hypotension, septic shock, peritoneal signs or absence of bowel sounds, or toxic megacolon.

6. This number (EC #6) has been intentionally left blank.

Prior/Concomitant Therapy

7. Have had more than the equivalent of 24 hours of dosing of antimicrobial treatment against the current episode of CDI prior to randomization. (i.e. more than four doses of oral vancomycin, two doses of fidaxomicin or teicoplanin, or three doses of metronidazole).

8. Prior or current use of anti-toxin antibodies including bezlotoxumab within the 6 months prior to randomization.

9. Are unable to discontinue products affecting disease progression at randomization (see Section 6.5.1 for a list of potentially confounding medications).

Prior/Concurrent Clinical Study Experience

10. Has been involved in a clinical trial and received an investigational medicinal product for indications other than CDI within 1 month or five half-lives (whichever is longer) or within 3 months if the investigational medical product was for CDI.

11. Have received an investigational vaccine against *C. difficile*.

Other Exclusions

12. Patients that the Investigator feels are inappropriate for the study:
    a. patients with any condition that, in the Investigator's judgment, would make the patient unsuitable for inclusion in the study, such as chronic diarrhea, vomiting that cannot be managed with anti-emetics, inability to swallow study medication, or medically unstable with critical illness (e.g. requiring vasopressors, intubation, etc.).
    b. patients who, in the opinion of the Investigator, are not likely to complete the study, e.g. life expectancy less than 100 days.
    c. patients with known hypersensitivity or intolerance to ridinilazole, vancomycin, and/or their excipients
    d. patients or their caregivers who are unable to comply with protocol requirements, e.g. attend study visits, report bowel movements and suspected recurrence, provide stool samples or undergo blood draws.

Note: Investigators are encouraged to contact the medical monitor to discuss individual cases as required.

5.3. Lifestyle Considerations

There are not any lifestyle restrictions applicable through the study.

5.3.1. Meals and Dietary Restrictions

No meal or dietary restrictions.

5.3.2. Caffeine, Alcohol, and Tobacco

No caffeine, alcohol, or tobacco restrictions.

5.3.3. Activity

No activity restrictions.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in any of the clinical study assessments but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons and any serious adverse event (SAE).

It is possible for patients to be rescreened once for this study. If a patient is rescreened a new patient number will be assigned.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient per the study protocol. All study treatments will be provided on behalf of Summit (Oxford) Limited.

6.1. Study Treatment(s) Administered

Patients will be randomized into one of two treatment arms

Table 1: Dosing Schedule per 24 Hours

	Dose 1	**Dose 2**	**Dose 3**	**Dose 4**
Ridinilazole Arm	Ridinilazole 200mg & Vancomycin Dummy Placebo	Ridinilazole Dummy Placebo & Vancomycin Dummy Placebo	Ridinilazole 200mg & Vancomycin Dummy Placebo	Ridinilazole Dummy Placebo & Vancomycin Dummy Placebo
Vancomycin Arm	Ridinilazole Dummy Placebo & Vancomycin 125mg	Ridinilazole Dummy Placebo & Vancomycin 125mg	Ridinilazole Dummy Placebo & Vancomycin 125mg	Ridinilazole Dummy Placebo & Vancomycin 125mg

Patients will take one dose (one tablet and one capsule) four times a day for 10 days (40 doses). It is important that patients:

- Are instructed to complete the full 10-day course of IMP in order to fully evaluate efficacy.
- Take doses strictly in numerical order to ensure correct timing of active vs placebo
    - Must only remove one dose at a time (one tablet and one capsule) from the provided wallet. Removing multiple doses from the wallet is not permitted.
- Do not crush or break the tablets or open the capsules (e.g. to pass through a feeding tube).

Study treatment will be provided in a blister wallet labeled per country requirements. Each wallet will have a unique identifier which will be used to allocate double-blind study treatment to each patient via the Interactive Response Technology (IRT) system. Each wallet will contain all doses required for the total treatment period (40 doses over 10 days). Doses will be clearly labeled 1 to 40 on the wallets. It is important the patient takes each dose in order number starting with 1 and finishing with 40. If a patient misses a dose, they should be instructed to take the missed dose before or with the next dose. No more than 2 doses should be taken at any one time. For example, if Dose 3 is missed, take Dose 3 before or with Dose 4.

6.2. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions (**below 25°C and not refrigerated or frozen**) have been maintained during transit for all study treatment received and any product complaints or discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment (as documented by the Investigator on the Delegation of Authority log). All study treatment must be stored in a secure, environmentally controlled, and

monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Any product complaints or storage temperature excursions identified during storage of investigational product should be reported to the Sponsor and resolved prior to use.

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

The Investigator or Pharmacist should arrange for destruction of any unused IMP following full reconciliation of IMP and Sponsor (or delegate) approval. Destruction will be conducted locally where possible using a method in line with Sponsor provided requirements. Destruction should be conducted per the sites standard operating procedure (SOP) and a destruction certificate, including method of destruction, should be issued. IMP may be returned to the Sponsor if local destruction is not possible.

Further guidance and information for the final disposition of unused study treatments are provided in the Investigator Trial Site File.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will occur on Day 1 after eligibility for the study has been confirmed.

Patients will be randomized to one of two treatment groups in a 1:1 ratio to either the ridinilazole arm or the vancomycin arm.

The Investigator or designee will use the IRT system to randomize a patient.

A computer-generated central randomization will be used which will 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 recurrent CDI (either none or 1 to 3 previous occurrences in the past 12 months). Once a randomization number has been assigned it will not be re-assigned.

Study treatment will be dispensed at the randomization visit (Day 1) as summarized in SoA (Section 1.3). Returned study treatment should not be re-dispensed to patients.

This is a double-blind study. To maintain the blind, a double-dummy approach for study treatment will be employed. Vancomycin will be encapsulated within a Size 0 Swedish Orange, hard gelatin, and immediate release capsule. There will be a matching vancomycin placebo. Ridinilazole is presented as a coated tablet. There will be a matching ridinilazole placebo. Patients randomized to ridinilazole will receive active ridinilazole, ridinilazole placebo and vancomycin placebo to achieve dosing with ridinilazole bid. Patients randomized to vancomycin will receive active vancomycin and ridinilazole placebo to achieve dosing with vancomycin *qid*. The study drug and packaging will be manufactured in such a way that patients and study site staff will not know to which arm a patient has been assigned.

The adverse event profile of vancomycin and ridinilazole indicates that most adverse events can be managed without unblinding. If the Investigator believes unblinding is necessary to manage a patient, then emergency unblinding may be conducted via the IRT system but should only be performed when knowledge of the treatment is *essential for medical decisions and/or further emergency management of the patient.*

In case of an emergency, the Investigator (whenever possible) is responsible for determining if unblinding is warranted. Patient safety must always be the first consideration.

If unblinding is determined to be warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding, unless this could delay emergency treatment of the patient.

If unblinding occurs, the Sponsor must be notified within 24 hours. The Sponsor should remain blind to the treatment assignment. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Treatment Compliance

In accordance with ICH-GCP, each study center will account for all supplies of blinded medication. Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one capsule or one tablet.

Several measures are in place to ensure patients are compliant with their medication schedule. These include clear labelling of treatment wallet, the use of a patient eDiary or frequent contact with the patient, and reminders from the site staff. Patients should record the time and date they take each dose.

Compliance with the study treatment and documentation of dosing and bowel movements is critical to the integrity of the primary endpoint.

To help ensure compliance the Investigator will discuss compliance with the patient:

- **At Day 5 to ensure the treatment is being administered per protocol and to remind the patient to continue to complete all doses regardless of resolution of symptoms.**
- **If records indicate that the patient has not been reporting dosing and/or bowel movements as required.**

The eDiary will be programmed with reminders for patients to take the medication and to complete their eDiary daily until D40.

The patient will be required to return all empty packaging and unused study medication to the Investigator at the Day 12 (AOC) visit so that a final compliance check can be conducted. If the patient is unable to attend in-clinic visits it may be shipped or couriered to the site.

