Protocol Title: A Randomized, Double Blind, Active Controlled Study to Evaluate the Safety and Tolerability of Ridinilazole Compared with Vancomycin and to Assess the Pharmacokinetics of Ridinilazole in Adolescent Subjects (Aged 12 to <18 years) with *Clostridioides difficile* Infection

Protocol Number: SMT19969/C006

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Compound Number: SMT19969 (Ridinilazole)

Short Title: Safety, Tolerability and the Pharmacokinetics of Ridinilazole in Adolescent Subjects

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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

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)	03 Sep 2020
Amendment 1; Protocol Version 2.0 Added the option to complete the 12-lead ECG assessment at screening or baseline	17 Sep 2020
Amendment 2; Protocol Version 3.0 Minor typographical and formatting changes Changed sponsor name to Summit Therapeutics, Inc. Deletion of primary endpoint, secondary endpoint, and assessment of clinical response referenced below schema Format changes to stool sample, physical exam, and ECG rows to further emphasize assessments can be performed once between 2 visits, as per corresponding footnote Clarification on requirements for stool collections and that GI pathogen test is part of the standard diagnostic workup for patients who present with diarrhea Consistency of Clinical Cure definition provided across sections Clarification of instructions on IP return by patient to site Addition of sponsor name on IP label to include both Summit Therapeutics, Inc., and Summit (Oxford) Limited Change on instructions for patients in the event of a missed dose, to allow intake of missed dose prior to or concurrently with the next scheduled dose but no more than 2 doses should be taken at any one time. Correction to text on the sponsor's use of previously collected patient data upon withdrawal of consent/assent Clarification on what data will be monitored by a DSMB Removal of compliance with GDPR Removal of registration in EU Clinical Trials Register	03 Dec 2020
Amendment 3; Protocol Version 4.0 Minor typographical and formatting changes Inclusion criteria were updated to provide clearer instruction on stool sample eligibility Exclusion criteria were updated to provided clearer instruction and examples for confounding conditions and exclusions for bone marrow or hematopoietic stem cell transplantation were removed Edited concomitant medication rules to avoid the potential that needed medication might be withheld due to interpretation of disallowed concomitant medicines	12 Nov 2021

DOCUMENT HISTORY	
Document	**Date**
Secondary endpoints of Clinical Response and Sustained Clinical Response, by Clinical Response, at 30-days post-End-of-Treatment was added to allow for extrapolation of results with the efficacy endpoint in the adult study Daily contact at EOT (including window) have been added to the study activities to capture data for the efficacy endpoint	

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Randomized, Double Blind, Active-Controlled Study to Evaluate the Safety and Tolerability of Ridinilazole Compared with Vancomycin and Assess the Pharmacokinetics of Ridinilazole in Adolescent Subjects (Aged 12 to <18 years) with *Clostridioides difficile* Infection

Short Title

Safety, Tolerability and the Pharmacokinetics of Ridinilazole in Adolescent Subjects

Rationale

Clostridioides difficile (formerly known as *Clostridium difficile)* Infection (CDI) is an infection of the colon that often develops following prior antibiotic use. An increase in the incidence of CDI in the pediatric population has been reported (Schutze, 2013). Although current standard treatments are effective with initial cure there is a considerable risk of recurrence, leaving the need for improved treatment options (Martin, 2016).

Summit is developing ridinilazole as a novel antimicrobial for CDI with the goal of achieving comparable cure rates to standard of care but reducing rates of recurrent disease. A Phase 2 proof of concept study in adults, comparing ridinilazole with vancomycin (the current standard of care), demonstrated a lower recurrence rate for ridinilazole. The confirmation of this improvement is currently being investigated in two Phase 3 studies in adults. The rationale for the Phase 3 study described in this protocol is to evaluate the safety, tolerability and the pharmacokinetics of ridinilazole in subjects aged 12 to <18 years old with CDI.

Objectives and Endpoints

Primary Objectives
• To assess the safety and tolerability of ridinilazole (200 mg bid), compared with vancomycin (125 mg qid), in adolescent subjects aged 12 to <18 years with *Clostridioides difficile* infection (CDI). • To assess the pharmacokinetics, including plasma and fecal concentrations, of ridinilazole in adolescent subjects aged 12 to <18 years with CDI.
Secondary Objective
• To assess the efficacy of ridinilazole (200 mg bid), compared with vancomycin (125 mg qid), in adolescent subjects with CDI.

Exploratory Objective
• To explore the medical resource utilization of adolescent subjects with CDI being treated with ridinilazole
Primary Endpoints
• Incidence and severity of treatment-emergent adverse events • Plasma and fecal concentrations of ridinilazole
Secondary Endpoints
• Sustained clinical response (SCR) over 30 days post end of treatment (EOT) - defined as clinical cure at the assessment of cure (AOC) visit and no recurrence of CDI within 30 days post EOT • Clinical cure at the AOC visit • Sustained clinical response over 60 days post EOT – defined as clinical cure at the AOC visit and no recurrence of CDI within 60 days post EOT • Sustained clinical response over 90 days post EOT – defined as clinical cure at the AOC visit and no recurrence of CDI within 90 days post EOT • SCR based on clinical response - defined as clinical response with no recurrence assessed through 30 days post-EOT • Clinical response at the AOC visit
Exploratory Health Economics and Outcome Research (HEOR) Endpoint
• Medical resource utilization and health economics endpoints

Definitions

Clinical cure

The investigator assessment of clinical cure at the AOC visit is defined by the following:

The resolution of diarrhea (< 3 unformed stools in a 1-day period) while on treatment, that is maintained until the AOC (EOT +2 days) visit, and no further requirement for further CDI antimicrobial therapy is needed through EOT + 2 days.

Recurrence

Recurrence is defined as a new episode of diarrhea and other signs and symptoms of *C. difficile* with a positive *C. difficile* free toxin test that requires CDI treatment.

Clinical response

Clinical response is defined as:

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

Overall Design

This is a Phase 3, multicenter, randomized, double blind, active-controlled, parallel group study designed to investigate the safety and tolerability of ridinilazole 200 mg bid, compared with vancomycin 125 mg qid, both administered for 10 days to adolescent subjects aged 12 to <18 years with CDI. The study will also assess the pharmacokinetics of ridinilazole, including plasma and fecal concentrations, in this population. Efficacy will be assessed as a secondary objective.

Subjects must have the presence of toxin A and/or B of *C. difficile* in a stool sample as confirmed by a positive free toxin test using sponsor-approved assays. Suitable tests will have appropriate FDA approval.

The study is comprised of a screening visit, a 10-day treatment period and a follow-up period of up to 90 days, to monitor safety and CDI recurrence. Following screening assessments and confirmation of eligibility, subjects will be randomized to receive ridinilazole or vancomycin in a 3:1 fashion.

An in-clinic or home visit will occur on Day 5 and a telephone check or clinic visit will be conducted at the end of treatment (EOT, Day 10). On Day 12, at least 48h after EOT, the AOC takes place and subjects will either attend an in-clinic visit, have a combined home/video visit or a videoconference visit with self-assessed vital signs (see Section 1.2, Schedule of Activities [SoA]). If the subject's 10 days of dosing is completed on Day 11, the AOC visit will be conducted on Day 13. All subjects will remain in the study until at least Day 40, when they will have a study visit in the form of either an in-clinic visit, combined home/video visit or a videoconference visit with self-assessed vital signs (with help from guardian(s)). A daily UBM contact will occur at EOT -2, EOT -1, EOT, EOT +1, and EOT +2 to collect UBM data. Subsequently weekly telephone contact will be made with subjects until Day 40 and at Day 70 and Day 100.

Subjects not cured at AOC or experiencing recurrent CDI prior to or at Day 40, will receive standard-of-care in accordance with the Investigators' clinical judgment and local practices. They will be encouraged to remain in the study and be monitored until Day 40. If the subject has a suspected recurrence prior to Day 40, the subject is to have either an in-clinic visit, a combined home/video visit or a videoconference visit with self-assessed vital signs for confirmation.

Those subjects cured at AOC and without a CDI recurrence by Day 40 will continue to be followed until Day 100 or recurrence (whichever comes earlier). If the subject has suspected recurrence after Day 40, the subject is to have either an in-clinic visit, a combined home/video visit or a videoconference visit with self-assessed vital signs for confirmation; if recurrent CDI is confirmed this visit will also serve as the subject's end-of-study visit. If the subject remains free of recurrence, the end-of-study visit will be on Day 100.

During the treatment period, subjects will be assessed for safety, tolerability, pharmacokinetics, and efficacy by reporting of clinical signs and symptoms, including adverse events, clinical laboratory assessments (including pharmacokinetics, chemistry and hematology), physical examinations, and vital signs.

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

Number of Subjects

The sample size has not been chosen on the basis of a formal hypothesis test. However, at least 40 subjects (with a 3:1 allocation) are considered sufficient to investigate the safety of ridinilazole compared to vancomycin and approximately 30 subjects are sufficient to assess the pharmacokinetics of ridinilazole in this subject population.

