Sponsor Name:	Vedanta Biosciences, Inc.
Protocol Number and Title:	VE303-002 A Double-Blind Placebo-Controlled Phase 2 Study of VE303 for Prevention of Recurrent *Clostridium (Clostridioides) Difficile* Infection
Protocol Version and Date:	Protocol Version 7.0
Author(s):	[redacted]
SAP Version:	2.0
SAP Version Date:	15 July 2021

Version: 2.0 **Version Date: 15 July 2021**

APPROVALS

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Vedanta Biosciences, Inc.	
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[redacted]	Date (dd-Mmm-yyyy)
[redacted]	
[redacted]	Date (dd-Mmm-yyyy)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CCNA	cell cytotoxicity neutralization assay
CDI	*Clostridioides difficile* infection
CFU	colony forming unit(s)
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CP	conditional power
CRE	carbapenem-resistant Enterobacteriaceae
CRO	contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EIA	enzyme immunoassay
ESBL	extended-spectrum beta-lactamase
FAS	full analysis set
FDA	Food and Drug Administration
GDH	glutamate dehydrogenase antigen
HIV	human immunodeficiency virus
IA	interim analysis
ICH	International Conference for Harmonisation
kg	kilogram
KM	Kaplan-Meier
MAR	missing at random

Abbreviation	Description
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
m	meters
mg	milligram
MNAR	missing not at random
pCDI	primary *C. difficile* infection
PCR	polymerase chain reaction
PPS	per-protocol set
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
QID	four times a day
rCDI	recurrent *C. difficile* infection
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SoC	system organ class
SOC	standard-of-care
SSR	sample size re-estimation
TEAE	treatment-emergent adverse event
TLF	table, listing and figure
VRE	vancomycin-resistant enterococci
WBC	white blood cell

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on protocol VE303-002, Version 7.0, dated 15 July 2021 and its associated electronic case report forms (eCRF) Version 6.0, dated 08 July 2020.

This SAP may contain modifications to the analysis plans described in the protocol, and thus serve as the overriding document describing the statistical analysis to be performed. Any changes from the SAP will be presented in the Clinical Study Report (CSR).

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings (TLFs).

2.2. TIMINGS OF ANALYSES

Besides the final analysis for the CSR, there are 3 interim analyses (IAs) planned for study administrative purposes only, to provide input to Vedanta senior management regarding business and development strategy. The results of the administrative IAs will not have any impact on the design or conduct of the protocol. These 3 administrative IAs will be performed after at least 24 subjects complete 8 weeks of the study, after at least 39 subjects complete 8 weeks of the study, and after at least 54 subjects complete 8 weeks of the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective is to determine a recommended VE303 dose regimen(s) for evaluation in a Phase 3 study based on safety and efficacy, as indicated by the *Clostridioides difficile (C. difficile)* infection (CDI) recurrence rate.

3.2. SECONDARY OBJECTIVES

Secondary objectives are to characterize VE303 colonization and changes in the fecal microbiome.

3.3. BRIEF DESCRIPTION

3.3.1. Study Design

As designed, VE303-002 is a Phase 2, randomized, parallel-arm, double-blind, placebo-controlled, dose-selection study to evaluate the safety, microbiota changes, and efficacy of VE303 in the prevention of subsequent CDI-associated diarrhea compared with placebo following completion of a successful course of standard-of-care (SOC) antibiotics for subjects with primary *C. difficile* infection (pCDI) at high risk for recurrence or subjects with recurrent *C. difficile* infection (rCDI).

Eligible subjects are randomized into 4 treatment groups in a 2:1:2:1 ratio to receive VE303 high dose (10 capsules): placebo high dose (10 capsules): VE303 low dose (2 capsules): placebo low dose (2 capsules), respectively.

The following is the design of the study, per Study Protocol v6.0, dated 18 September 2019.

Approximately 146 to 300 subjects were anticipated for enrollment, depending on results of an IA and sample size re-estimation (SSR), which was planned to be performed when safety and efficacy data up to and including the Week 8/Day 56 follow-up visit were available for at least 62 evaluable subjects.

A data monitoring committee (DMC), which includes independent clinicians with knowledge of the target population, a biostatistician, and Sponsor representatives, was established to review accruing results and safety and to make recommendations based on results of the IA and SSR.

Investigators and study subjects will remain blinded for the duration of the study period. Similarly, the Sponsor study clinical operations team that interacts with the sites and the database remain blinded until the final analysis dataset is cleaned and unblinded.