In the event of overdose see Section 8.4.

6.5. Concomitant Therapy

Concomitant therapy is any medication, vaccine, procedure or therapy (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study.

All concomitant therapies should be recorded from 4 weeks prior to randomization and throughout the study up to D100 (see Section 6.5.1). The reason for use, dates of administration and dosing information should be recorded in the CRF.

6.5.1. Potential Confounding Medications

Refer to Table 2A and B below for a list of medications that may impact CDI status and hence have the potential to confound study results. Control over administration of these medications is necessary, considering the primary endpoint of the study, but it is understood that a medication should not be withheld for purposes of the study if an alternative and comparable treatment cannot be provided and the patient's health would otherwise be compromised.

Potentially Confounding Medications:

Medications that could potentially confound data analysis should be avoided if possible, without compromising the care of the patient.

If antimicrobial therapy is required for infections other than those due to *C. difficile*, antimicrobials without activity/efficacy against *C. difficile* should be prescribed,

Confounding medications include, but are not limited to, these listed in the following table.

Table 2A: Potentially Confounding Medications Which May Exclude Patients from Randomization

Contact the Medical Monitor to discuss individual cases as required

Drug Class	At Randomization
CDI Treatments	
Antimicrobial treatments for CDI (including but not limited to oral vancomycin, IV or oral metronidazole, fidaxomicin, oral teicoplanin)	Exclude patient if more than 24 hours (or equivalent) of treatment for the current/baseline CDI.
Anti-toxin antibodies including bezlotoxumab	Exclude patient if taken within 6 months of randomization
Antimicrobial treatments that may be effective at treating CDI (including but not limited to oral rifaximin, tigecycline, nitazoxanide, oral bacitracin, fusidic acid)	Exclude patient if more than 24 hours (or equivalent) of treatment immediately prior to randomization
Probiotics or prebiotics	None permitted
Intravenous immunoglobulin (IVIG)	Exclude patient if taken within 3 months prior to randomization
Fecal microbiota replacement	Exclude patient if taken within 3 months prior to randomization
IMP for CDI	Exclude patient if taken within 3 months prior to randomization
Investigational vaccine against *C. difficile*	Exclude patient if taken any time prior to randomization
Non-CDI Treatments	
Other antimicrobials not active against *C. difficile*[1]	Permitted
Opiates	Stable, decreasing or planned to be stopped by Day 7 of randomization
Anti-diarrheals, anti-peristaltics	Stable, decreasing or planned to be stopped by Day 7 following randomization.
IMP for other indications	Exclude patient if used within one month or five half-lives (whichever is longer) prior to randomization
Treatment of cancer using chemotherapy, radiotherapy, biologic treatments including (monoclonal) antibodies, immune-oncological treatments	Only exclude patient if the cancer treatment given is generally associated with or is causing diarrhea, vomiting and/or severe nausea that cannot be managed with antiemetics, severe mucositis and/or severe immunosuppression

[1] May contribute to recurrence. Important to document in the eCRF throughout the study.

Table 2B: Potentially Confounding Medications Which May Not Be Permitted During Study Treatment (Day 1 to Day 12 and/or during Follow-up (Day 12 to Day 100)

Contact the Medical Monitor to discuss individual cases as required

Drug Class	From Randomization to Day 12/AOC	During Follow Up
CDI Treatments		
Antimicrobial treatments for CDI (including but not limited to oral vancomycin, IV or oral metronidazole, fidaxomicin, oral teicoplanin)	None permitted	For recurrence, as per standard clinical practice
Anti-toxin antibodies including bezlotoxumab	None permitted	For recurrence, as per standard clinical practice
Antimicrobial treatments that may be effective at treating CDI (including but not limited to oral rifaximin, tigecycline, nitazoxanide, oral bacitracin, fusidic acid)	None permitted	Prescribe alternative antimicrobial if use is for conditions other than CDI where possible.
Probiotics or prebiotics	None permitted	For recurrence, as per standard clinical practice
Intravenous immunoglobulin (IVIG)	None permitted	For recurrence, as per standard clinical practice
Fecal microbiota replacement	None permitted	For recurrence, as per standard clinical practice
IMP for CDI	None permitted	None permitted
Investigational vaccine against *C. difficile*	None permitted	None permitted
Non-CDI Treatments		
Other antimicrobials not active against *C. difficile*[2]	Permitted	Permitted
Opiates	Allowed if stable, decreasing or planned to be stopped by Day 7 following randomization[3]	Allowed if stable, decreasing or stopped[3].
Anti-diarrheals, anti-peristaltics	Allowed if stable, decreasing or planned to be stopped by Day 7 of randomization[3]	For recurrence, as per standard clinical practice.

[2] May contribute to recurrence. Important to document in the eCRF throughout the study.
[3] Preference is to stop use by Day 7 following randomization

Drug Class	From Randomization to Day 12/AOC	During Follow Up
IMP for other indications	None permitted	None permitted
Treatment of cancer using chemotherapy, radiotherapy, biologic treatments including (monoclonal) antibodies, immune-oncological treatments	Not permitted if the cancer treatment given is generally associated with or is causing diarrhea, vomiting and/or severe nausea that cannot be managed with antiemetics, severe mucositis and/or severe immunosuppression	Not permitted if the cancer treatment given is generally associated with or is causing diarrhea, vomiting and/or severe nausea that cannot be managed with antiemetics, severe mucositis and/or severe immunosuppression

Any potential confounding medications taken 4 weeks prior to randomization should be recorded in the CRF along with any potential confounding medications started, stopped, or changed during the study (up to Day 100).

During the study both the treatment period and follow up period, patients who take any confounding medications should not necessarily be discontinued from study treatment and should not be withdrawn from the study.

Investigators should contact the medical monitor for any questions regarding concomitant or prior therapy.

6.6. Dose Modification

Not applicable

7. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL FROM STUDY

7.1. Discontinuation of Study Treatment

A patient will discontinue study treatment for any of the following reasons:

- Withdrawal of consent to continue taking treatment. The reason for this will be documented if provided.
- The study Investigator or Sponsor, for any reason, decides the patient should be discontinued from the treatment.
- Adverse events, classed as possibly or probably study drug-related by the Investigator, which cannot be tolerated by the patient.
- Pregnancy during the treatment period. See Section 10.4 and Section 8.3.5 Pregnancy.

If a patient is discontinued from treatment, they should continue with all study visits and assessments so that data can be collected. If patients will not agree to this then they should complete early termination assessments and return the study treatment wallet.

See the SoA (Section 1.3) for data to be collected at the time of study treatment discontinuation and early termination of follow-up and for any further evaluations that need to be completed.

Study drug assigned to the discontinued patient must not be assigned to another patient.

7.2. Patient Withdrawal from the Study

All patients are encouraged to continue through to the end of the study at Day 100 even if they discontinue from study treatment early. However, a patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. The reason for withdrawal is to be documented on the CRF and in the source document.

7.3. Lost to Follow Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions will not be granted by the Sponsor or delegate.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator or study team designee will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Patient Reporting of Diarrhea/Suspected Recurrence

Patients should be instructed to contact the site if their diarrhea returns (≥ 3UBMs per day for at least 1 day).

Additionally, patients will report dosing information daily until EOT and bowel movement information daily until D40. After D40 the site will contact the patient weekly to check for new episodes of diarrhea/suspected recurrence.

Patients will be asked to report the following:

- Date and time of each dose of study medication to EOT.
- Date, time, and consistency (using the Bristol Stool Chart) of all bowel movements up to Day 12/AOC.
- Date, time, and consistency of all unformed bowel movements (UBMs) through Day 40.
- During weekly contacts with the patient after Day 40 and through Day 100, any episodes of ≥3 UBMs within 1 day since the last site contact.

Able patients will be provided with an electronic diary (eDiary) to report this information up to Day 40. Adequate time should be allocated to ensure that the patient understands how to complete the eDiary and is willing and able to do so every day up to and including Day 40 (at least 30 days following the last dose of study treatment). The site should contact the patient to collect this information if use of an eDiary is not possible.