Key Inclusion/Exclusion Criteria

Subjects aged 12 to <18 years are eligible to be included in the study if they meet the following criteria:

- Has signs and symptoms of CDI, including diarrhea, such that, in the investigator's opinion, CDI antimicrobial therapy is required, and the subject has tested positive for toxin A and/or B of *C. difficile* in the stool
    - Diarrhea is defined ≥3 UBMs based on types 5, 6, 7 on the Bristol stool chart and diarrhea information is within 24 hours prior to randomization

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

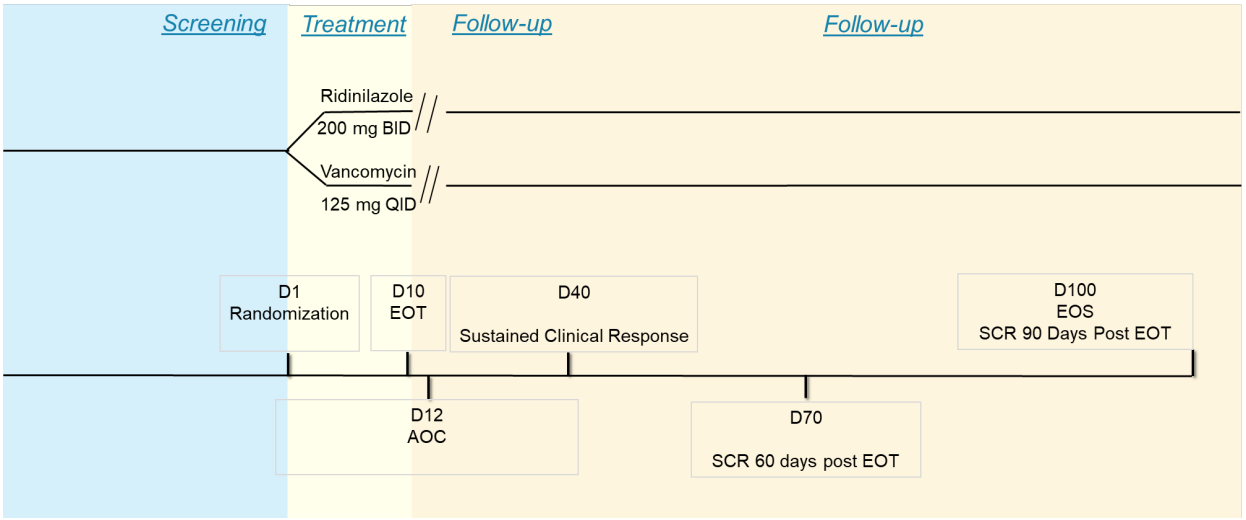
- Has received treatments for CDI confounding with the study treatment as follows:
    - Has had more than the equivalent of 48 hours of dosing of antimicrobial treatment active against the current episode of CDI prior to randomization or
    - Has received ridinilazole or an investigational vaccine against *C. difficile* any time in the past; anti-toxin antibodies including bezlotoxumab within the past 6 months; or any other investigational medicinal product for treatment of CDI or fecal microbiota replacement therapy within the past 3 months
- Has a clinically relevant positive stool test for pathogens other than *C. difficile*, within 48 hours of randomization
- Has life-threatening or fulminant CDI with evidence of hypotension, septic shock, peritoneal signs or absence of bowel sounds, toxic megacolon, or ileus

- Has had major GI surgery (e.g., significant bowel resection or pancreatectomy, but not including appendectomy or cholecystectomy) within the past 3 months or has the presence of a colostomy or ileostomy or has the likely requirement of an ostomy during the study
- Is receiving treatment that generally is associated with severe diarrhea, intractable vomiting, severe nausea, or inability to swallow that cannot be managed with antiemetics or antidiarrheals and that limits the ability to take oral medications. Cancer treatment that does not compromise ability to take study medication or cause severe diarrhea is allowed.

Data and Safety Monitoring Board

There is no plan to conduct a formal interim analysis. An independent DSMB will review unblinded safety data on a regular basis during the course of the study. Following each review, the DSMB will recommend action regarding the study (continue, continue with changes, temporarily stop or stop). The DSMB will comprise of 3 independent medical experts and an independent statistician. The specifics regarding the DSMB organization and procedures will be outlined in the DSMB Charter.

Schema



AOC = Assessment of Cure; EOT = End of Treatment; EOS = End of Study; SCR = Sustained Clinical Response Assessment

1.2. Schedule of Activities (SoA)

Phase	**Screening**	**Treatment Period**			**Follow-Up Period**				**Recurrence**
Day(D)	D-3 to D1[1,3]	D1[1,2]	D5[3]	D10[3]	D12[4] ≥48 h from last dose	D40[4] or early term pre-D40	D70[3,5]	D100[3,5] or early term post-D40	Day 12 to D100[4,5]
Assessment	Screening	Baseline	Check-in	End of Treatment	Assessment of Cure	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	≤48 h of identification
Visit format	Clinic/ Tel[1,3]	Clinic/ HHC with VC[1,2]	Clinic/ HHC with VC[3]	Clinic/Tel[3]	Clinic/ HHC/ VC[4]	Clinic/ HHC/ VC[4]	Clinic/Tel[3]	Clinic/Tel[3]	Clinic/ HHC/ VC[4]
Written informed consent/assent[6]	X								
Inclusion and exclusion criteria	X	X							
Demographics	X								
C. diff free toxin test[7]	X								X
Medical/CDI history + prior/current medications[8]	X	X							
Stool sample[9]	[X	X][9]	X	[X	X][9]	X			X
Weekly UBM Review[10]		←				→	X	X	
Daily UBM Contact				X[11]					
Height and Weight[12]	X				X	X			
Physical exam and vital signs[13]	[X	X][13]			X	X			X
12-lead ECG[14]	[X	X][14]							
Blood samples (hematology and clinical chemistry)		X			X	X			

Phase	**Screening**	**Treatment Period**			**Follow-Up Period**				**Recurrence**
Day(D)	D-3 to D1[1,3]	D1[1,2]	D5[3]	D10[3]	D12[4] ≥48 h from last dose	D40[4] or early term pre-D40	D70[3,5]	D100[3,5] or early term post-D40	Day 12 to D100[4,5]
Assessment	Screening	Baseline	Check-in	End of Treatment	Assessment of Cure	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	≤48 h of identification
Visit format	Clinic/ Tel[1,3]	Clinic/ HHC with VC[1,2]	Clinic/ HHC with VC[3]	Clinic/Tel[3]	Clinic/ HHC/ VC[4]	Clinic/ HHC/ VC[4]	Clinic/Tel[3]	Clinic/Tel[3]	Clinic/ HHC/ VC[4]
Urine pregnancy test (dipstick) for WOCBP[15]		X			X	X			
Randomization		X							
IMP Dosing *(four times daily for 10 days)*[16]		←	———	→					
Signs and symptoms of CDI		X		X	X				X
Investigator assessment of cure/sustained clinical response[17]					X	X	X	X	X
PK Stool Sample[18]		X	X						
PK Blood Sample (4 hours post dose)[19]		X	X						
Medical resource utilization questions		X			X	X	X	X	X
Concomitant medications	←	———	———	———	———	———	———	———	→
AE reporting[20]		←	———	———	———	———	→		X
SAE reporting	←	———	———	———	———	———	———	———	→

Note: Unscheduled telephone calls and/or visits may be conducted, if necessary, for the subject's safety.

Numbered notes:

1. Screening and D1/baseline assessments may occur on the same day or within a 1 to 3-day window. Subjects can be rescreened once for this study.
2. Preferably the Baseline visit should be completed as an in-clinic visit; however, to maximize potential enrolment (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 subject's home. The Investigator will join by video conference to perform their assessments. 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 that is <24h old), and medical resource utilization questions.
3. The Day 5 visit will preferably be an in-clinic visit; however, if this is not appropriate (e.g., during a pandemic) a sponsor-contracted home healthcare vendor or properly trained and delegated site staff can conduct assessments and collect samples at the subject's home. The visits for screening, D10, D70 and D100 may be conducted in-clinic or by telephone. If Day 10 conducted by telephone, stool sample drop off or collection of the sample from the subject's home must be arranged.
4. D12, D40 and recurrence visits are preferably in-clinic visits; however, these visits may be conducted remotely. If so, the following approaches may be taken:
    a. if the subject has been provided with vital sign equipment by the site, the visit may be conducted with only a video conference between the Investigator and the subject in the presence of a guardian.
    b. a sponsor-contracted home healthcare vendor or properly trained and delegated site staff may conduct the visit at the subject's home with a guardian present and with the Investigator joining by video conference
5. Subjects who are cured at AOC and have SCR at Day 40 will continue to be followed until Day 100 or recurrence (whichever comes earlier).
6. Documented informed consent/assent must be provided by the subject/guardian prior to any study procedure being conducted. Electronic consent (eConsent) should be used; however, subject may sign a paper consent form when the screening visit is performed in-clinic. If the visit is performed remotely and the subject cannot adhere to eConsenting, they may receive an email copy of the consent/assent form and carry out a synchronous consent discussion over the phone.
7. Free Toxin Test: sites may use an established local free toxin test laboratory service if it is a suitable test and is prospectively agreed with the Sponsor. Suitable tests will have appropriate regulatory approvals (FDA approval). Subjects with a negative free toxin test will be excluded from the study. Suspected recurrence: the local free toxin test (FTT) must be conducted as soon as possible and at a maximum of 48 hours after identifying a suspected recurrence. Cell Cytotoxicity Neutralization Assay (CCNA) will be conducted at a specialized central laboratory for negative free toxin tests.
    a. 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.
8. Record all known historical CDIs along with associated treatment, information on the baseline CDI including signs and symptoms, any potential confounding medications taken up to 4 weeks prior to randomization, relevant medical history 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. Aliquots should be sent to the Central Laboratory. Only one sample is required at either Screening or D1. Only one sample is required at either D10 or D12. One other sample is required at D40. An additional stool sample is required at recurrence. If the visit is conducted remotely, stool sample drop off or collection from the subject (e.g., courier) must be arranged.

a. Screening: GI pathogen test (as part of standard diagnostic workup) and *C. diff* toxin test. Suspected recurrence: *C. difficile* toxin test (refer to footnote 7). All stool samples: sample should be aliquoted and frozen within 24 hours of sample being produced where possible and sent to the central laboratory for future research.