The DMC was to be unblinded for the IA to allow for analysis of results (safety and efficacy) and to provide a recommendation to potentially discontinue one of the VE303 dosing arms based on safety and/or an observed lack of efficacy, and/or to potentially increase the sample size.

As described in the protocol, some members of the Sponsor team were to be unblinded after an IA to enable dose selection decisions and/or possible changes in the overall development plan for VE303, as outlined in the protocol's statistical methods and DMC Charter.

If the decision were made to drop an inferior VE303 dose treatment arm based on the IA, enrollment into that arm was to stop but subjects already randomized to that arm were to continue on study with no change to their treatment.

Randomization per Version 6 of the protocol was to assign subjects into stratification groups by:

- number of previous CDI episodes at Baseline (0 vs ≥ 1 episodes, excluding the qualifying episode; i.e., Inclusion criterion 2a vs 2b/2c subjects)
- SOC antibiotic treatment received (non-vancomycin [fidaxomicin or metronidazole] or an alternative oral vancomycin dosing regimen vs the standard four-times-per-day (QID) vancomycin dosing [this category will include subjects who receive vancomycin QID on at least the last day of treatment]), and
- results of CDI laboratory diagnostic method (free toxin [enzyme immunoassay (EIA) for Toxin A/B or cell cytotoxicity neutralization assay (CCNA)] vs other [polymerase chain reaction (PCR)/cytotoxic culture if enzyme immunoassay (EIA) for Toxin A/B and/or CCNA results are negative or not available]).

Note that prior to Version 6 of the protocol, the randomization stratification was defined as:

- Per Version 2 of the protocol, stratification by two age groups (≤ 65 years and > 65 years) and by number of previous CDI episodes at Baseline (2 to 3 and > 3 occurrences, inclusive of the qualifying episode).
- Per Version 3 of the protocol, stratification by age group (≤ 65 years and > 65 years), by number of previous CDI episodes at Baseline (2 to 3 and > 3 occurrences, inclusive of the qualifying episode), and by SOC antibiotic treatment received (non-vancomycin [fidaxomicin or metronidazole] or tapered vancomycin vs vancomycin QID).
- Per Version 4 of the protocol, Stratification by age group (≤ 65 years and > 65 years), by number of previous CDI episodes at Baseline (2 to 3 and > 3, inclusive of the qualifying episode), and SOC antibiotic treatment (non-vancomycin [fidaxomicin or metronidazole] or an alternative vancomycin dosing regimen vs vancomycin QID [subjects receiving vancomycin QID on at least the last day of treatment]).
- Per Version 5 of the protocol, stratification by 1) number of previous CDI episodes at Baseline (0 vs ≥ 1 episodes, excluding the qualifying episode; i.e., Inclusion criterion 2a vs 2b/2c subjects), and 2) by SOC antibiotic treatment received (non-vancomycin [fidaxomicin or metronidazole] or an alternative vancomycin dosing regimen vs vancomycin QID)

On the last planned day of SOC antibiotics for a qualifying episode of CDI, or no later than 1 day after completion of antibiotic dosing, subjects were to begin daily oral administration of placebo or VE303 (both at low and high doses) for 14 consecutive days.

The first dose of the study drug was to be administered under the supervision of study personnel at the Day 1 visit. After the 14-day dosing period was completed, follow-up was to be performed every 2 to 4 weeks for 24 weeks after the first dose of study drug.

3.3.2. Changes in Analyses from Original Protocol

Recruitment for Study VE303-002 was far slower than planned, in spite of expansion of the eligibility criteria, changes in the diagnostic algorithm, and attempts to engage participating sites and investigators. During the first year of the study, enrollment averaged <2 subjects/month, which was significantly lower than the expectation at the onset of recruitment. The poor enrollment in the study was further exacerbated by the advent of the COVID-19 pandemic, when all the sites had to shut down completely for varying lengths of time.

In consultation with Vedanta senior leadership, thought leaders in the field, and external advisors that included the Vedanta Scientific Advisory Board, a decision was reached in Q2 2020 to forgo the planned IA and SSR and instead implement a series of unblinded administrative IAs. This decision was made to achieve overall business goals and in accordance with Section III of, "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic." This decision was in accordance with Protocol v6.0, Section 10.4, and subsequently outlined in further detail in correspondence with FDA (17 April 2020, SN0025, 1.11.3 Clinical Information Amendment):

> *"Additional interim analyses other than the one for dose selection and sample size re-estimation may be carried out to inform business and development strategy outside of this trial. There is no intention to alter the conduct of this trial based on any additional interim analysis other than the one planned for 62 subjects."*

Furthermore, the total sample size for the trial was re-evaluated. Per discussion with advisors on the Board of Directors and the Scientific Advisory Board, approximately 60 to 80 total subjects were deemed realistic, based on clinical consideration and not on statistical power calculations, given the external pressures on enrollment and were expected to be an appropriate size for internal decision-making and publication purposes.