Patient Reported Bowel Movement Data

- **Assessment of response to study treatment and identification of all episodes of CDI recurrence rely on bowel movement data collected from the patient.**
- **It is critical that the Investigator and patient understands that accurate, complete, and contemporaneous data is required to meet the study primary objective.**
- **It is specifically important to ensure each patient provides this information every day to Day 40 (at least 30 days following the last dose of study treatment).**
- **Following Day 40 the site will contact the patient weekly to ask about potential diarrhea and assess for suspected recurrence as required.**

Reported information on bowel movements will be used by the Investigator to determine if a suspected recurrence of CDI requires assessment. The Investigator or designee will be required to monitor the patient's unformed bowel movement (UBMs) and assess any suspected recurrence of CDI.

Suspected Recurrence:

After the patient was deemed cured, if ≥3 UBMs are experienced over a 1-day period, the Investigator should arrange an assessment for suspected recurrence. If a free toxin test is not conducted, the reason should be recorded in the CRF along with a determination of whether recurrence of CDI was suspected.

Changes to eDiary Data:

For data collected via an eDiary, data changes are not permitted. Changes to eDiary data will be limited to administrative corrections such as erroneous patient number, visit date, patient status, timestamps and elimination of duplicate data or merging of data sets for the same patient.

Patient reported eDiary errors will be reported in the CRF describing the error and the correct information.

eDiary Programmed Alerts:

For data collected via an eDiary, Investigators will be alerted if a daily eDiary completion is missed. In these cases, the Investigator will contact the patient, within 72h of the day missed, to determine if any UBMs occurred. This information will be documented in the CRF.

Care Provider Support:

The preference is that patients enter their own data into the eDiary directly. However, it is expected that some patients will have difficulty completing the eDiary. Such patients may be supported by a care provider entering the data into the eDiary on behalf of the patient. This is permitted if the Investigator is confident that the support provided is adequate to ensure accurate entries into the eDiary on the patient's behalf. The Investigator must document agreement for a care provider to enter information into the eDiary on behalf of the patient and the rationale. The care provider must only enter information into the eDiary using a unique user ID and PIN following training.

A care provider will not complete the EQ-5D on behalf of the patient.

Alternative to the eDiary:

The CDI patient population is frequently comorbid, elderly, and reliant on family members. For patients that are unable to complete the eDiary, and where the care provider option is not possible, an alternative to completion of the eDiary can be utilized.

The Investigator/site staff or delegate will contact the patient daily to collect dosing and bowel movement information. A detailed report of the contact must be documented in the source records including date and time of contact, contact participants, details of dosing and bowel movement information since the last contact. Details of dosing and bowel movement will be entered into the CRF. If an Investigator chose this method of collection the site and patient must be willing to make every effort to report this daily. Exceptions may be made (if necessary) over the weekend/national holidays. Sites are expected to make all efforts to have adequate holiday and vacation coverage to ensure information is collected within 72h of the event. In general information collected >72h after the event will be considered missing data for that day unless there is adequate supporting documentation to confirm the data (especially for the date and time of each BM).

Where feasible (available and with applicable local regulatory approvals), a second alternative to the eDiary will be made available. Sites may use a 3rd party vendor to contact patients to collect dosing and bowel movement information daily. Patients must provide specific consent to use this option. Even when utilizing a 3rd party vendor, the Investigator is still responsible for ensuring any episodes of ≥3 UBMs in 1- day period are assessed.

8.1.2. Signs and Symptoms of CDI

The Investigator should record the patient's current signs and symptoms of CDI at baseline/D1 and at the Day 12/AOC visit. Current signs and symptoms will also be recorded during an assessment of suspected recurrence. The investigator should ask the patient for signs and symptoms that have occurred over the 1-day period prior to assessment.

Suspected recurrence: if there is no recurrence of CDI per the protocol definition (≥3 UBMs in a 1-day period, a positive *C. difficile* free toxin test or CCNA and requiring CDI treatment) any reported signs and symptoms (or preferably the associated diagnosis) should be reported as AEs/SAEs if prior to the Day 40 visit.

Record all symptoms (loose stools, abdominal cramps or pain, fever, visible blood or pus in stool, nausea, vomiting, loss of appetite or other) that apply to the patient at that evaluation on the CRF at the visits indicated.

The Investigator will refer to the patient reported signs and symptoms when assessing cure and/or recurrence of CDI.

8.1.3. Suspected Recurrence

A recurrence of CDI is considered a disease related event (DRE) and not an adverse event (AE or SAE). See Section 8.3.7. In the case of a suspected recurrence, a suspected recurrence of CDI CRF page should be completed-. Certain specified - DRE complications of CDI should be reported as SAEs (refer to Section 8.3.7).

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 treatment.

A UBM is defined as a Type 5, 6 or 7 bowel movement on the Bristol Stool Chart.

Following cure of the baseline CDI, if diarrhea returns (≥3 UBMs in a 1-day period) the Investigator will contact the patient to assess for recurrence.

It is required that every new episode of diarrhea (≥3 UBMs in a 1-day period) is investigated via a free toxin test unless the Investigator is highly confident that the diarrhea is due to a cause other than *C. difficile.*

- If recurrence of CDI is **not** suspected: record the reason in the CRF on the "Suspected Recurrence of CDI" CRF page.
- If recurrence is suspected:
    - Conduct a free toxin test as soon as possible and no later than 2 days after identifying a suspected recurrence. If the test is invalid it should be repeated. If the FTT test is negative it can be repeated once on the same sample or fresh sample.
    - Complete the "Suspected Recurrence of CDI" CRF page
    - In all instances of suspected recurrence of CDI that are associated with a negative free toxin result obtained locally by the site, a stool sample should be collected and sent for testing by Cell Cytotoxicity Neutralization Assay (CCNA) at a central laboratory. This is a requirement irrespective of any locally conducted CCNA.

In addition, at the scheduled visits indicated in the SoA (Section 1.3), the Investigator should also assess whether the patient has met the criteria for recurrence.

Investigators are requested, subject to local treatment guidelines and Investigator judgement, to await the results of the free toxin test prior to initiating antimicrobial treatment for a suspected recurrence. The Investigator should discuss with the Medical Monitor if required.

All the assessments as indicated in the SoA Recurrence Visit (Section 1.3) should be carried out.

Investigators are urged to follow the patient closely and directly assess and provide medical management of each suspected recurrence throughout the study. If a patient is assessed and/or treated by a non-study health care professional, the Investigator should obtain as much information as possible for CRF entry.

To ensure the data integrity of the primary and secondary endpoints, it is critical that the following requirements are met for all patients where possible:

- **A free toxin test is conducted as soon as possible following suspicion of recurrence.**
- **Any potentially confounding medications initiated must be recorded in the CRF**
- **For all suspected recurrences associated with a negative free toxin test result obtained locally by the site, a stool sample should be collected for testing by CCNA at a central laboratory.**

8.1.4. Investigator Assessments of Cure and Sustained Clinical Response

Assessed by the Investigator at the times outlined in the SoA (Section 1.3).

Investigator assessment of cure:

- At the D12/AOC visit the Investigator or medically qualified designee will determine if the patient is CURED or has FAILED to respond to study medication.
- If the Investigator assesses a patient as FAILED at D12/AOC visit, the Investigator will continue to follow the patient and record an unscheduled visit as soon as the subject is assessed as cured into the CRF. 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.
    - At D40, D70 and D100 the Investigator or medically qualified designee will determine if the patient was CURED since the previous assessment or continues to be FAILED. Once CURED has been recorded once (on D40 or D70), the subsequent assessments are not required (not applicable).
- Following cure of the baseline CDI (including patient that initially failed at D12/AOC and subsequently cured (meaning their baseline CDI resolved), the Investigator will continue to follow-up on any subsequent suspected recurrences and record them in the CRF.