10. Weekly Unformed Bowel Movement (UBM) Contact: Weekly telephone contact will be made with subjects until Day 40, and thereafter on Day 70 and Day 100. Over the daily UBM contact period, it is not necessary to conduct separate weekly phone calls.
11. Daily Unformed Bowel Movement (UBM) Contact: Daily contact (either by telephone or in clinic) to collect the total number of UBMs in a 1-day period at the following timepoints: EOT -2 days, EOT -1 day, EOT, EOT +1 and EOT +2. Contacts should be made +/- 2 days of the expected EOT timepoint.
12. Height will be collected at screening only.
13. Vital signs include blood pressure, pulse, and body temperature. The 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.
14. ECG: The ECG may be performed at the screening or baseline visit. The ECG does not need to be performed if most recent ECG was normal (using the parameters and qualifications mentioned in Section 8.1.4) and was done in the 12 months prior to randomization.
15. Post-menarche female subjects testing to be performed on D1 and D12. Testing in the case of missed menses should also be conducted up to 30 days following the last dose of study treatment.
16. Subjects who have discontinued study drug early should remain in the study and be monitored, e.g., for adverse events.
17. Clinical response is defined as less than 3 UBMs for 2 consecutive days and maintained through the EOT without further CDI antimicrobial treatment at EOT+2 days or the investigator's assessment that the subject no longer needs specific CDI antimicrobial treatment after completion of the course of study medication. The investigator assessment of clinical cure at the AOC visit is defined by the following: The resolution of diarrhea (< 3 unformed stools in a 1-day period) while on treatment, that is maintained until the AOC (EOT +2 days) visit, and no further requirement for further CDI antimicrobial therapy is needed through EOT + 2 days. Recurrence is defined as a new episode of diarrhea with a positive *C. difficile* free toxin test that requires CDI antimicrobial treatment. Sustained Clinical Response is defined as clinical response with no recurrence assessed through 30 days post-EOT.
18. A PK Stool Sample will be collected on Day 1 (after dosing) or Day 2, and on Day 5 or Day 6. If the day of last dose is prior to Day 5, stool sampling is to be done on that last dosing day.
19. One blood PK sample will be collected at approximately 4 hours (+ 1 hour) post-dose on Day 1 or Day 2 (following either Dose 1, 3, 5 or 7) and Day 5 or Day 6 (following either Dose 17, 19, 21 or 23), or the subject's last 'odd' dose of study treatment (if earlier than Day 5). An accurate date and time of dose and sampling is required.
    a. A home healthcare vendor or appropriately trained and delegated site staff may perform this procedure at the subject's home.
20. AEs only need to be reported up to the D40 visit. AE's meeting the definition of serious should be reported throughout the study. Recurrence Visit: AE's to be reviewed if the recurrence is before D40.

2. RATIONALE FOR STUDY

2.1. Introduction

Clostridioides difficile (formerly known as *Clostridium difficile)* Infection (CDI) is an infection of the colon that invariably develops following prior antibiotic use. An increase in the incidence of CDI in the pediatric population has been reported (Schutze, 2013). Recurrence of CDI occurs in up to 30% of pediatric patients following initial therapy, hence the prevention of recurrent disease remains a key unmet medical need in the management of CDI (Nicholson, 2017). 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. Identified risk factors for recurrence of CDI in children include malignancy, recent surgery, antibiotic exposures, and the presence of a tracheostomy tube (Sammons, 2013; El Feghaly, 2013).

While administration of standard CDI antibiotics (vancomycin or metronidazole) may result in a reduction in *C. difficile* and subsequent relief of symptoms, these antibiotics have been shown to have ongoing and deleterious effects to the gut microbiome. As such, repeated courses of treatment for CDI may exacerbate the situation with ongoing disturbance of the microbiome leaving patients prone to further episodes of CDI. Therefore, therapeutic approaches that allow restoration of the gut towards a normal microbiome and resistance to *C. difficile* colonization, especially with narrow spectrum *C. difficile*-targeted antibiotics, are expected to reduce rates of recurrent disease.

Summit is developing ridinilazole which is associated with a highly targeted activity that has been shown to result in minimal collateral impact on the gut microbiota during therapy; therefore, it is expected that treatment with ridinilazole will lead to reduced rates of CDI recurrence. Reduced risk of recurrence was demonstrated in a Phase 2 proof of concept study in adults where superior efficacy was observed with ridinilazole treatment compared to vancomycin. There was a marked reduction in rates of CDI recurrence (ridinilazole: 14% recurrence; vancomycin: 36%) and hence improved sustained clinical response rates (Vickers, 2017).

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.

2.2. Background

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 (Smits, 2016).

C. difficile can often be a harmless resident of the GI tract with levels typically kept in check by the complex community of microorganisms that make up the indigenous gut microbiota and metabolome. However, disruption to the healthy ecological balance of the gut, typically by antibiotic use, diminishes the ability of the host to resist germination of spores and colonization by *C. difficile*, leading to toxin production and disease symptoms (Rupnik, 2009; Kelly, 2008).

CDI is a leading cause of nosocomial infectious diarrhea in adults (Smits, 2016). It is recognized as a significant concern within the healthcare system and is increasingly becoming a recognized issue in the community as well. Currently, up to 30% of patients who are treated for an initial episode of CDI experience a recurrence of infection once therapy is discontinued. This recurrence can occur within days or weeks of completing initial treatment. The risk of recurrence increases with each episode; following a second recurrence, 40% to 60% of patients may experience a subsequent episode (Kelly, 2012).

2.3. *Clostridioides difficile* Infection in Children

C. difficile clearly has a pathogenic role in adults and older children. However, in infants and neonates, *C. difficile* is more commonly found as a commensal organism and is recovered from an average of 37% (range 25% to 80%) of stools from healthy infants <1 month of age. Colonization rates fall slightly to an average of 30% by 6 months of age and to approximately 10% by 1 year of age. By the time a child reaches approximately 3 years of age, the colonization rate is similar, at approximately 0% to 3%, to that of asymptomatic adults (Schutze, 2013; Jangi, 2010).

An increase in the incidence of CDI in the pediatric population has been reported, especially in those children who are hospitalized but also in the community setting (Schutze, 2013; Sammons, 2013).

CDI in children is typically associated with co-morbidities such as underlying gastrointestinal disease (e.g., IBD), gastrointestinal surgery, renal insufficiency, and malignancy (El-Matary, 2019). Of note is the association of gastrointestinal disease, such as IBD or Hirschsprung's disease, with pediatric CDI (Kim, 2018).

2.4. Treatment

The most recent Infectious Diseases Society of America (IDSA) guidelines on the treatment of CDI include specific recommendations for the treatment of pediatric patients (McDonald, 2018). Metronidazole or vancomycin are recommended for treatment of a first episode or first recurrence of non-severe CDI. In severe disease and in cases of second recurrences, oral vancomycin is recommended over metronidazole (El Feghaly, 2013).

Fidaxomicin was recently approved in the US and European Union (EU) for the treatment of *Clostridioides difficile*-associated diarrhea (CDAD) and has been shown to be non-inferior on clinical response to vancomycin at the end of treatment and superior to vancomycin on sustained clinical response to 28 days post end of therapy. However, fidaxomicin was not shown to be superior to vancomycin on sustained clinical response for patients infected with BI/NAP1/027 strains (Louie, 2011; Cornely, 2012).

Since the IDSA guidelines have been published, data on fidaxomicin in children have been published. One study in 38 patients has been completed with fidaxomicin in the pediatric population where fidaxomicin was demonstrated to be well tolerated (Sears, 2014). Overall, the early clinical response rate was 92.1%. and the rate of sustained clinical response through 28 days after treatment was 65.8% (O'Gorman, 2018). Subsequently, in a Phase 3 study in pediatric patients, the clinical response rates were 77.6 % (76/98) and 70.5% 931/41 for fidaxomicin and vancomycin respectively. Global cure (end of therapy cure and no recurrence at 30 days) rates were 68.4% (67/98) and 50% (22/44) respectively (Wolf, 2019).

As fidaxomicin was not approved for use in pediatric patients at the time of compiling the most recent IDSA guidelines, no recommendation on its use was made. Recently, FDA approved the use of fidaxomicin in the pediatric population (aged 6 months to <18 years; January 2020).

Given the paucity of therapeutic options that reduce the risk of recurrence of CDI and the increased incidence of CDI in children, there continues to be an unmet medical need for improved antimicrobial treatment in the pediatric population including those who are undergoing antibiotic therapy, suffer IBD, or who have immunodeficiency, a poor diet, super-infections, cancer, or similar comorbidities (Ghose, 2013).

Ridinilazole is being developed with the objective to reduce the risk of recurrence of CDI. A Phase 2 randomized, double blind, active comparator study (SMT19969/C002) conducted in 100 adult 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. In the modified intent to treat population (confirmed diagnosis with positive free toxin test) the incidence of recurrence was 14.3% for ridinilazole-treated patients and 34.8% for vancomycin-treated patients, contributing to the sustained clinical response (clinical response at test of cure and no recurrence in 30 days) rates of 24/36 (66.7%) and 14/33 (42.4%) for patients on ridinilazole and vancomycin, respectively. The estimated difference of 21.2% (90% CI: 3.1%, 39.1%) between the two groups indicated superiority of ridinilazole compared to vancomycin at the pre-specified 10% level of significance. Furthermore, ridinilazole tested non-inferior for cure compared to vancomycin (cure rate for ridinilazole 77.8%, for vancomycin 69.7%) (Vickers, 2017).