These 3 administrative IAs will be performed after at least 24 subjects complete 8 weeks of the study, after at least 39 subjects complete 8 weeks of the study, and after at least 54 subjects complete 8 weeks of the study. Furthermore, Sensitivity Analysis 2 was added to the analysis plan.

A tabular summary of the original plan and revised plan is detailed below:

Note: a data cut-off for each Administrative IA pertains to Week 8 of last randomized subject in the group.

	Original Plan	Revised Plan	Comments
Total Sample Size	140-300	Approximately 60 to 80	
Admin IA#1	N/A	Minimum 24	
IA#1 SSR	62	N/A	SSR not to be performed under revised plan
Admin IA#2	N/A	Minimum 39	
Admin IA#3	N/A	Minimum 54	

This updated version of the SAP provides more detail on the approach for the administrative IAs, in addition to the final analyses, which are intended to understand the safety and clinical activity of VE303. The goal of the administrative analyses and final analysis is to define future development steps for VE303 in patients with rCDI, beyond this ongoing Phase 2 trial. The administrative analyses do not change the design, objectives, endpoints, or conduct of this Phase 2 study. The intent is to guide future business strategy and inform potential design of subsequent pivotal trials.

No unblinded data will be reviewed by those with day-to-day interactions for the trial (e.g., the DMC, investigators, Study Steering Committee, medical monitors, contract research organization [CRO] or the Vedanta project team) as a result of this strategy change.

3.4. SUBJECT SELECTION

Inclusion and exclusion criteria for study entry must be met prior to screening and randomization. See Section 5.0 of the protocol for the most recent list of eligibility criteria.

3.5. DETERMINATION OF SAMPLE SIZE

The original protocol was based on a planned 2-stage adaptive design with potential for sample size increase, where the total sample size was expected to range from 124 to 255 evaluable subjects (approximately 146 to 300 randomized subjects, accounting for a 15% non-evaluable rate) depending on whether the sample size was to be increased after interim analysis.

As per Section 3.3.2, a total revised sample size of approximately 60 to 80 subjects was deemed appropriate for the study in view of poor enrollment and external events from the pandemic.

3.6. TREATMENT ASSIGNMENT & BLINDING

On the last planned day of SOC antibiotic administration for a qualifying CDI episode, or no later than 1 day after completion of antibiotic dosing, eligible subjects will be randomized into 4 treatment groups in a 2:1:2:1 ratio to receive 1 of 2 placebo doses or 1 of 2 VE303 doses daily

for 14 consecutive days as outlined in Table 3-1. Each study dose will comprise 2 or 10 capsules per day administered orally (see protocol Section 6.3). Subjects will ingest the first dose in the clinic on Day 1 and subjects will remain at the study site for at least 30 minutes after the first dose for monitoring of potential adverse events (AEs).

Table 3-1: Planned Study Arms

Study Arm	VE303 Daily Dose	VE303 Total Dose Over 14 Days	Number of Capsules Ingested Per Day (Active/Placebo)
VE303 (low)	1.6×10^9 CFU	2.2×10^{10} CFU	2 (2/0)
VE303 (high)	8.0×10^9 CFU	1.1×10^{11} CFU	10 (10/0)
Placebo ("low")	Not applicable	Not applicable	2 (0/2)
Placebo ("high")	Not applicable	Not applicable	10 (0/10)

Abbreviations: CFU = colony-forming unit(s)

Randomization will be used to avoid bias in the assignment of subjects to double-blind treatment (VE303 or placebo) and to increase the likelihood that known and unknown subject characteristics will be evenly distributed between the treatment groups.

After all Screening procedures and assessments have been performed and eligibility has been confirmed on Day 1, a centralized Interactive Web Response System will assign each subject a randomization number and subjects will receive study drug.

Investigators and subjects will remain blinded for the duration of the study period.