Investigator assessment of sustained clinical response:

- At D40, D70 and D100 the Investigator or medically qualified designee will determine if the patient has a sustained clinical response or experienced RECURRENCE since the previous assessment. When recurrence has been recorded once, the subsequent assessments are not required (not applicable).
- If the Investigator assesses a patient as FAILED for sustained clinical response, then a future assessment of sustained clinical response, at subsequent time points, is no longer required.

The Investigator will assess cure/failure and recurrence based on available information which includes, but is not limited to, improvement from baseline in the number of UBMs, signs & symptoms of CDI, and the requirement for CDI medication. The Investigator should assess cure/failure in a way that best reflects the Investigator's standard clinical practice.

NOTE: In line with treatment guidelines, laboratory and/or diagnostic testing for CDI should not be used to determine AOC [17, 31-33].

8.1.5. Stool (Fecal) Collection for Characterization

Patients will be required to provide a stool sample at the time points specified in the SoA (Section 1.3). Patients will be provided with a home collection kit. If a sample is requested by the Investigator, the patient will provide the sample to the study site within 24 hours of producing the sample. Samples will be immediately tested with a free toxin test, in the event of a suspected recurrence. Aliquots of the sample will be prepared and immediately frozen and stored for shipment to the Central Laboratory. Guidance and instructions for Investigators will be available in the lab manual.

Stool samples will be subject to the following analyses:

- **Free toxin test** for confirmation of eligibility and in the event of suspected recurrence. Sites may use an established local free toxin test 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). Free toxin tests will be provided for the site/site laboratory use if a suitable test is not available locally. A negative free toxin test may only be repeated once on the same sample or a fresh sample.
    - Since *C. difficile* free toxin EIA (enzyme immunoassay) kits can have sub-optimal sensitivity, a CCNA will be conducted via a central laboratory for those suspected recurrence events that had a negative free toxin test result obtained locally by the site.
- **Microbiology, microbiome, and bile acid analysis** at specialized centralized laboratories. The Investigator or designee will follow instructions in the lab manual and aliquot the samples as required.

- **A free toxin test is conducted as soon as possible following suspicion of recurrence.** This is critical to meet the primary objective of the study.
- **Stool samples for free toxin testing should be as fresh as possible (preferably produced less than 24 hours prior to the time of the test).**
- Sites should request patients keep samples refrigerated from the point of production and sites should maintain refrigeration to the point of testing.
- A stool sample produced by the patient should be processed and frozen by the site **within 24 hours** for microbiology, microbiome, and bile acids. If the sample used for CDI testing was produced by the patient >24 hours, a fresh sample should be provided where possible. Suspected cases of CDI with a negative free toxin test will be tested at a Central Laboratory via a CCNA.

The samples from all patients will undergo the following assessments:

- *C. difficile* isolates recovered from samples (at baseline, end of treatment, and recurrence) will undergo ribotyping and susceptibility testing using a panel of antimicrobials that may include, but is not be limited to, ridinilazole, fidaxomicin, vancomycin, metronidazole, rifaximin, and tigecycline.
- The presence or absence of vancomycin resistant Enterococci (VRE) may also be assessed.

In addition, the relative impact of ridinilazole and vancomycin on the gut microbiome and bile acid composition will also be assessed. Fecal samples will be collected from all patients at the time points specified in the SoA (Section 1.3). Selection of samples to be analysed will be based on pre-specified criteria. Specific assessments may include:

- Shotgun metagenomic sequencing will be used to investigate the gut microbiome (microbiota and gene composition) beyond the cultivable species and thus determine deeper effects on the bowel microbiome during therapy.

- Using Liquid Chromatography-mass spectrometry (LC-MS/MS), fecal samples will be analyzed for bile acids.

Stool samples will be stored for up to 5 years for potential future microbiology, microbiome and/or metabolome analysis.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Medical History (Including CDI History)

The following will be recorded prior to randomization:

- All relevant and significant medical history for 12 months prior to randomization
- All medications taken up to 4 weeks prior to randomization
- All known CDIs along with the treatment administered
- Use of any potential confounding medication up to 4 weeks prior to randomization
- Information on the current/baseline CDI including confirmation of positive *C. difficile* free toxin, the number of UBMs in the 24 hours prior to randomization and current signs and symptoms of CDI.

Relevant medical history includes events that may contribute to the outcome of a treatment for CDI such as: major gastrointestinal surgery, nonsurgical gastrointestinal procedures, significant infections, conditions requiring immunosuppression, gastrointestinal disorders/diseases, or cancer.

Significant medical history includes pathology (events, diseases, disorders, or conditions) that may be useful in assessing a safety event occurring during the study such as: major non-gastrointestinal surgery and major pathology of the cardiovascular, respiratory, endocrine, immunological (including HIV status) and neurological systems.

8.2.2. Physical Examinations

The ECG and physical exam may be conducted at the screening or baseline visit; if conducted at screening, the vital sign assessment will still need to be repeated at baseline.

A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height (baseline only) and weight will also be measured and recorded.

At the discretion of the Investigator, focused physical examinations may be completed on Day 12, Day 40, and recurrence visits. The examination should include the measurement of vital signs (temperature, blood pressure, pulse) and an abdominal examination.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3. Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure and pulse.

The same arm should be used to measure blood pressure throughout the study for each patient.

8.2.4. Electrocardiograms

A single 12-lead ECG will be obtained prior to randomization using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Manual measurements and calculations may be conducted in the absence of automated reporting of such intervals.

The screening ECG will be reviewed and signed by the Investigator or a medically qualified designee. Any abnormalities will be marked as clinically significant or not clinically significant. Clinically significant abnormalities will be documented as current medical history and reported as an SAE if the definition of serious is met. Importantly, an ECG does not need to be completed if patient's most recent ECG was normal and was completed in the 12 months prior.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests (with the exception of pregnancy tests) with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

Refer to Section 10.3 for definitions and for details on how to assess, classify, and report AEs/SAEs.

Adverse Events (AEs) will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative/guardian).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment. (See Section 7)

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All Serious Adverse Events (SAEs) will be collected from the signing of the informed consent form (ICF) until the D100 End of Study visit.

All AEs will be collected from the time and date of first dose of study treatment until the D40 follow up visit.

Changes in medical conditions that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History page of the CRF and not the AE CRF page.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness of the event, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must notify the Sponsor within 24 hours of awareness.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient should be used to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) per local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate per local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female patients and, female partners of male patients will be collected after the start of study treatment and until 30 days after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Events NOT Meeting the AE/SAE Definition:

- Disease Related Events (refer to Section 8.3.7)
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

8.3.7. Disease-Related Events Not Qualifying as AEs or SAEs:

Disease-related events (DREs) are associated with the disease under study and will not be reported according to the standard process for reporting of SAEs even though the event may meet the definition of an SAE.

The following DREs are common in patients with CDI:

- CDI recurrence
    - CDI recurrences will be recorded for the patient on the "Suspected Recurrence of CDI" CRF page.

      Note: If on evaluation, no recurrence is deemed to have occurred, any symptoms (or preferably diagnosis) reported by the patient must be reported as AEs (up to Day 40) and as SAEs (anytime during the study if the criteria for an SAE are met).
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with CDI.
- Treatment failure/lack of efficacy is not an adverse event but will be captured as an efficacy endpoint.
- Signs or symptoms of CDI, including expected progression or worsening of CDI

However, if any of the following complications related to CDI occurs, then the event must be recorded and reported as such as an SAE (instead of a progression or worsening of CDI):

- Toxic megacolon

- Fulminant colitis
- Colonic perforation

A medical monitor will monitor suspected recurrence events on a regular basis.

8.4. Treatment of Overdose

The date and time of each dose will be recorded by patients in the eDiary. There is no specific treatment for overdose; general medical support measures are to be in place, if required. Any SAE or SAE associated with excessive dosing (overdose) must be followed as any other SAE or AE. Overdose is only considered AEs or SAEs if there are associated clinical signs and symptoms (see Section 10.3).