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, randomized, active-controlled, parallel-group study in adults (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*). A total of 27 patients (14 ridinilazole: 13 fidaxomicin) were randomized to study treatment and all were included in the safety and efficacy analysis populations. 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.

Overall, ridinilazole was considered safe and generally well tolerated. All patients in the safety population, except two patients in the fidaxomicin group, experienced treatment-emergent adverse events (TEAEs). The majority of TEAEs were mild in severity and resolved without treatment and there were no discontinuations due to TEAEs.

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

2.5. Study Rationale

As discussed above, there is an unmet medical need for improved treatment options in children with CDI. Ridinilazole is being developed by Summit for the use in the pediatric population.

Ridinilazole is a novel antibiotic currently being investigated for the treatment of CDI and reducing the recurrence of CDI in adults. Ridinilazole has been shown to exert 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 includes hyper virulent ribotypes such as 027 and isolates showing reduced susceptibility to vancomycin and metronidazole. Ridinilazole is a non-absorbed and effective GI drug, with a narrow spectrum of activity; typically, >1000-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 compared with vancomycin (Thorpe, 2018), giving it a very good safety profile and excellent tolerability 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.

The primary objective of this study is the evaluation of the safety and tolerability of ridinilazole in adolescents with CDI. The safety results of the Phase 2 studies and the currently ongoing Phase 3 studies have demonstrated a benign safety profile to date. Similarly, animal toxicology studies showed few adverse events. This benign safety profile probably relates to the very limited systemic exposure of ridinilazole. Prior adult studies have indicated that most plasma samples from adult humans are near or below the limit of quantification of the assay. To further assess and confirm the low systemic exposure in adolescents, the current study will collect one PK sample at approximately 4 hours (±1 hour) post-dose on Day 1 (or 2) and Day 5 (or 6), or on the day of the subject's last dose of study medication if earlier.

2.6. Dose Justification of Study Medications

Vancomycin

The most recent IDSA guidelines on the treatment of CDI include specific recommendations for the treatment of pediatric patients (McDonald 2018). Metronidazole is only recommended for treatment of a first episode or first recurrence of non-severe CDI. In contrast, vancomycin or fidaxomicin are recommended for all disease severities, based on data showing metronidazole to be inferior to vancomycin across all disease severities in adults (Johnson 2014). However, the IDSA guidelines note the lack of comparative data between vancomycin and metronidazole in pediatric patients and consequently make no specific recommendation of using vancomycin over metronidazole in non-severe disease in pediatric patients. In severe disease and in cases of second recurrences, oral vancomycin is recommended over metronidazole. As such, Summit will use 125 mg of vancomycin dosed four times daily as the active comparator in the Phase 3 adolescent study.

Ridinilazole

In a Phase 2 study in adults, 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). 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.*

Additionally, ridinilazole demonstrated negligible absorption in healthy adult volunteers. Provided there is similarly negligible absorption of ridinilazole from the gut in adolescents and local gut toxicity in adolescents is similar to that observed in adults, the adult dose of 200 mg is also considered suitable to adolescents.

2.7. 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 lower limit of quantification (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 subjects 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* with no additional safety signals observed. The most frequent AEs were GI related. The safety profile of ridinilazole in Study SMT19969/C002 was comparable to the comparator, vancomycin, which will be used in this proposed study.

In the Phase 2 study SMT19969/C002 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 Study SMT19969/C003 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 potential safety risks for ridinilazole.

Although this will be the first-time adolescent patients are evaluated with this drug, it is expected that the maturity of the GI tract in this age group will be comparable to adults and as such the safety profile and the tolerability should be comparable to adults. However, this will need to be monitored carefully during the duration of the trial, particularly in view of the multiple comorbidities that these patients may have, including cancer, cystic fibrosis, and inflammatory bowel disease (IBD).

Together with non-clinical data showing ridinilazole has a narrow spectrum activity against *C. difficile* and microbiome sparing properties, these clinical data are considered to provide a positive benefit-risk profile for subjects 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. A risk assessment for vancomycin can be found in the package insert.

Summit Therapeutics believes it is important to continue developing ridinilazole for patients with CDI while ensuring the safety of study subjects, study personnel, and the public during Coronavirus Disease 2019 (COVID-19) pandemic caused by SARS-COV-2. 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., those with pre-existing medical conditions) and can result in significant morbidity and mortality. Like SARS-COV-2, *Clostridioides 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.

3. OBJECTIVES AND ENDPOINTS

Primary Objectives
• To assess the safety and tolerability of ridinilazole (200 mg bid), compared with vancomycin (125 mg qid), in adolescent subjects aged 12 to <18 years with *Clostridioides difficile* infection (CDI). • To assess the pharmacokinetics, including plasma and fecal concentrations, of ridinilazole in adolescent subjects aged 12 to <18 years with CDI.
Secondary Objective
• To assess the efficacy of ridinilazole (200 mg bid), compared with vancomycin (125 mg qid), in adolescent subjects with CDI.
Exploratory Objective
• To explore the medical resource utilization of adolescent subjects with CDI being treated with ridinilazole
Primary Endpoints
• Incidence and severity of treatment-emergent adverse events • Plasma and fecal concentrations of ridinilazole
Secondary Endpoints
• Sustained clinical response (SCR) over 30 days post end of treatment (EOT) - defined as clinical cure at the assessment of cure (AOC) visit and no recurrence of CDI within 30 days post EOT • Clinical cure at the AOC visit • Sustained clinical response over 60 days post EOT – defined as clinical cure at the AOC visit and no recurrence of CDI within 60 days post EOT • Sustained clinical response over 90 days post EOT – defined as clinical cure at the AOC visit and no recurrence of CDI within 90 days post EOT • SCR based on clinical response - defined as clinical response with no recurrence assessed through 30 days post-EOT • Clinical response at the AOC visit
Exploratory Health Economics and Outcome Research (HEOR) Endpoint
• Medical resource utilization and health economics endpoints

Definitions

Clinical cure

The investigator assessment of clinical cure at the AOC visit is defined by the following:

The resolution of diarrhea (< 3 unformed stools in a 1-day period) while on treatment, that is maintained until the AOC (EOT +2 days) visit, and no further requirement for further CDI antimicrobial therapy is needed through EOT + 2 days.

Recurrence

Recurrence is defined as a new episode of diarrhea and other signs and symptoms of *C. difficile* with a positive *C. difficile* free toxin test that requires CDI treatment.

Clinical response

Clinical response is defined as:

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

4. STUDY DESIGN

4.1. Subject Enrolment and Overall Design

Enrollment

SMT19969/C006 is a randomized, double blind, active-controlled study to evaluate the safety and tolerability of ridinilazole compared with vancomycin and to assess the pharmacokinetics of ridinilazole in adolescent subjects (aged 12 to <18 years) with *Clostridioides difficile* infection. At least 40 subjects with a confirmed diagnosis of CDI will be randomized into the study.

The study includes a screening visit, a 10-day treatment period (beginning on the day of screening or the following day) and up to 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/Day 1 assessments will be conducted on the same day, but it is allowed to conduct the screening visit within 3 days prior to the baseline/Day 1 visit if required for practical reasons. Due to the potential impact of the COVID-19 pandemic, there is flexibility built into the protocol to allow all study visits to be completed remotely, however, subjects should continue to attend in-clinic visits wherever possible.

Study Periods

Randomization will occur after confirmation of eligibility is established at the Screening/Baseline clinic visit. Subjects will be randomized to receive ridinilazole or vancomycin in a 3:1 ratio.

Dosing with study treatment starts on Day 1 continuing for 10 days. Another in-clinic visit (or alternative, see the SoA) will be scheduled at Day 5 (or 6) in order to collect samples for PK analysis. A telephone check or clinic visit will be conducted at Day 10 to confirm completion of study treatment, end of treatment (EOT). At Day 12, at least 48h after EOT, there is an in-clinic visit (or alternative, see the SoA) for Assessment Of Cure (AOC). If the subject's 10 days dosing is completed on Day 11, the EOT + 2 days visit will be conducted on Day 13. A daily UBM contact will occur at EOT -2, EOT -1, EOT, EOT +1, and EOT +2 to collect UBM data. Subsequently there are weekly telephone checks until Day 40 and at Day 70 and Day 100.

All subjects will remain in the study until at least Day 40, when they will attend an in-clinic visit (or alternative, see the SoA). Subjects not cured at AOC or experiencing recurrent CDI prior to or at Day 40, will receive standard-of-care in accordance with the investigators' clinical judgment and local practices for treatment of their CDI. Subjects not cured at the AOC visit or having recurrence nevertheless must remain in the study and be monitored, e.g., for adverse events, until Day 40. Those subjects cured at AOC and without a CDI recurrence by Day 40 will continue to be followed until Day 100 or recurrence (whichever comes earlier). If the subject has suspected recurrence after Day 40, the subject should make an in-clinic visit (or alternative, see the SoA) for confirmation and for providing a stool sample; if recurrent CDI is confirmed this visit will also serve as the subject's end of study visit. Following Day 40, a telephone call to check for CDI recurrence will be made on Day 70. If the subject remains free of recurrence, he/she will have the end of study visit at Day 100 either by a telephone call or clinic visit.

All subjects considered cured at AOC who experience suspected CDI recurrence are expected to provide a stool sample for free toxin testing no later than 48 hours after identifying the suspected recurrence. Details on the timing of treatment and assessments are given in the Schedule of Activities Table (Section 1.2).