Unblinding of study drug assignment may be requested in an emergency if unblinding is considered necessary for the medical management of a subject. The Investigator will discuss the circumstances for the requested unblinding with the Sponsor's Medical Monitor. Emergency unblinding without the Medical Monitor's input should occur only if knowledge of study drug assignment will affect the immediate workup or treatment of an AE. Communications related to unblinding will be documented, including the date, time, and reason for the requested unblinding.

3.7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Events per Table 7-1 in protocol v6 is as follows:

	Screening: Start of SOC Antibiotics[a, b]	**Study Drug Administration Period**					**Postdose Follow-Up Period**					
Study Day **Assessment[c]**	-22	1[d]	2–6[q]	7	8–13[q]	14 (+ 1 day)/ EOT	28 (± 3 days) (Week 4)	56 (± 3 days) (Week 8)	84 (± 7 days) (Week 12)	112 (± 7 days) (Week 16)	140 (± 7 days) (Week 20)	168 (± 7 days) (Week 24/EOS/ET)
Informed consent	X											
Confirm eligibility criteria	X	X[k]										
Medical history	X											
Medications [e]	X											
Physical examination [f]	X	X				X	X	X				X
Height	X											
Weight [g]	X	X				X	X	X				X
Vital signs [h]	X	X		X		X	X	X				X
12-lead ECG [i]	X						X					
Hematology/Chemistry	X	X		X		X	X	X				X
Exploratory serum	X					X		X				X
Urinalysis	X					X						
Pregnancy test [j]	X	X										
Randomization [k]		X										
Study drug dosing [c, l]		X										
C. difficile testing [m, n]	X[m]											
Stool microbiota composition [n]	X	X		X		X	X	X				X
VE303 detection [n]	X	X		X		X	X	X				X
Antibiotic resistance gene detection [n]	X	X		X		X	X	X				X
Stool antibiotic concentrations [n]		X		X								
Stool metabolomics evaluation [n]	X	X		X		X		X				
Glycerol-preserved stool culture [n]	X	X				X		X				X

	Screening: Start of SOC Antibiotics[a, b]	**Study Drug Administration Period**					**Postdose Follow-Up Period**					
Study Day **Assessment**[c]	-22	1[d]	2–6[q]	7	8–13[q]	14 (+ 1 day)/ EOT	28 (± 3 days) (Week 4)	56 (± 3 days) (Week 8)	84 (± 7 days) (Week 12)	112 (± 7 days) (Week 16)	140 (± 7 days) (Week 20)	168 (± 7 days) (Week 24/EOS/ET)
Stool culture for whole genome sequencing [n]	X	X				X	X	X				X
Stool/fecal calprotectin extraction [n]		X				X	X	X				X
PROMIS® questionnaire [o]		X		X		X						
Adverse events [p]	X											
Telephone follow-up		X [q]							X	X	X	

Abbreviations: AE = adverse event; CDI = *C. difficile* infection; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; LAR = legally authorized representative; PCR = polymerase chain reaction; SOC = standard of care; ET = Early Termination

a Once identified as potential study candidates, subjects or their LAR will sign an informed consent form to enable collection of a stool sample to confirm the qualifying event of CDI recurrence in accordance with eligibility criteria.

b Upon confirmation of CDI recurrence, subjects will be evaluated for eligibility criteria.

c All tests/assessments scheduled on in-clinic dosing days will be performed prior to study drug administration.

d Day 1 (i.e., the day of the first dose of study drug) is the beginning of the study drug administration period, which will begin on the last planned day of SOC antibiotic administration for a qualifying CDI episode, or no later than 1 day after completion of antibiotic dosing. Day 1 tests/assessments will be considered baseline. The Screening results must be available for confirmation of eligibility. Vital signs and physical examinations should be performed on Day 1; tests/assessments must be performed prior to study drug administration.

e Medications administered within 14 days prior to Screening and/or on study will be recorded continuously for the duration of each subject's study participation.

f A complete physical examination will be performed during Screening; subsequent physical examinations must include abdominal examinations performed by the study physician, with limited symptom-directed examinations performed for other organ systems.

g To be collected in the same manner each time – without heavy items/shoes/bulky clothing.

h Includes pulse, blood pressure, and body temperature. Subjects are required to remain in the supine position for at least 3 minutes prior to obtaining vital signs. On Day 1, vital signs will be measured prior to administration of study drug.

i Additional ECGs may be performed if clinically indicated.

j For females of childbearing potential, serum pregnancy testing will be performed during Screening; a rapid urine pregnancy test will be performed at the study site on Day 1 prior to administration of study drug.