8.5. Pharmacokinetics

- PK samples will be collected on Day 1 or 2, and at EOT. As the study is blinded, samples will be collected from approximately 100 patients to ensure approximately 40 patients have received ridinilazole. It is understood that patients randomized to the ridinilazole arm will receive active ridinilazole in Dose 1, placebo in Dose 2, active ridinilazole in Dose 3, placebo in Dose 4, etc. Therefore, to ensure that PK is taken following an active dose of ridinilazole, the blood draws for all patients will occur as follows:
  - Day 1 or 2 - at 2 and 4 hours (±30 minutes) post either Dose 1, 3, 5 or 7, and
  - EOT - at 2 and 4 hours (±30 minutes) post either Dose 33, 35, 37 or 39.

  PK sampling must be conducted following in-clinic administration of study medication. Accurate times of dosing and sampling should be recorded.
- It is expected that some of the PK patients will meet the IDSA definition for severe disease (white blood cell count ≥15,000 cells/mm^3 or serum creatinine >1.5mg/dL). The PK samples will be used to assess the impact of severe disease on the plasma exposure of ridinilazole.
- The bioanalytical laboratory will be unblinded for these 100 PK patients and samples from ridinilazole assigned patients will be analyzed. Appropriate measures will be taken to ensure that the laboratory does not disclose unblinded information to the study sites or Sponsor/CRO/Vendor. Sites will not receive any PK results until after database lock.
- Residual plasma samples may be retained for up to 5 years from the end of the study for exploratory analysis of circulating metabolites and/or assessing vancomycin concentrations. If performed, this work will be reported separately.
- Patients selected will be those who consent to take part from sites that are qualified to conduct the PK sampling.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Quality of Life

8.9.1. Medical Resource Utilization

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the Investigator and study-site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. Data collected will include (but will not be limited to):

- Length of hospital stay
- Hospital admission and readmission rates and reasons for admission
- Patient location at admission and discharge location

8.9.2. EQ-5D-5L

The EQ-5D-5L [34] is a five-item questionnaire, which has been developed as a standardized measure of health status, which can provide a simple, generic measure of health for clinical and economic appraisal. It is cognitively undemanding, taking only a few minutes to complete. Patients will be asked to complete the EQ-5D-5L at certain intervals throughout the study. Instructions to respondents are included in the questionnaire. The EQ-5D-5L essentially consists of 2 pages – the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

If, at any visit, the patient is unable to complete the EQ-5D-5L independently then it should not be completed for that visit.

Refer to Section 10.7.

8.9.3. Cdiff32 Patient Reported Outcome

The Cdiff32 [35] will be administered at US sites. It consists of 32 questions covering 3 major domains (physical, mental, and social) with 4 associated subdomains with each question scored on a five-point scale.

If, at any visit, the patient is unable to complete the Cdiff32 independently then it should not be completed for that visit.

Refer to Section 10.8.

9. STATISTICAL CONSIDERATIONS

9.1. 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 response rates for ridinilazole and vancomycin respectively.

9.2. Sample Size Determination

Approximately 680 patients (340 patients per treatment arm) 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 more than 95% power of concluding superiority of ridinilazole over vancomycin using a 2-sided test at the 5% significance level. This assumes a 1:1 randomization of 680 patients (340 per group), an improvement of 15% with ridinilazole over vancomycin and a SCR rate of 57% with vancomycin [36].

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

To preserve the Type 1 error a fixed sequence testing procedure will be adopted for the mITT population. The order of testing for secondary endpoints will be detailed in the statistical analysis plan.

A blinded review of the efficacy endpoints will be conducted after approximately 70% of patients have completed their AOC assessment. The review will determine if increase sample size is needed to maintain adequate power for the primary endpoint. The maximum sample size increase will be 25% of the initial sample size. Any increase above 25% of the initial sample size will require a protocol amendment.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All patients who sign the ICF
Randomized	All patients randomly assigned to study treatment.

Population	Description
Modified ITT [mITT] (Efficacy)	All randomized patients who take at least 1 dose of study treatment and have a diagnosis of CDI confirmed by the presence of free toxin in stool using a free toxin test and have ≥3 UBMs in the 24 hours prior to randomization.
PK Population	All ridinilazole randomized patients with at least one ridinilazole concentration (including below the lower limit of quantification).
Safety	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment. Patients will be analyzed according to the treatment they received.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Any deviations from the planned analyses post database lock will be described and justified in the final clinical study report.

9.4.1 Efficacy Analyses

Efficacy analyses will be conducted on the combined database from the SMT19969/C004 and SMT19969/C005 studies for the mITT population.

Endpoint	Statistical Analysis Methods
Primary	The primary analysis of SCR over 30 days post EOT will be analyzed using the Cochran Mantel Haenszel (CMH) test which will be stratified by age (<65 years of age and ≥65 years of age), number of UBMs (<10 or ≥10) in the 24 hours prior to randomization, immunocompromised (YES/NO), and history of recurrent CDI (either none or 1-3 previous occurrences in the past 12 months). The treatment difference and 95% confidence interval, based on the stratified Miettinen and Nurminen method, will also be presented.
Secondary	The secondary endpoints, Clinical Response and Clinical Cure, will be analyzed. The difference between treatment proportions will be presented together with the 95% confidence interval, based on the stratified Miettinen and Nurminen method. Non-inferiority will be established if the lower limit of the 2-sided 95% confidence interval for the difference between treatment proportions (ridinilazole – vancomycin) is greater than -10%. The same methods of analysis as described for the primary endpoint will also be used to assess SCR over 60 days post EOT and SCR over 90 days post EOT. Additional endpoints and corresponding analysis details will be described in the statistical analysis plan.
Exploratory	Will be described in the statistical analysis plan.

9.4.2 Safety Analyses

All safety analyses will be performed on the combined database from the SMT19969/C004 and SMT19969/C005 studies for the Safety Population.

The number and percentage of patients experiencing treatment-emergent all causality AEs/SAEs will be summarized by treatment group. Summaries will also be produced for each body system as well as each preferred term. Those events regarded as at least possibly treatment related by the Investigator will be summarized separately. The number and percentage of patients experiencing SAEs will also be summarized by treatment group.

Changes from baseline in laboratory parameters and vital signs will be summarized for each visit and by treatment group.

9.4.3 Pharmacokinetic Analyses

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

9.5. Interim Analyses

An interim analysis may be conducted. Details would be provided in the statistical analysis plan prior to the analysis.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki.
  - Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Ensuring patient safety and medical care is paramount
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

- Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.
- Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient. If a patient is unable to read, an impartial witness will be used to confirm to the patient that the consent was accurately read to them. If a patient is unable to understand and sign the Informed Consent form, the patient's legally authorized representative (LAR) may provide consent on the patient's behalf if allowed by the Institutional Review Board or Ethics

Committee. Patients must be informed that their participation is voluntary and that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

- Patients or their legally authorized representative and impartial witness (if applicable) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- If the screening visit must be done remotely remote consenting per site's local procedure can be performed, including eSignature or eConsenting if available at the site. Consent form(s) must be received and acknowledged by the site prior to the commencement of any study procedures. Original, signed consent form(s) must be returned to the site either at the next in-clinic visit, posted to the site, or returned via courier or any other approved alternate method. The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the ICF(s)/must be provided to the patient.
- Patients who are rescreened are required to sign a new ICF
- The sponsor considers that consent is not required for either a toxin test conducted per standard of care, or to complete a free toxin test on a stool sample collected per standard of care for any other diagnostic purpose. This is subject to local regulations; if the above approach is not approved, then written or telephone/verbal consent, using the initial free toxin test consent form, may be obtained to conduct the free toxin test. If using telephone/verbal consent, sites must have, or put in place, a documented procedure to conduct telephone/verbal consent including detailed description of the consent and follow-up with written informed consent prior to baseline assessments if the patient FTT test is positive and interested in participating in the study.
- There will be a separate signature line within the main ICF for retention of samples, to be stored for up to 5 years after study completion for exploratory research.
- There will be a separate ICF that addresses the following optional assessment:
    - Use of blood sample for PK analyses. The Investigator or authorized designee will explain to each patient the objectives of the PK research.