PK plasma sampling will occur on Day 1 or Day 2 and on Day 5 or Day 6. If the last day of dosing with study medication occurs prior to Day 5, the sample is to be taken on the last dosing day. The PK fecal (stool) samples will be collected on Day 1 (after dosing) or Day 2 and on Day 5 or Day 6. If the last day of dosing with study medication occurs prior to Day 5, the sample is to be taken on the last dosing day.

Unscheduled visits may occur at the Investigator's discretion (e.g., in the case of AEs) and subjects should be requested to attend for a recurrence visit (or alternative, see the SoA) in the event of suspected recurrences of CDI. Of note, the term "Investigator" refers to the Principal Investigator of a clinical site or a delegate as documented on the site Delegation of Authority log.

COVID-19

Where possible, it is preferred for visits with an in-clinic option to be done in-clinic, especially the highly complex baseline visit, however, subjects may need to carry out one or more study visits remotely to ensure their safety during the global COVID-19 pandemic. Modifications for subjects needing remote visits include:

Screening visit

The assent process (informed consent process) should be captured electronically via eConsent with an impartial witness, however, subjects may sign a paper consent form when the screening visit is conducted in-clinic. If the visit has to be conducted remotely and the subject cannot adhere to eConsenting, they may have the consent/assent form(s) emailed to them and carry out a synchronous consent discussion over the phone. Consent/assent form(s) must be received and acknowledged by the site prior to the commencement of any study procedures. The original signed consent/assent 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.

The ECG and physical exam may be conducted at the screening visit to allow the subject to return home while awaiting FTT results. If the physical exam is conducted at screening, the vital sign assessment will still need to be repeated at baseline. An ECG does not need to be performed if most recent ECG was normal (using the parameters and qualifications mentioned in Section 8.1.4) and was done in the 12 months prior to randomization.

Baseline visit

A sponsor contracted home healthcare vendor or appropriately trained and delegated site staff may assist with the baseline visit in extreme cases where the subject is unable to complete the visit in- clinic for safety reasons.

The home healthcare vendor or site staff may bring vitals equipment to the subject's home to collect baseline assessments and leave the equipment with the subject for use during follow up visits at Days 12, 40, and/or recurrence. The 'physical exam and vital signs' and 'signs and symptoms of CDI' assessments must be performed via synchronous sponsor approved video

conferencing with the Investigator. It is imperative for any visit completed by home healthcare vendor or site staff that the physical exam and vitals be the first study procedures completed, once consent/assent has been collected, so the subject may be sent to an acute care clinic should they require immediate care.

Blood and urine samples should be collected by the home healthcare vendor or site staff at the subject's home at the baseline visit if the visit is conducted remotely.

Following Investigator assessment of eligibility and randomization, IMP may be shipped directly to the subject's home, delivered by courier, or delivered by a home healthcare vendor or site staff.

Day 5 visit

The Day 5 visit is preferably an in-clinic visit. However, if a subject is unable to complete the visit in-clinic for safety reasons, a sponsor-contracted home healthcare vendor or properly trained and delegated site staff can conduct assessments and collect samples at the subject's home.

Day 10 visit

The Day 10 visit may be conducted in-clinic or by telephone. If conducted by telephone, stool sample drop off or collection of the sample from the subject's home must be arranged.

Used IMP wallets and any unused medication should be returned to the site during a visit, or couriered to site as soon as study treatment has been completed.

Day 12, Day 40 and recurrence visit

Day 12, Day 40, and/or any recurrence visit(s) are preferably in-clinic visits, however, may be completed remotely. If so, the following approaches may be taken:

- if the subject has been provided with vital sign equipment by the site, the visit may be conducted with only a video conference between the Investigator and the subject in the presence of a guardian, including a focused physical exam and vital signs by the subject themself with the help of a guardian or
- a sponsor-contracted home healthcare vendor or properly trained and delegated site staff may conduct the visit at the subject's home with a guardian present and with the Investigator joining by video conference.

If Day 12 and/or Day 40 visits are completed at home over video conference without the presence of site staff or a home healthcare vendor, the site will need to arrange for an appropriately qualified person to collect the blood (hematology and clinical chemistry) and urine samples.

If utilizing a home healthcare vendor or site staff for remote Day 12 and/or Day 40 visits, they may complete the blood (hematology and clinical chemistry) and urine collections.

If Day 12, Day 40 or Recurrence visits are completed at home stool sample drop off or collection of the sample from the subject's home must be arranged.

4.2. End of Study Definition

A subject is considered to have completed the study if he/she has attended the following visit:

- Day 40 visit: if not cured at AOC or if cured at AOC but experiences CDI recurrence prior to Day 40
- Recurrence visit: if the subject has SCR to Day 40 but has a confirmed recurrence between Day 40 and Day 100.
- Day 100 visit: if the subject is cured at AOC and has no recurrence of CDI up to Day 100

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

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

At screening, subjects are eligible to be included in the study only if all the following criteria apply.

Legal

1. Has signed informed consent by parents or legally authorized representatives and assent by the child according to local requirements (e.g., Protected Health Information [PHI]) prior to initiation of any study-mandated procedure.
2. Is aged 12 to <18 years.

Disease Characteristics

3. Has 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, see Appendix 5) in the 24 h prior to randomization.
4. Has tested positive for toxin A and/or B of *C. difficile* in the stool determined by a positive free toxin test (using a Sponsor agreed test).

Contraception

5. Has contraceptive measures in place as follows (see Appendix 4 for details):

   Male subject:

   - Agrees to use a highly effective contraceptive method as detailed in Appendix 4 of this protocol during the treatment period and for at least 30 days after the last dose of study treatment

     OR
   - Agrees to adhere to abstinence
   - Refrains from donating sperm during the treatment period and for at least 30 days after the last dose of study treatment

   Female subject:

   - Is not pregnant or breastfeeding and must have a documented negative pregnancy test at screening
   - Complies with one of the following three conditions:
     i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4
     ii. A WOCBP who agrees to follow the guidance in Appendix 4 on highly effective contraceptive methods during the treatment period and for at least 30 days after the last dose of study treatment.

iii. A WOCBP adhering to abstinence.

5.2. Exclusion Criteria

At screening, subjects are excluded from the study if any of the following criteria apply.

Treatments for CDI confounding with the study treatment

1. Has received treatments for CDI confounding with the study treatment as follows:
    - Has had more than the equivalent of 48 hours of dosing of antimicrobial treatment active against the current episode of CDI prior to randomization or
    - Has received ridinilazole or an investigational vaccine against *C. difficile* any time in the past; anti-toxin antibodies including bezlotoxumab within the past 6 months; or any other investigational medicinal product for treatment of CDI, or fecal microbiota replacement therapy within the past 3 months

Conditions confounding with the assessments of CDI

2. Has a clinically relevant positive stool test for pathogens other than *C. difficile*, within 48 hours of randomization. Routine stool cultures and examinations for other pathogens are not required by the protocol unless they are suspected by the investigator and performed as part of standard of care.
3. Has life-threatening or fulminant CDI with evidence of hypotension, septic shock, peritoneal signs or absence of bowel sounds, toxic megacolon, or ileus.
4. Has had major GI surgery (e.g., significant bowel resection or pancreatectomy, but not including appendectomy or cholecystectomy) within the past 3 months or has the presence of a colostomy or ileostomy or has the likely requirement of an ostomy during the study
5. Is receiving treatment that generally is associated with severe diarrhea, intractable vomiting, severe nausea, or inability to swallow that cannot be managed with antiemetics or antidiarrheals and that limits the ability to take oral medications. Cancer treatment that does not compromise ability to take study medication or cause severe diarrhea is allowed.

Conditions confounding with the safety assessments

6. Has been involved in a clinical trial and received an investigational medicinal product for an indication other than CDI within the past month or five half-lives (whichever is longer).

Compliance with the study protocol

7. Is unable to tolerate oral medications
8. Has a known history of hypersensitivity or allergic reaction to vancomycin or any excipient of vancomycin or ridinilazole.

9. Is, in the Investigator's judgment, inappropriate for participation in the study including for example those subjects
    a. with any other (medical) condition that would make the subject unsuitable for inclusion in the study
    b. who are not likely to complete the whole study for whatever reason, e.g., a short life expectancy
    c. who are unwilling or unable to comply with protocol requirements, for example complete the full course of study treatment, attend study clinic visits, provide stool samples, ingest capsules, tolerate blood draws

5.2.1. Subject Suitability

Subjects may participate in the study provided they are expected to be able to take oral study medication for 10 days and complete study assessments.

Examples of subjects who may need to be excluded include those suffering from vomiting and/or severe nausea that cannot be managed with antiemetics and is limiting the ability to take oral medication, intubated subjects, subjects likely to require antibiotics that have activity against *C. difficile* especially in the first 40 days. Investigators are encouraged to contact the medical monitor to discuss individual cases as required.

5.3. Lifestyle Considerations

There are no lifestyle restrictions applicable through the study.

5.3.1. Meals and Dietary Restriction

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 subjects who assent 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 subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and torespond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons and any serious adverse event (SAE).

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

6. STUDY TREATMENT

Subjects will be randomized to receive a 10-day course of ridinilazole tablets (200 mg, *bid*), or vancomycin (125 mg, *qid*) capsules. Blinding will be maintained by also orally administering matching placebo tablets/capsules. Study treatment will be provided in a blister wallet labelled per country requirements. Each wallet will have a unique identifier which will be used to allocate double-blind study treatment to each subject via the Interactive Response Technology (IRT) system. Study treatment wallets may be labelled as Summit Therapeutics, Inc., or Summit (Oxford) Limited as the listed sponsor.