k After all Screening assessments and procedures have been performed and eligibility has been confirmed on Day 1, subjects will be randomized and receive the first dose of blinded study drug.

l The study drug administration period is from Day 1 to Day 14, inclusive. On Day 1, study drug will be administered under the supervision of study personnel, and subjects will remain at the study site for at least 30 minutes after the first study drug dose for monitoring of potential AEs. On Day 1, the subject diary will be given to each subject and the subject will be instructed to complete the diary for study drug accountability and compliance.

m A stool sample or documentation of recent *C. difficile* testing must be collected and/or submitted as soon as a potential qualifying CDI episode is identified. Ideally, this sample will be obtained prior to starting SOC antibiotics for CDI; however, if SOC antibiotics have been started, the stool sample must be collected no later than 72 hours after the first antibiotic administration. Every effort must be made to collect the diagnostic sample before SOC antibiotic therapy or within 24 hours after SOC antibiotic therapy initiation, whenever possible. Samples collected as part of SOC within this window may be submitted for the purpose of *C. difficile* diagnosis. Diagnostic tests may be performed at the local laboratory or at the central laboratory. Subjects with a positive test (either EIA for Toxin A/B or PCR or CCNA or toxigenic culture assay performed at the local laboratory or at the central laboratory) may be enrolled in the study. Confirmation of a positive local test by the central laboratory test is not required for subject enrollment, provided documentation of a local positive test is available. To ensure subjects are allocated to a proper stratum, an effort should be made to obtain and send a stool sample to the central laboratory for confirmation of toxin or toxigenic C. *difficile* prior to randomization.

n Stool samples must be sent to a central laboratory. The Day 1 stool sample must be collected prior to administration of any study drug. This sample should be collected predose on Day 1, if possible; however, if a subject cannot produce a stool sample predose on Day 1, a sample from up to 24 hours prior to Day 1 may serve as the Day 1 sample. Thereafter, if a subject cannot produce a stool sample on the planned day of a clinic visit or at the time of diarrhea that may indicate CDI recurrence (see Section 9.3.1 of the protocol), then a stool sample may be obtained within ± 24 hours of the visit/diarrhea event. However, if CDI recurrence is suspected after ingestion of the first dose of study drug, all attempts should be made to collect a stool sample before administration of antibiotics to treat the recurrence.

o PROMIS® gastrointestinal symptom questionnaires (see Appendix 3 of the protocol) are to be completed by each subject or LAR before the first dose of study drug on Day 1. Subsequently, questionnaires should be completed on Days 7 and 14. All attempts must be made to have questionnaires completed at approximately the same time of day at every time point.

p AEs will be collected continuously from the time of informed consent through Week 24/Day 168.

q Study personnel will telephone outpatient subjects daily during the 14-day study drug administration period to ensure dosing compliance; explore any concerns or issues with study drug ingestion, administration, handling or storage; capture potential AEs; review potential *C. difficile*-associated symptoms and assess the need for an unscheduled visit or stool test for CDI; remind subjects to collect stool to bring to their next clinic visit (if applicable); and answer any questions that the subject may have. If a subject is inpatient or attending a site visit on a scheduled telephone follow-up day, this contact will be performed in person, when possible. Telephone follow-up may be omitted on weekends or public holidays if this is necessary for logistical reasons. If a subject is discovered to have had an SAE or a recurrence of diarrhea at any time, an unscheduled visit must be arranged as soon as possible.

4. ENDPOINTS

4.1. PRIMARY AND SECONDARY EFFICACY ENDPOINTS

The primary efficacy endpoint is the proportion of subjects with CDI recurrence before or at Week 8 (i.e., 8 weeks after the first dose of study drug). See Section 8.1, Primary Efficacy Endpoint and Analysis, for more details regarding the definition of an on-study CDI recurrence.

Secondary endpoints include the proportion of subjects without:

- CDI recurrence before or at Week 4 (4 weeks after the first dose of study drug)
- CDI recurrence before or at Week 12 (12 weeks after the first dose of study drug)
- CDI recurrence before or at Week 24 (24 weeks after the first dose of study drug)

4.2. SAFETY ENDPOINTS

- Incidence of AEs
- Laboratory results
- Vital signs
- Electrocardiogram (ECG)
- Physical examination findings

4.3. PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS

Pharmacodynamic and pharmacokinetic endpoints include:

- Fecal VE303 component bacteria colonization abundance and duration
- Changes in fecal microbiota diversity and taxonomic composition
- Changes in the fecal metabolomic profile, including short chain fatty acids and bile acids

5. ANALYSIS POPULATION

5.1. FULL ANALYSIS SET (FAS)

All subjects who were randomized and received at least 1 dose of study drug. Subjects will be classified according to the planned study drug assignment. The FAS will be the default analysis set for all efficacy analyses, unless otherwise specified.