10.1.4. Data Protection

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

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. Data protection laws governing the trial include EU GDPR and any local regulation as applicable. The level of disclosure must also be explained to the patient.

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

10.1.5. Dissemination of Clinical Study Data

The study will be registered in EU Clinical Trials Register, will be posted on ClinicalTrials.gov in the United States and posted on other equivalent global registries as required. The results from this trial will be uploaded to the various registries when appropriate to do so and in line with the requirements of the individual registries.

Summit will provide the Clinical Study Report to regulatory authorities as required. The Investigator will be provided with the full summary of the study results.

10.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data, eDiary data).
- The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).
- Although no changes will be permitted to patient reported data, the Investigator must review the eDiary data with patients to verify completeness, accuracy and contemporaneous data entry. Follow-up with patients is required if missing or inaccurate data is entered to ensure re-training and prevent repeated non-compliance.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Sponsor and the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- eDiary data, and/or patient contact reports of dosing and bowel movement information, are considered source data.
- Definition of what constitutes source data can be found in the Investigator Trial Site File.

10.1.8. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

10.1.9. Publication Policy

Summit fulfils its commitment to publicly disclose complete clinical trial results, regardless of outcome, through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.summitplc.com and other public registries in accordance with applicable local laws/regulations. Additionally, the results from this study may be presented in a peer-reviewed journal or at scientific meetings after finalization of the clinical study report. As this is a multi-centre trial, the primary manuscript will contain the complete results across all sites; authorship will be determined by mutual agreement. All publications relating to this study will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

After publication of the primary manuscript, principal Investigators may publish results based on the information collected and data generated at their site, regardless of study outcome. This secondary manuscript must reference the primary manuscript. The principal Investigator will submit their draft publication to Summit for review at least 30 days prior to submission to a journal for review of potentially confidential material and/or intellectual property.

Summit is committed to sharing key data, relevant to their ongoing care, with patients who participate in their clinical trials. After publication of the primary manuscript, patients may request their individual data from their Investigator.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by a Central Laboratory except for the pregnancy test.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 3: Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
Red blood cell (RBC) Count
Hemoglobin
Hematocrit</td><td colspan="2"><u>RBC Indices</u>:
MCV
MCH
%Reticulocytes</td><td><u>White blood cell (WBC) count with Differential</u>:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry[1]</td><td>Blood urea nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose [non-fasting]</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>Other Tests</td><td colspan="4">• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
• The PK, microbiology, microbiome & bile acid analyses and CCNA testing will be performed by specialized centralized laboratories.</td></tr>
<tr><td colspan="5">NOTES:
[1] All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law). These liver chemistries or the diagnosis explaining them must be reported as an SAE.
[2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. If serum testing is required, it may be conducted via the local or central laboratory whichever is most convenient.</td></tr>
</table>

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

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

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

Events <u>Meeting</u> the AE Definition

- Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of an overdose or suspected overdose of either study treatment or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE/SAE Definition
• Refer to Section 8.3.6 and 8.3.7 for events not meeting the AE/SAE definition.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the SAE coordinator in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the SAE coordinator or Medical Monitor. In this case, all patient identifiers, except for the patient number, will be redacted on the copies of the medical records before submission to the SAE coordinator. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment (ridinilazole/vancomycin) and each occurrence of each AE/SAE as "related" or "not related" by answering the question:

  ''Do you consider that there is a reasonable possibility that the adverse event has been caused by the study treatment? ''

  The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will consult both the Investigator's Brochure (IB) for ridinilazole and the Product Information for vancomycin, in his/her assessment.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Pharmacovigilance (the SAE coordinator). However, **it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to the SAE coordinator.** If there are limited or insufficient information about the event to make an informed judgment, and in the absence of any indication or evidence to establish a causal relationship, a causality assessment of "not related" is to be considered. In such instances, the Investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information.
- The causality assessment is important to be provided because it is one of the criteria used when determining regulatory/authority reporting requirements
- The investigator is requested to provide an explanation for the causality assessment for each SAE and must document this in the medical notes, on the SAE form and in the CRF.
- Following a review of the relevant data, the causal relationship between the study treatment (vancomycin/ridinilazole) and each (S)AE will be assessed by answering 'yes' or 'no' to the question:

  ''Do you consider that there is a reasonable possibility that the adverse event has been caused by the study treatment? ''

- When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study treatment (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:
  - Plausible temporal relationship between exposure to the study treatment and (S)AE onset and/or resolution. Has the subject actually received the study treatment? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study treatment?
  - Plausibility; i.e., could the event have been caused by the study treatment? among others biologic and/or pharmacologic mechanism, half-life, and preclinical and

clinical study data (information can be found in, the IB) or can the event be explained by the underlying disease(s) or concomitant drugs?
- De-challenge/Dose reduction/Re-challenge:
  Did the (S)AE resolve or improve after stopping the dose of the study treatment? Also consider the impact of treatment for the event when evaluating a de-challenge experience.
  Did the (S)AE re-occur when the suspected study treatment was reintroduced after having been stopped?
- Laboratory or other test results; a specific laboratory investigation supports the assessment of the relationship between the (S)AE and the study treatment (e.g., based on values pre- during and post-treatment).
- Available alternative explanations independent of study treatment exposure (such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc.) and strength of the alternative explanation.

- The Investigator may change his/her opinion of causality considering follow-up information and send a SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the SAE coordinator to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the SAE coordinator with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the SAE coordinator within 24 hours of receipt of the information.

SAE Reporting to Pharmacovigilance via email

- SAEs will be transmitted to IQVIA using the Serious Adverse Event Form, which must be completed and signed by a member of the study team and transmitted to IQVIA pharmacovigilance with 24 hours of awareness of the event.

All initial and follow up SAE reports should be sent to IQVIA Drug safety Centre
Email: QLS_SMT19969@quintilesims.com

- Country specific toll-free fax numbers for SAE reporting will also be provided in the Investigator site file.
- Initial notification by email does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Trial Site File.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal

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

   Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male patients

Male patients must use a barrier contraceptive method during sexual intercourse with a woman of childbearing age or abstain from sexual intercourse during the study if it is their preferred and usual lifestyle.

In addition, male patients must refrain from donating sperm for 30 days after the last dose of study treatment.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for 30 days after the last dose of study treatment.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method if the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the treatment period and continuing for 30 days after the end of study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test (a urine test will be provided by the Central Laboratory).
- Pregnancy testing will be performed at Day 12, Day 40 and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected up to 30 days after the last dose of study treatment.

Collection of Pregnancy Information:

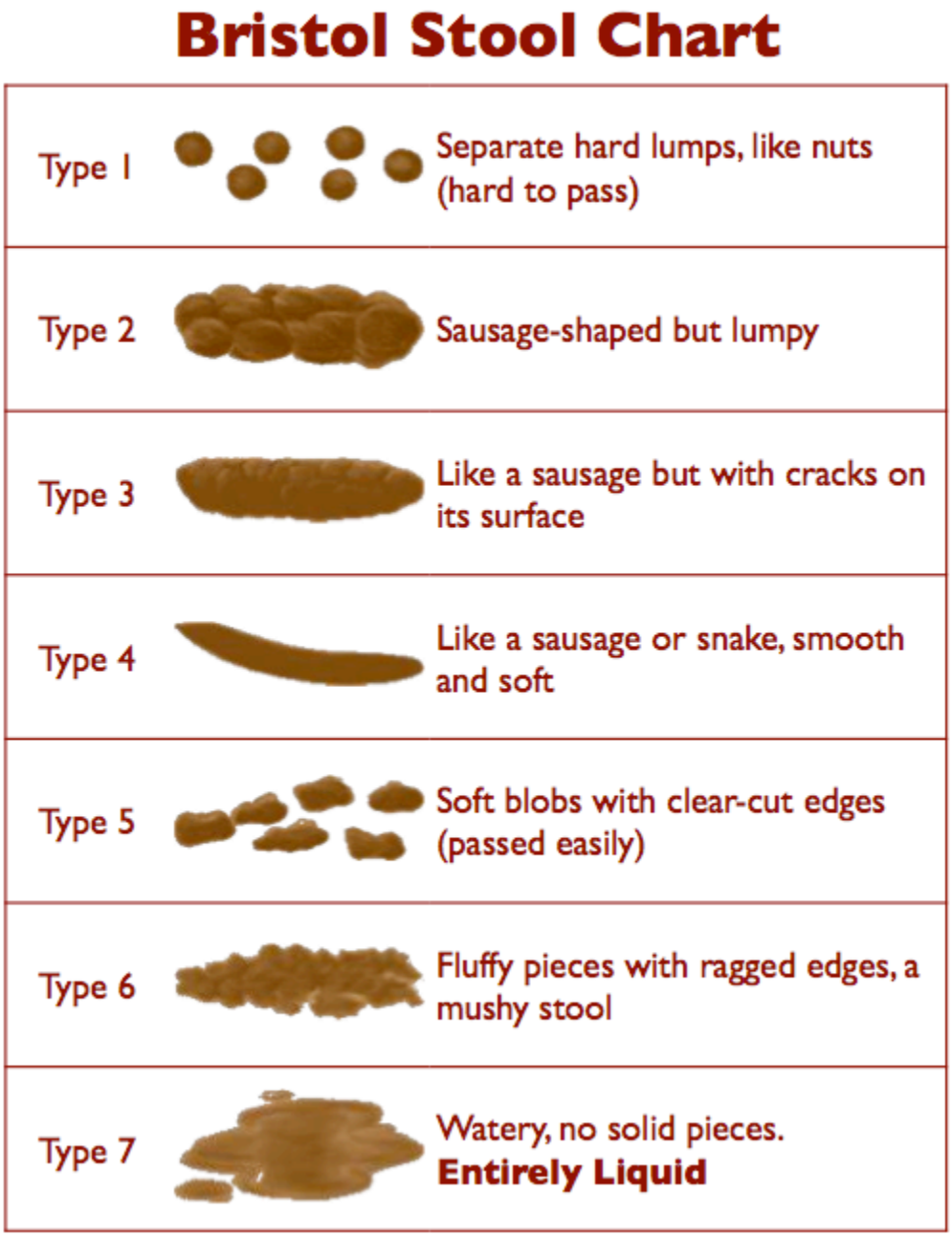
Male patients with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study up to 30 days following the last dose of study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant up to 30 days after the last dose of study treatment. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.1. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Bristol Stool Chart



10.6. Appendix 6: Sponsor Agreed Free Toxin Tests

The following are Sponsor agreed Free Toxin Tests that can be utilized during the study for assessment of eligibility and suspected recurrence. Further tests may be agreed during the course of the study without a protocol amendment. Any such test will have FDA, EU or other appropriate regulatory approval.

FDA and EU Approved:

- bioMerieux Test System (Vidas and miniVidas) C. difficile Toxin A & B (CDAB) Assay
- Meridian Bioscience ImmunoCard Toxin A&B
- Meridian Bioscience Premier Toxins A & B (visual or spectrophotometric)
- Remel ProSpecT Clostridium difficile Toxin A/B Microplate Assay (visual or spectrophotometric)
- Remel Xpect Clostridium difficile Toxin A/B Test
- TechLab C. DIFF QUIK CHEK COMPLETE
- Techlab C. difficile Tox A/B II (visual or spectrophotometric)
- Techlab TOX A/B QUIK CHEK

EU Approved only:

- Acro Biotech Inc. Clostridium difficile Toxin A + Toxin B Combo Rapid Test Cassette
- AllTest JusChek Clostridium difficile GDH+ Toxin A + Toxin B Combo
- Beta Diagnostici Clostridium difficile toxin A+B+GDH
- Acro Biotech Inc. Clostridium difficile Toxin A + Toxin B Combo Rapid Test Cassette
- CerTest BIOTEC Clostridium difficile Toxin A + B
- CerTest BIOTEC Clostridium difficile GDH + Toxin A + B
- DiaSorin LIAISON C. difficile Toxins A&B
- Mascia Brunelli S.p.a., CLOSTRIDIUM DIFFICILE TOXIN A+B CARD PLUS
- MonlabTest C. difficile toxins A+B
- Operon Simple GDH-Toxins
- RIDA QUICK Clostridium difficile Toxin A/B
- RIDASCREEN Clostridium difficile Toxin A/B
- Savyon Diagnostics CoproStrip C. difficile GDH + Toxin A + Toxin B
- Stamar Clostridium difficile Toxin A and B
- Trinity Biotech Uni-Gold C. difficile Toxin A/B
- Veda Lab Toxin A+B (Clostridium difficile) DUO
- VITASSAY Clostridium difficile GDH+Toxin A+B
- Vitrotrack Clostridium difficile GDH+Toxin A+Toxin B cassette combo

GDH, Nucleic Acid Amplification Test (NAAT) or PCR may be done per site's standard of care prior to study start as part of pre-screening reviews but are not acceptable to meet eligibility requirements for the study.

10.7. EQ-5D-5L

Effective_USA (English) EQ-5D-5L Digital Self complete PDA v1.1 (ID 36597)

EQ-5D-5L	
EQ-5D-5L PDA version	
English (USA) **Health Questionnaire** **English version for the USA**	Country (Language) Health Questionnaire Version (Target Language) Version (English)
On the following screens please tap the statement that best describes your health TODAY.	Instruction
Your mobility TODAY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
Your self-care TODAY	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
Your usual activities TODAY *(e.g. work, study, housework, family or leisure activities)*	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
Your pain / discomfort TODAY	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
Your anxiety / depression TODAY	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
On the next screen you will see a scale numbered 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health

***Disclaimer:** This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

10.8. Cdiff32

Ri-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE FOR *CLOSTRIDIUM DIFFICILE* INFECTION (*C. diff* infection)

How to fill the questionnaire

The following questions are about your state of health over the last 7 days. Each question has five different responses. For each statement, please circle or check the corresponding box for the response that best describes your feelings. Please respond to all questions even if you think some are similar. Please do not leave any question unanswered. If you make a mistake, cross out the wrong answer and circle or check the corresponding box for the one that best applies to you. Thank you for your participation.

Questionnaire Creator: K.W. Garey
12/06/2015

1

Ri-CoDiFy CDI-HRQOL study/ patient questionnaire Site Investigator:

DAILY ACTIVITIES

Over the last 7 days, because of your *C. diff* infection,

1. Have you had any difficulties and/or disruption carrying out your daily activities?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

2. Have you had any difficulties carrying out your leisure activities like gardening, walking, etc?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

3. Has it taken you longer to perform certain tasks at work (including work in the home)?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

4. Has your *C. diff* infection prevented you from leaving your house?

☐1 Never ☐2 Rarely ☐3 Sometimes ☐4 Often ☐5 Always

ANXIETY

5. Are you afraid that your *C. diff* infection could come back again?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

6. Are you afraid that your *C. diff* infection could get worse in the future?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

7. Are you afraid that the next time you'll need antibiotics, your *C. diff* infection will appear again?

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

Questionnaire Creator: K.W. Garey
12/06/2015

2

Ri-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

Over the last 7 days,

8. Have you been worried about not knowing when the next diarrhea would arise?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

DIET

9. Are you afraid that certain food will worsen your *C. diff* infection?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

Over the last 7 days, because of your *C. diff* infection,

10. Have you felt frustrated about what you can eat and when?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

Questionnaire Creator: K.W. Garey
12/06/2015

3

RI-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

SLEEP

Over the last 7 days,

11. Because of your *C. diff* infection, have you had trouble sleeping?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

12. Because of your *C. diff* infection have you been woken up from sleep?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

Questionnaire Creator: K.W. Garey
12/06/2015

4

Ri-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

DISCOMFORT

Over the last 7 days,

13. Have you been bothered by abdominal pain?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

14. Have you been bothered by flatulence (wind)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

15. Have you been bothered by a bloated stomach?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

16. Have you avoided wearing some clothes (tight clothes, dress, light-colored clothes ...)?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

17. Have you been bothered by the smell caused by your *C. diff* infection related diarrhea?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

18. Have you been bothered by how much time you spend on the toilet?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

Questionnaire Creator: K.W. Garey
12/06/2015

5

Ri-CoDiFy CDI-HRQOL study/ patient questionnaire Site Investigator:

COPING WITH DISEASE/ HEALTH PERCEPTION

Note! The following sentences are statements. Please indicate whether you agree or disagree with these statements.