6.1. Administration of the Study Treatment

Each wallet will contain all doses required for the total treatment period (i.e., 40 doses over 10 days; 4 doses a day). Doses will be clearly labeled 1 to 40 on the wallets. It is important the subject takes each dose in number order starting with 1 and finishing with 40. If you miss a dose, then 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 you miss Dose 3, take Dose 3 before or with Dose 4.

Do not crush or break the tablets or open the capsules (e.g., to pass through a feeding tube).

Table 1: Dosing schedule per 24 hours (four doses)

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

6.2. Preparation, Handling, Storage and Accountability

The Investigator or designee must confirm appropriate temperature conditions (below 25°C/77°F 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 subjects randomized 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.

Study treatment wallets may be labelled as Summit Therapeutics, Inc., or Summit (Oxford) Limited as the listed sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will occur on Day 1 after subject eligibility for the study has been confirmed. Subjects will be randomized to one of two treatment groups in a 3:1 ratio to either the ridinilazole arm or the vancomycin arm.

The Investigator or designee will use the IRT system to randomize a subject. A computer-generated central randomization will be used which will be stratified by current comorbidities (see Section 4.1). Once a randomization number has been assigned it will not be re-assigned. Study treatment will be dispensed at the randomization visit (Day 1). Returned study treatment should not be re-dispensed to other subjects.

This is a double-blind study. To maintain the blind, a double-dummy approach for study treatment blinding 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. Subjects randomized to ridinilazole will receive active ridinilazole, and vancomycin placebo to achieve dosing with ridinilazole *bid*. Subjects 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 subjects and study site staff will not know to which arm a subject 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 subject, 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 subject.*

In case of an emergency, the Investigator (when possible) is responsible for determining if unblinding is warranted. Subject 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 subject.

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 (study treatment). Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one capsule or one tablet.

Compliance with the study treatment is critical to the integrity of the study objectives.

To help ensure compliance the Investigator will discuss the following with the subject and the subject's guardian(s) on Day 1 and on Day 5:

the importance of administering study treatment (medication; all tablets and capsules) per protocol and to remind the subject to continue to complete all doses regardless of resolution of symptoms.

The subject's guardian or subject will be required to return all empty packaging and unused study treatment (wallet, capsules, tablets) to the Investigator at the Day 12 (AOC) visit so that a final compliance check can be conducted.

During the treatment period, the subject is requested to fill out the Study Drug Administration form daily indicating at which time points the study medication has been taken. A guardian can help filling out this form (that will be provided by 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 subject 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 subject's duration in the study (i.e., until end of study; see Section 6.5.1). The reason for use, the dates of administration and the dosing information should be recorded in the eCRF.

6.5.1. Potential Confounding Medications

Refer to Table 2 for a list of medications that may impact CDI status or assessment of adverse events and hence have the potential to confound study results. Control over administration of these medications is necessary, considering the safety and efficacy endpoints 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 subject's health would otherwise be compromised. Confounding medications include but are not limited to these listed in the following tables.

Potentially Confounding Medications

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

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

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

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

Table 2: 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)

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)	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 rifamycins, tigecycline, nitazoxanide, bacitracin, fusidic acid, oral teicoplanin)	None permitted unless used for conditions other than CDI	Prescribe alternative antimicrobial if use is for conditions other than CDI where possible.
Prescribed probiotics, prebiotics and herbal products or non-prescribed intended to treat CDI	None permitted unless patient was taking the treatment prior to enrolment	For recurrence, as per standard clinical practice
Intravenous immunoglobulin (IVIG)	None permitted unless patient was receiving regular IVIG treatment prior to enrolment	For recurrence, as per standard clinical practice

Drug Class	From Randomization to Day 12/AOC	During Follow Up
CDI Treatments		
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*[1]	Permitted	Permitted
Anti-diarrheals, anti-peristaltics, laxatives	Permitted	For recurrence, as per standard clinical practice.
IMP for other indications	None permitted	None permitted

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

During the study, both during the treatment period and during the follow up period, subjects 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 subject will discontinue study treatment for any of the following reasons:

- Withdrawal of consent/assent to continue taking study treatment. The reason for this will be documented if provided.
- The study Investigator or Sponsor, for any reason, decides the subject should be discontinued from the study treatment.
- Adverse events, classed as possibly or probably study treatment related by the Investigator, which cannot be tolerated by the subject
- Pregnancy during the study treatment period. See Appendix 4 and Section 8.3 Pregnancy.
- Death
- Non-compliance
- Persistent diarrhea (moved to standard of care)
- Lost to follow-up
- Other

Subjects discontinued from study treatment, should continue with all study visits and assessments so that (safety) data can be collected. If subjects do not agree to this, then they should complete the early termination assessments.

Study treatment (wallet, capsules/tablets) assigned to the discontinued subject must not be assigned or handed over to another subject.

7.2. Withdrawal from Study

A subject may withdrawal or be withdrawn from the study for any of the following reasons:

- Withdrawal of consent/assent to continue study participation; the reason for this will be documented if provided.
- The study Investigator or Sponsor, for any reason, decides the subject should be discontinued from the study
- Adverse event(s)
- Death
- Lost to follow-up
- Other

7.2.1. Withdrawal of Consent/Assent

All subjects are encouraged to continue through to the end of the study. However, a subject may withdraw from the study at any time at his/her own or parental/responsible adult request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

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

See the Schedule of Assessments for data, evaluations, and samples to be collected when a subject ends participation in the study. The reason for withdrawal is to be documented on the eCRF and in the source documentation (e.g., patient file).

7.2.2. Lost to Follow Up

A subject 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 staff of the study site.

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

- The site staff must attempt to contact the subject and/or subject's guardian and reschedule the missed visit as soon as possible. The subject and subject's guardian should be counselled on the importance of maintaining the assigned visit schedule and the site should ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject and/or subject's guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject 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 1.2). Protocol waivers or exemptions will not be granted by the Sponsor or delegate. Adherence to the study design requirements, including those specified in the SoA (Section 1.2), is essential and required for study conduct.

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

Immediate safety concerns should be discussed with the Sponsor Medical Monitor or delegate instantaneously upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

8.1.1. Medical History (Including CDI History)

The following will be recorded prior to randomization:

- All relevant and significant medical history diagnosed or treated within the last 12 months and relevant chronic conditions that have not had an exacerbation in the last 12 months prior to randomization
- All medications taken up to 4 weeks prior to randomization
- All known episodes of CDI along with the treatment administered
- 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 infection, condition resulting in 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.

8.1.2. Physical Examinations

The physical exam may be conducted at either screening or baseline. If conducted at screening, then only the vital signs must be repeated at the baseline visit if done on a different date. A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at screening only) and weight will also be

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

8.1.3. 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 subject, if possible.

8.1.4. Electrocardiograms

A single 12-lead ECG will be obtained at screening or baseline visit, 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.

An ECG does not need to be performed if most recent ECG was normal (using the parameters and qualifications mentioned in Section 8.1.4) and was done in the 12 months prior to randomization, the screening/baseline 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.

8.1.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests that will be performed at a central laboratory and the SoA (Section 1.2) for the timing and frequency. However, the urine pregnancy test will be performed locally.

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 eCRF. 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 subject'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 Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

8.2. Adverse Events and Serious Adverse Events

Refer to Appendix 3 for definitions and for details on how to assess, classify, and report adverse events (AEs)/ serious adverse events (SAEs).

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

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 subject to discontinue the study treatment. (See Section 7)

8.2.1. 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 Day 100/ the 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 eCRF and not the AE eCRF page.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness of the event, as indicated in Appendix 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 subject 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 Appendix 3.

8.2.2. 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 subject should be used to inquire about AE occurrences.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2.2). Further information on follow-up procedures is given in Appendix 3.

8.2.4. 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 all other subjects 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.

8.2.5. Events NOT Meeting the AE/SAE Definition:

- Disease Related Events (refer to Section 8.2.6)
- 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).

8.2.6. 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.

8.3. Pregnancy

- Details of all pregnancies in female subjects and, female partners of male subjects 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 Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

There is no specific treatment for overdosing; general medical support measures are to be in place, if required. Any SAE or AE associated with excessive dosing must be followed as any other SAE or AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

8.5. Pharmacokinetics

8.5.1. Plasma PK Samples

PK plasma samples will be collected on Day 1 or Day 2 and on Day 5 or Day 6. If the last day of dosing with study medication occurs prior to Day 5, the sample is to be taken on the last dosing day. An accurate time of dosing and plasma sampling should be recorded.

It is understood that subjects 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 subjects will occur as follows:

- Day 1 or 2 - at 4 hours (±1 hour) post either Dose 1, 3, 5 or 7
- Day 5 or 6 - at 4 hours (±1 hour) post either Dose 17, 19, 21 or 23.

The bioanalytical laboratory will be unblinded and all samples from the ridinilazole-treated subjects 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 team. Transfer of PK data will not be conducted until after the study is unblinded.

Residual plasma samples may be retained for up to 5 years from the end of the study for exploratory analyses of circulating ridinilazole metabolites, biomarkers and/or assessing vancomycin concentrations. If performed, this work will be reported separately.

8.5.2. Fecal PK Samples

Fecal samples to determine ridinilazole concentrations in the stool will be collected on Day1 (after dosing) or Day 2 and on Day 5 or Day 6. If the last day of dosing with study medication occurs prior to Day 5, the sample is to be taken on the last dosing day.