5.2. PER-PROTOCOL ANALYSIS SET (PPS)

All subjects in the FAS who had no major protocol deviations. The PPS will be used for the primary and secondary efficacy endpoint analyses. Major protocol violations are defined as those that may have a substantial impact on efficacy assessments. The criteria to be used for excluding subjects from the PPS population will be determined before database lock and will be documented. The PPS analysis may be performed only for the primary and secondary efficacy endpoints, to provide supportive evidence for efficacy.

5.3. SAFETY ANALYSIS SET (SAS)

All subjects who were randomized and received at least 1 dose of study drug. Subjects will be classified according to the actual study drug assignment. The SAS will be the primary set for the analysis of safety data.

5.4. PROTOCOL DEVIATIONS

Protocol deviations will be identified during monitoring visits, discussions with sites, correspondence, manual review of data, and programmatically within the iMedidata RAVE Electronic Data Capture system. Protocol deviations for all subjects who signed an informed consent will be entered into [redacted]Clinical Trial Management System. The deviation categories based on protocol v7.0 are:

- Violation of inclusion and/or exclusion criteria
- Violation of the informed consent process
- Non-compliance with dosing, such as wrong treatment (kit assignment), incorrect dose, or not taking all capsules by 4:00pm each day
- Missing data for the primary endpoints
- Administration of prohibited concomitant medications
- Not tracking diarrhea events
- Not collecting protocol-required samples associated with rCDI
- Treating subject with SOC antibiotic for an on-study CDI recurrence without a positive Toxin A/B or CCNA result (subsequently added as permissible and included

in a sensitivity analysis, as described in Section 17.1.2 of SAP v1.0 and Section 14.1.2 of this document)

- Subjects who develop withdrawal criteria but were not withdrawn
- Any deviation related to COVID-19

A protocol deviation is any noncompliance with the clinical study protocol, International Conference for Harmonisation (ICH) Good Clinical Practices, or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. Deviations must be reviewed by the site, clinical research associate, Sponsor, and designee, as appropriate for potential corrective actions development.

All deviations will be reviewed by Vedanta and [redacted] medical and clinical (including statisticians) personnel and classified as either minor or major deviations prior to database lock and unblinding. Protocol deviations will be summarized by presenting all incidences of protocol deviations counted separately in each deviation category as a major or minor deviation by treatment group. The total count of protocol deviations within each treatment group will be used as the denominator for percentages in this table.

A listing of all protocol deviations by subject and deviation category will be provided, indicating which are major deviations as determined before unblinding.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- Descriptive statistics, including the numbers and percentages for dichotomous or categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided.
- Unless otherwise specified, summaries will be presented for each treatment group (VE303 high dose, VE303 low dose, and Placebo), where placebo subjects will be from Placebo low dose and Placebo high dose combined.
- Inferential statistical analyses of the primary and secondary clinical efficacy endpoints will be conducted as outlined below. All comparisons will be between each VE303 dose versus placebo.
- Continuous variables will be summarized using the number of subjects with evaluable data, mean, standard deviation (SD), median, minimum, and maximum values. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD.
- Categorical variables will be summarized using the number of observations (n), frequency and percentage of subjects. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.
- Unless stated otherwise, the percentages will be based on the number of non-missing observations, and the header will contain the number of subjects in the treatment group. There will be a row for the number of non-missing observations in the table (at each time point, if required) for each variable being summarized.
- Unless otherwise stated, all formal tests of hypotheses for the primary and secondary endpoints will be assessed one-sided at alpha=0.05 to be consistent with the one-sided overall power calculations.
- Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as ‘$p<0.001$’ and p-values greater than 0.999 will be presented as ‘$p>0.999$’.
- All relevant subject data will be included in listings and sorted by treatment, subject number, and visit, as applicable, for all randomized subjects.
- Unscheduled or repeat assessments will not be included in summary tables, unless otherwise specified, but they will be included in the subject listings.