19. Despite my C diff infection I can live a normal life.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

Questionnaire Creator: K.W. Garey
12/06/2015

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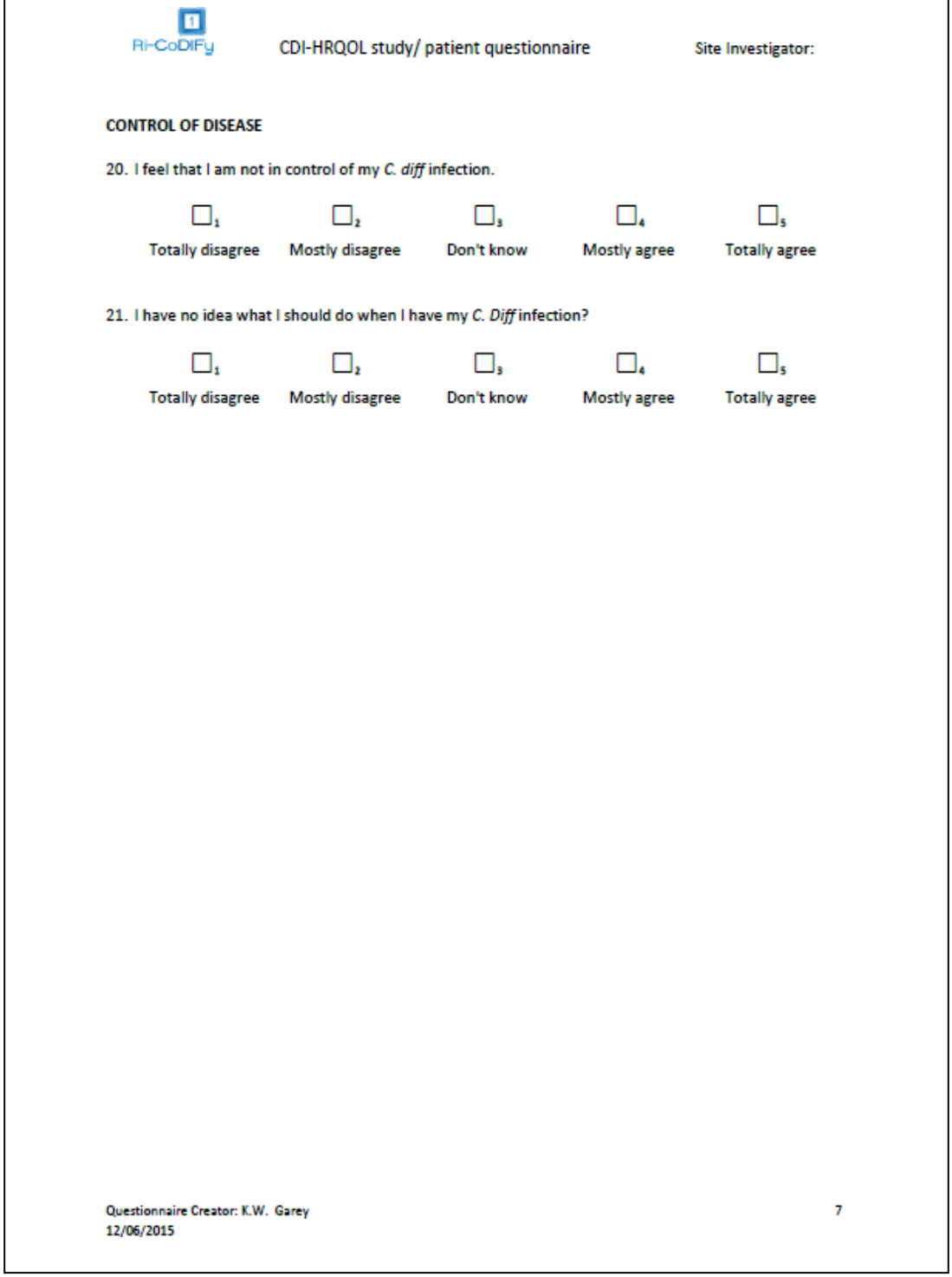

Ri-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

CONTROL OF DISEASE

20. I feel that I am not in control of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

21. I have no idea what I should do when I have my *C. Diff* infection?

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

Questionnaire Creator: K.W. Garey 7
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Ri-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

IMPACT OF STRESS

22. I believe that any stress can worsen my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

Questionnaire Creator: K.W. Garey 8
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Ri-CoDiFy CDI-HRQOL study/ patient questionnaire Site Investigator:

DYSPHORIA

23. I feel irritable because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

24. I feel isolated from others because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

25. I feel depressed because of my *C. diff* infection

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

26. I feel my life is less enjoyable because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

27. I worry about transmitting my *C. diff* infection to my family and/or friends.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

28. I feel much stressed because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

Questionnaire Creator: K.W. Garey 9
12/06/2015

RI-CoDIFy CDI-HRQOL study/ patient questionnaire Site Investigator:

RELATIONSHIPS

29. Because of my *C. diff* infection, I have difficulty being around people I do not know.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

30. My *C. diff* infection is affecting my closest relationships.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

Questionnaire Creator: K.W. Garey 10
12/06/2015

CDI-HRQOL study/ patient questionnaire Site Investigator:

SOCIAL REACTION

31. I feel like I irritate others because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

32. How would you rate your overall quality of life during the past week (that is, how have things been going for you)?

☐1	☐2	☐3	☐4	☐5
Very bad: could hardly be worse	Pretty bad	Good and bad part about equals	Pretty good	Very well: could hardly be better

Questionnaire Creator: K.W. Garey 11
12/06/2015

10.9. Appendix 7: Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AOC	Assessment of cure
AST	Aspartate Amino Transferase
bid	*Bis in die* (twice daily)
BLQ	Below the level of quantification
BUN	Blood Urea Nitrogen
CCNA	Cell Cytotoxicity Neutralization Assay
CDI	*Clostridioides* (formerly *Clostridium*) *difficile* infection
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed plasma concentration
CMH	Cochran Mantel Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case report form
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DRE	Disease related event
EC	Ethics Committee
ECG	Electrocardiogram
eDiary	Electronic diary
EIA	Enzyme Immunoassay
EOS	End of study
EOT	End of treatment
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FTT	Free Toxin Test
GC-MS	Gas Chromatography Mass Spectrometry
GCP	Good clinical practice
GDH	Glutamate dehydrogenase
GI	Gastrointestinal
hCG	Human Chorionic gonadotropin
HEOR	Health Economic Outcomes Research
HHC	Home Healthcare
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy

i.v.	Intravenous
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
INR	International Normalized Ration (for blood clotting time)
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive Response Technology
ITT	Intention-to-treat
IRT	Interactive Response Technology
IUD	Intrauterine contraceptive device
IUS	Intrauterine system
IVIG	Intravenous immunoglobulin
LAR	Legally Authorized Representative
LLOQ	Lower limit of quantification
MIC	Minimum inhibitory concentration
MITT	Modified intention-to-treat
NOAEL	No observable adverse effect level
NAAT	Nucleic Acid Amplification Test
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PHI	Protected Health Information
PK	Pharmacokinetics
PP	Per protocol
PRO	Patient Reported Outcome
qid	*Quarter in die* (four times daily)
QTc(F)	QT interval corrected according to Fridericia's formula
RBC	Red Blood cell
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SAE	Serious adverse event
SCR	Sustained clinical response
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SOA	Schedule of Activities
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TMF	Trial master file

TOC	Test of Cure
UBM	Unformed bowel movements
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VC	Video Conference
VRE	vancomycin resistant Enterococci
WBC	White Blood Cell
WOCBP	Woman of childbearing potential

10.10. References

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