As for plasma PK samples, the bioanalytical laboratory will be unblinded and all samples from the ridinilazole-treated subjects 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 team. Transfer of PK data will not be conducted until after the study is unblinded.

8.6. Efficacy Assessments

8.6.1. Assessment of Cure/Sustained Clinical Response

Efficacy endpoints are secondary endpoints and will be assessed at the times outlined in the SoA (Section 1.2).

The Investigator will assess whether a subject was a clinical cure or failure at Day 12 (AOC) and whether a subject has a recurrence. Sustained clinical response (SCR) at 30 days post End-of-Treatment (EOT) is defined as clinical cure at the AOC visit and no recurrence of CDI at Day 40. Those subjects cured at AOC and with a SCR at Day 40 will continue to be followed until Day 100 or recurrence of CDI (whichever comes earlier). SCR at 60- or 90-days post EOT are defined as cure at the AOC visit and no recurrence of CDI at Day 70 or Day 100 respectively.

Clinical response will be assessed at the AOC visit. SCR based on clinical response, defined as clinical response with no recurrence assessed through 30 days post-EOT will be assessed through 30 days post-EOT.

The following definitions will be used:

Clinical cure

The investigator assessment of clinical cure at the AOC visit is defined by the following:

The resolution of diarrhea (< 3 unformed stools in a 1-day period) while on treatment, that is maintained until the AOC (EOT +2 days) visit, and no further requirement for further CDI antimicrobial therapy is needed through EOT + 2 days.

Recurrence

Recurrence is defined as a new episode of diarrhea and other signs and symptoms of *C. difficile* with a positive *C. difficile* free toxin test that requires CDI treatment.

Clinical response

Clinical response is defined as:

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

Subjects/guardians will be encouraged to contact the site if diarrhea occurs. The Investigator or site staff indicated on the site delegation log will contact the subject/guardian weekly to enquire about any episodes of diarrhea until Day 40 and thereafter on Day 70 and Day 100.

The Investigator will request the subject be assessed for recurrence of CDI if a new episode of diarrhea is reported, unless the Investigator is highly confident that the diarrhea is due to a cause other than C. difficile. Where possible the assessment, including a free toxin test, should occur as soon as possible, and within 48 hours of the report.

8.6.2. Weekly Unformed Bowel Movement Contact

Weekly telephone contact will be made with subjects until Day 40, and thereafter on Day 70 and Day 100. Subject will be asked if CDI recurrence is suspected if 3 or more UBMs have occurred within a 24-hour period since last contact.

8.6.3. Daily Unformed Bowel Movement Contact

Daily telephone contact will be made with subjects on the following days: EOT -2, EOT -1, EOT, EOT +1, EOT +2. Subject will be asked if 3 or more UBMs have occurred within a 1-day period. Alternatively, may occur in person.

8.6.4. Signs and Symptoms of CDI

The Investigator should record the subject's current signs and symptoms of CDI at baseline/ Day 1, Day 10 and at Day 12/EOT +2 days. Signs and symptoms will also be recorded during an assessment of suspected recurrence. The Investigator should ask the subject for signs and symptoms that have occurred over the 1-day period prior to the assessment of suspected recurrence.

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 subject at that evaluation on the eCRF at the visits indicated.

8.6.5. Suspected Recurrence

If there are signs and symptoms that could relate to CDI (e.g., diarrhea), that situation is referred to as a 'suspected recurrence'.

It is required that every new episode of diarrhea considered a 'suspected recurrence' 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 the signs and symptoms (e.g., diarrhea) are **not** considered a 'suspected recurrence': record the reason in the eCRF on the 'Suspected Recurrence of CDI' eCRF page.
- If the signs and symptoms (e.g., diarrhea) are considered a 'suspected recurrence':
    - Conduct a local free toxin test (FTT) as soon as possible and no later than 48 hours 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.
    - Refer to the free toxin test result to determine whether CDI treatment is required.
    - Complete the "Suspected Recurrence of CDI" eCRF page

Since *C. difficile* free toxin EIA kits (i.e., the FTT) can have sub-optimal sensitivity, in all instances of suspected recurrence of CDI that are associated with a negative free toxin test (FTT) result (obtained locally by the site), a stool sample should be collected for testing by Cell Cytotoxicity Neutralization Assay (CCNA) at a specialized central laboratory. The sample should be frozen within 24 h of production and stored to shipment to the Central Laboratory (as for all other samples). Alternatively, an aliquot of the original sample used to perform the FTT can be prepared for the CCNA if not older than 24 h of production. This requirement to prepare an aliquot for CCNA testing at a specialized central laboratory in case of a negative FTT at suspected recurrence is irrespective of any locally conducted CCNA.

Recurrence of CDI per protocol is defined as a new episode of signs and symptoms of C. *difficile* with a positive *C. difficile* free toxin test that requires CDI treatment. A confirmed recurrence of CDI is considered a disease-related event (DRE) and not an adverse event (AE or SAE; see Section 8.2).

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); see also Section 8.2 and Section 10.3.

8.6.5.1. Recurrence Visit

Investigators are requested, subject to local treatment guidelines and Investigator judgement, to await the results of the local free toxin test (i.e., the FTT and not the CCNA assay) prior to initiating antimicrobial treatment for a suspected recurrence. The Investigator may discuss with the Medical Monitor if required.

At the scheduled visits indicated in the SoA (Section 1.2), the Investigator should also assess whether the subject has met the criteria for recurrence. In case of a 'suspected recurrence' all the assessments as indicated in the SoA Recurrence Visit (Section 1.2) should be carried out.

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

To ensure the data integrity of the efficacy endpoints, it is critical that the following requirements are met for all subjects where possible:

- **A free toxin test is conducted as soon as possible following suspicion of recurrence.**
- **Refer to the results of the free toxin test to determine if CDI treatment is required.**
- **Any potentially confounding medications initiated must be recorded in the eCRF**

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 specialized central laboratory.

8.7. Stool (Feces) Collection for Future Research

Subjects will be required to provide a stool sample at the time points specified in the SoA (Section 1.2). Subjects will be provided with a home collection kit. If a sample is requested by the Investigator, the subject 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 for future research will be prepared and frozen within 24 h of production and stored for shipment to the Central Laboratory. Guidance and instructions for Investigators will be available in the lab manual.

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

A stool sample produced and frozen **within 24 hours** is required. If the sample used for CDI testing was produced >24 hours, a fresh sample should be provided where possible.

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9. Genetics

Genetics are not evaluated in this study.

8.10. Biomarkers

Biomarkers are not evaluated in this study.

8.11. HEOR, Medical Resource Utilization

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the Investigator and study-site personnel for all subjects 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
- Subject location at admission and subject's discharge location
- Other location of healthcare access that didn't result in hospitalization, i.e., urgent care facility, doctor visit, telemedicine

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size has not been chosen on the basis of a formal hypothesis test. However, 40 subjects (with a 3:1 allocation) are considered sufficient to investigate the safety of ridinilazole compared to vancomycin and 30 ridinilazole subjects are considered sufficient to assess the pharmacokinetics of ridinilazole in this subject population.

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All subjects who sign the ICF
Randomized	All subjects randomly assigned to study treatment.
Safety	All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they received.
Pharmacokinetic [PK]	All subjects who are treated with ridinilazole and have at least one measured concentration of ridinilazole (including values less than the lower limit of quantification).
Modified ITT [mITT] (Efficacy)	All subjects in the ITT population who have a diagnosis of CDI confirmed by the presence of free toxin in stool and have ≥3 UBMs in the 24 hours prior to randomization.

9.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before unblinding and database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing data. 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.

9.3.1. Safety Analyses

All safety evaluation will be performed on the safety population.

Treatment-emergent adverse events, i.e., any adverse events emerging after the first dose of study medication, will be summarized by treatment group and by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as related to study treatment by the Investigator.

Changes from baseline in laboratory parameters and vital signs will be summarized by treatment group and visit. Baseline will be taken as the last measurement prior to dosing.

9.3.2. Pharmacokinetic Analyses

Summary statistics will be reported for ridinilazole plasma and fecal concentrations by time point for the PK population. A count of the number of samples below the level of quantification (BLQ) will be provided for each time point.

9.3.3. Efficacy Analyses

All efficacy analyses will be performed on the mITT population.

The proportion of subjects with SCR at 30 days post EOT will be presented for each treatment group, along with its 95% 2-sided binomial confidence intervals. A similar summary will be produced for the proportions of subjects with clinical cure at AOC, SCR at 60 days post EOT and SCR at 90 days post EOT.

Details of any exploratory analyses will be documented in the SAP that will be finalized before database lock.

9.4. Interim Analyses

The Sponsor and Delegate medical monitors will review the safety data periodically during the study.

An independent Data and Safety Monitoring Board (DSMB) will review unblinded safety data on a regular basis during the course of the study, as defined in the DSMB Charter. Following each review, the DSMB will recommend action regarding the study (continue; continue with changes; temporarily stop; or stop). The specifics regarding the DSMB organization and procedures will be outlined in the DSMB Charter.

There is no plan to conduct a formal interim analysis. However, the sponsor may request an interim analysis to support the regulatory submission of ridinilazole if, at the time of filing for adults, this study is still ongoing. The results of this interim analysis will not be used to modify or terminate the study; therefore, no formal stopping rules will be applied. The interim analysis will include all subjects who have completed the study at the time of the data-cut date. All data will be cleaned and verified prior to reporting. Any changes to the data previously reported will be fully auditable and discussed in the final report.