- All TLFs will include footers that identify the name of the program that created the item, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

6.2. KEY DEFINITIONS

6.2.1. Study Day

Study Day 1 is defined as the randomization day. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Before the day of study drug administration, study days are numbered sequentially with negative values (Day -2, Day -1, etc.). There is no Day 0.

6.2.2. Baseline Values

Baseline values will be taken as the last assessments before the first dose of study drug on Day 1. In general, these will be taken from the pre-dose assessment on Day 1.

6.2.3. Completion of Study

A subject will be flagged as having completed the study if the question "Did subject complete the study per protocol?" on the End of Study eCRF page is answered as Yes.

6.3. MISSING DATA

Every effort will be made to collect all data at specified time points according to the schedule of study events. Reasons for withdrawal from the study will be recorded on the eCRF.

See Section 7.4 for imputation of partial dates for prior and concomitant medications.

See Section 9.2 for imputation of partial dates for adverse events.

In general, missing values will not be imputed for the primary analysis of the primary efficacy endpoint analysis. However, see 8.1 for further imputation rules for treating dropouts as a treatment failure (as having a recurrence at Week 8).

6.4. ANALYSIS VISIT WINDOWS

For the primary efficacy endpoint of CDI recurrence before or at Week 8, and secondary endpoints of CDI recurrence up to 4 weeks, 12 weeks, and 24 weeks after treatment, CDI recurrences will be included in the analyses for the specified endpoints as follows:

Endpoint	Recurrences Included in Analysis
CDI recurrence up to 4 weeks after treatment	Up to Day 35

CDI recurrence up to 8 weeks after treatment	Up to Day 63
CDI recurrence up to 12 weeks after treatment	Up to Day 91
CDI recurrence up to 24 weeks after treatment	Up to Day 175

6.5. STUDY DRUG EXPOSURE

Study drug exposure will be summarized as the total number of capsules taken with counts and percentages of subjects by treatment group. The summary will be presented for the FAS and SAS populations.

The high dose of VE303 is 10 capsules per day administered orally for 14 days, for a maximum VE303 daily dose of 8.0×10^9 colony-forming units (CFU) and a maximum total dose over 14 days of 1.1×10^{11} CFU. The low dose of VE303 is 2 capsules per day administered orally for 14 days, for a maximum VE303 daily dose of 1.6×10^9 CFU and a maximum total dose over 14 days of 2.2×10^{10} CFU. High dose of Placebo is 10 capsules per day administered orally for 14 days, and low dose Placebo is 2 capsules per day administered orally for 14 days. The first dose of the study drug will be administered under study personnel supervision at the Day 1 visit.

6.6. POOLING OF SITES

All sites will be pooled together for analysis purposes.

6.7. POOLING OF PLACEBO

For the purposes of both interim and final analyses, the 2 placebo arms will be pooled to represent a single treatment group.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Summary tables for demographics and baseline disease characteristics, medical history, and prior and concomitant medication will be summarized by treatment group for the FAS.

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Summary statistics will tabulate the number and percentage of subjects who are screened, screen failures, randomized, received study drug, completed the study, who prematurely discontinued the study prior to Weeks 2, 4, 8, 12, 16, 20, and 24, and who prematurely discontinued the study overall, together with reasons for discontinuation by treatment group at each of these timepoints. The number and percentage of subjects included in each of the analysis populations will be presented. No statistical testing will be performed on these data. The number of randomized subjects in the FAS of each treatment group will be used as the denominator for percentages.

A listing of subject disposition will be presented.

7.2. DEMOGRAPHIC AND OTHER BASELINE DISEASE CHARACTERISTICS

Demographics (age, age group, sex, race, ethnicity, childbearing potential, height, weight, body mass index [BMI]) and baseline disease characteristics (number of CDI recurrences prior to and including the current episode at baseline, number of previous CDI episodes at Baseline (0 vs ≥1 episodes, excluding qualifying episodes), SOC antibiotic treatment (non-vancomycin [fidaxomicin or metronidazole] or an alternative oral vancomycin dosing regimen vs vancomycin QID, and results of CDI laboratory diagnostic method (free toxin or other) will be summarized descriptively by treatment group for the FAS and SAS.

Age group will be categorized as 18 to ≤64 years, 65 to ≤74 years, and ≥75 years old.

BMI will be calculated using the standard measures of weight in kilograms (kg) and height in meters (m) as:

$$\text{BMI (kg/m}^2\text{)} = \text{[Weight (kg)]/[Height(m)]}^2$$

Demographic and other baseline disease characteristics will be listed.