The sponsor recognizes that by performing this interim analysis the study will be unblinded for the reported subjects at the interim and this may introduce bias with the ongoing study. To minimize this bias investigators and site staff will remain blinded, so the impact on the ongoing care and recruitment of subjects is limited. In addition, any changes in the reporting of the data after unblinding will be clearly documented in the final clinical study report.

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 and 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 subjects.

The Investigator will be responsible for the following:

- 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/Assent Process

Written or electronic informed consent and/or assent must be obtained from each subject (and their parents/guardian) prior to participation in the study. Written informed consent and/or assent will be collected following a review of the subject's information leaflet by the potential subject and

their parents/guardian and a discussion between the subject and their parents/guardian and the Investigator or suitably qualified designee.

The Investigator or his/her representative will explain the nature of the study to the subject and/or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary and that they are free to refuse to participate and may withdraw their consent/assent at any time and for any reason during the study period.

Subjects or their legally authorized representative (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.

The medical record must include a statement that written informed consent/assent was obtained before the subject was randomized in the study and the date the written consent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF. Subjects who are rescreened are required to sign a new ICF. A copy of the ICF(s)/must be provided to the subject or the subject's legally authorized representative. Subjects who are rescreened are required to sign a new assent.

For electronic Consent (eConsent), the informed consent process should be captured electronically via eConsent platform with an impartial witness, however, subjects may sign a paper consent/assent form when the screening visit is done in-clinic. If the visit must be done remotely and the subject cannot adhere to eConsenting, they may have the consent/assent form(s) emailed to them and carry out a synchronous consent/assent discussion over the phone. Consent form(s) must be received and acknowledged by the site prior to the commencement of any study procedures. Original, signed consent/assent 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.

Sites may provide an initial assent form for the free toxin test before requesting the subject's assent for the full study (subject to requirement and local regulations). Consent for a toxin test conducted per standard of care is not required.

A separate signature will be required to document a subject's agreement to allow any remaining specimens to be stored for up to 5 years to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

To ensure the privacy and safety of children, the sponsor will not knowingly collect data on children without the consent of the parent or guardian.

Where possible, the processing of the personal data of participants will be minimized by making use of a unique participant study number only on study documents and electronic database(s). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or information which would make the subject directly identifiable will not be transferred.

All documents will be stored securely and only accessible by study staff and authorized personnel. The study staff will safeguard the privacy of participants' personal data.

The subject will be informed how his/her personal study-related data will be used by the Sponsor in accordance with relevant data protection law. The subject will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

The study 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 subject data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

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). 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 eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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 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

Describe procedures for the identification of data to be recorded directly on the eCRF considered as source data. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

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

must be available. 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, provided there is reasonable cause 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 subjects by the Investigator
- Discontinuation of further study treatment development

10.1.9. Publication Policy

Summit fulfills 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 http://www.summitplc.comand 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-center 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 subjects who participate in their clinical trials. After publication of the primary manuscript, subjects 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

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic- Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [non-fasting]	Calcium	Alkaline phosphatase	Albumin
Other Tests	Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)2 The PK, CCNA, microbiology, microbiome & metabolome analysis will be performed by specialist centralized laboratories.			

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.

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 subject or clinical study subject, 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 subject 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 subject 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 subject 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 Meeting the AE/SAE 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).
- 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), must be reported as an SAE.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.
- If on evaluation of diarrhea or other signs and symptom associate with CDI, no recurrence is deemed to have occurred, any symptoms (or preferably diagnosis) reported by the subject must be reported as AEs (up to Day 40) or as SAEs (anytime during the study if the event meets the definition of an SAE)
- "Lack of efficacy" or "failure of expected pharmacological action" per se is not to 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 8.2.5 and Section 8.2.6 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 eCRF. • It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the SAE coordinator in lieu of completion of the AE/SAE eCRF 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 subject identifiers, except for the subject 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 subject, 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 and/or Product Information for vancomycin, for marketed products, 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 eCRF.
- 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 subject 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 eCRF.
- 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@iqvia.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 eCRF 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)

If the subject has a uterus and ovaries and has experienced menarche and is not permanently sterile or postmenopausal (postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) and is having vaginal sex with someone with a penis and testicles, pregnancy can be a risk. These subjects are of childbearing potential and are defined as women of childbearing potential (WOCBP).

Highly Effective Contractive Methods

A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly. This includes implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or a vasectomized partner. A vasectomy or a condom used with a spermicide is a medically acceptable form of birth control for males

Contraception Guidance

Male Subjects

Male subjects 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.

Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 4 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

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

Male subjects 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 Subjects

Female subjects 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 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 subject.*
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 subjects 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 1 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

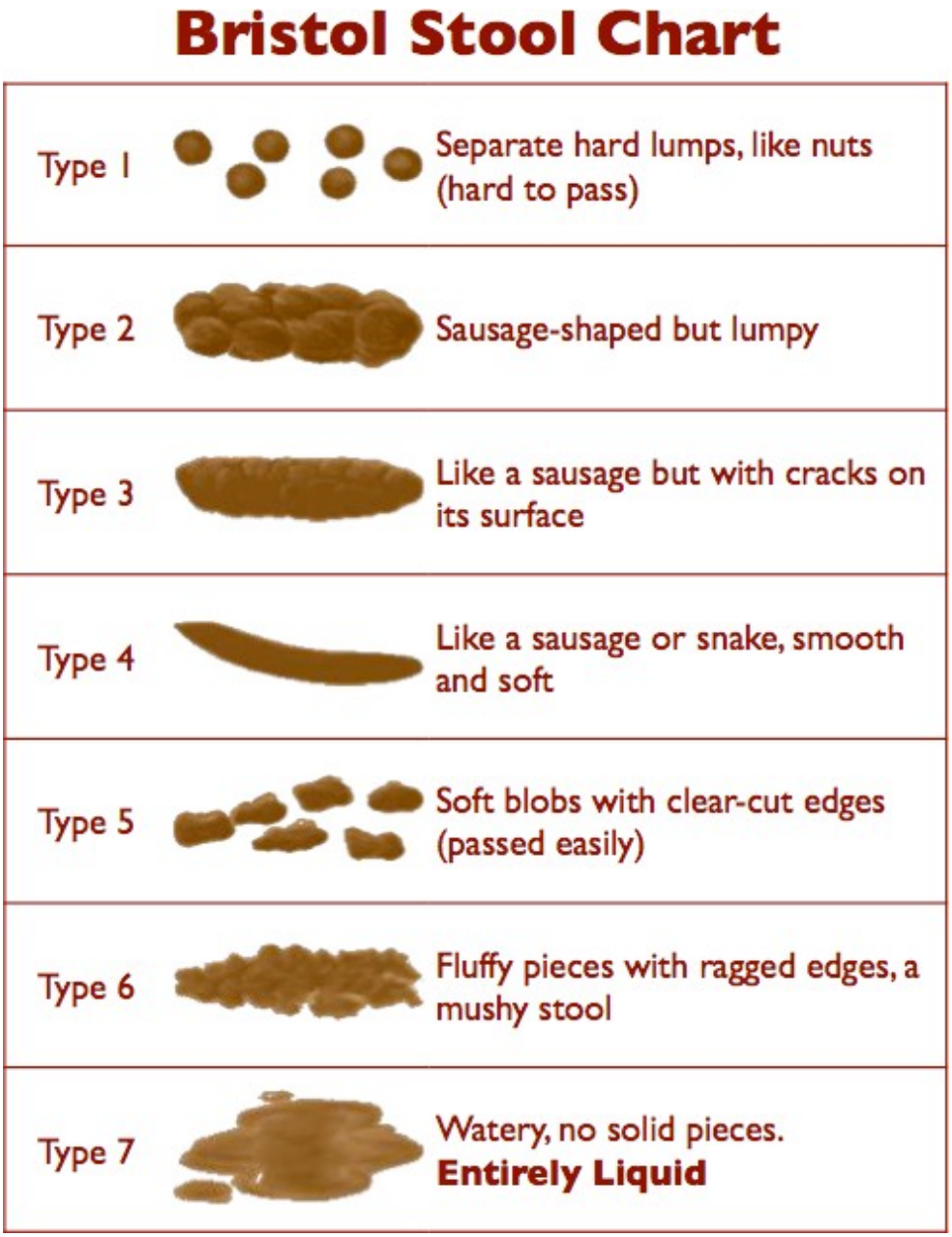
Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject 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 fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject 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 subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject 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 fetal 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. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Bristol Stool Chart



10.6. Appendix 6 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
CDAD	*Clostridioides difficile*-associated diarrhea
CDI	*Clostridioides difficile* infection (formerly known as *Clostridium difficile*)
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
eCRF	Electronic Case report form
CRO	Contract Research Organization
DRE	Disease related event
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
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
GDPR	General Data Protection Regulation
GI	Gastrointestinal
hCG	Human Chorionic gonadotropin
HEOR	Health Economic Outcomes Research
HIPAA	Health Insurance Portability and Accountability Act
HHC	Home Healthcare
HRT IB	Hormone replacement therapy Investigator's Brochure

IBD	Inflammatory bowel disease
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
IUD	Intrauterine contraceptive device
IUS	Intrauterine system
IVIG	Intravenous immunoglobulin
LLOQ	Lower limit of quantification
MCH MCV	Mean Corpuscular Haemoglobin Mean Corpuscular Volume
MIC	Minimum inhibitory concentration
MITT	Modified intention-to-treat
NOAEL	No observable adverse effect level
PD	Pharmacodynamics
PHI	Protected Health Information
PK	Pharmacokinetics
PP	Per protocol
PRO	Subject 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
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Sustained clinical response
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOA	Schedule of Activities
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
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

10.7. References

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