7.3. MEDICAL HISTORY

The number and percentage of subjects with medical history by system organ class (SoC) and preferred term (PT) will be produced for subjects in the FAS by treatment group. Medical history will be sorted in alphabetical order of SoC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, V21.1. For the summary tables, a subject may appear more than once if the subject has more than one medical history finding coded under different SoC terms or more than one medical history finding with a different PT under the same SoC term. However, the subject will be counted only once in the overall category.

A table for CDI medical history will also be presented and include Yes/No counts for "Did subject have at least one episode of CDI, prior to the current episode, within the last 6 months" and descriptive statistics for the number of CDI recurrences prior to baseline (including current episode).

A by-subject listing with coded SoC and PT along with verbatim eCRF term will also be provided.

7.4. PRIOR AND CONCOMITANT MEDICATION

Prior medications are defined as medications that started before the date of first dose. Any medication that started on the first date of dosing will not be considered prior. Concomitant medications are defined as all medications (excluding study treatment) taken on or after the first date of dosing. This also includes medications ongoing on the first dosing date. Medications that started before the date of first dose and are ongoing after the date of first dose will be considered as both prior and concomitant.

Partial start dates in prior and concomitant medications will be imputed with a conservative algorithm, to the first day of the month (if missing day) or to the first month of the year (if missing month). Partial end dates in prior and concomitant medications will be imputed to the last day of the month (if missing day) or the last month of the year (if missing month).

Prior and concomitant medications will be included in the same listing including a column indicating if medication is prior, concomitant, or both. Medications will be coded by using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug name according to the World Health Organization Drug Version SEP2018 GLOBAL B3 dictionary. Separate summary tables will be provided for prior and concomitant medications for the FAS, presenting the number and percentage of subjects by treatment group, and will be sorted in alphabetical order of ATC Level 2 and then by PT in the overall column. For each subject, the medication will be counted only once within a given ATC level 2 and only once within a given preferred drug name level. A subject may appear more than once if he/she has more than one concomitant medication coded under different ATC categories, however, the subject will be counted only once in the overall category.

All medications will be listed.

7.4.1. Antibiotic Medication

A separate by-treatment summary table and a separate by-subject listing will be provided for antibiotic medication taken within 60 days prior to baseline and for concomitant antibiotic medication taken in the FAS.

8. EFFICACY

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the proportion of subjects with CDI recurrence before or at Week 8 (i.e., 8 weeks after the first dose of study drug). An on-study CDI recurrence is defined as an episode of diarrhea consistent with diarrhea due to *C. difficile* infection, which includes a stool sample positive for free toxin (EIA for Toxin A/B or CCNA) per test performed at the local laboratory or at the central laboratory. An on-study CDI recurrence may occur at any time after administration of the first dose of study drug.

- If recurrent CDI is suspected, a stool sample must be collected for laboratory confirmation. Regardless of the test(s) performed at the local laboratory, samples must be collected from all subjects during each episode of diarrhea for CDI testing at a central laboratory.
- After an initial sample is collected for suspected recurrence, it is required to collect and submit samples on subsequent day(s) if the laboratory test results are not available or negative for free toxin (EIA for Toxin A/B or CCNA) before initiating antibiotic therapy.

The difference in the proportion of subjects with CDI recurrence before or at Week 8 between each VE303 treatment group and placebo will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) method. Stratification will involve the stratification factors as determined from the clinical database, i.e., number of previous CDI episodes at Baseline (0 vs ≥1 episodes, excluding qualifying episodes), SOC antibiotic treatment (non-vancomycin [fidaxomicin or metronidazole] or an alternative oral vancomycin dosing regimen vs vancomycin QID), and results of CDI laboratory diagnostic method (free toxin or other).

Stratification factors are determined at the time of randomization to randomize subjects to the treatment groups. However, in order to assess any possible post-randomization changes to the stratification factor values (e.g., the number of previous CDI episodes for a subject determined at the time of randomization could have been updated after randomization), a table of randomization stratification factors as determined at the time of randomization and as determined from the clinical database will be presented by treatment group. Any discrepancies between stratification factor values as randomized versus as determined by the clinical database will be presented descriptively with counts and percentages by treatment group.

The number and percentage of subjects with confirmed CDI recurrence, along with 90% C,I will also be presented by treatment group descriptively, as well as each VE303 treatment difference from placebo, along with 90% CI, for descriptive purposes. This primary efficacy endpoint analysis will be presented for the FAS and PPS.

A similar CDI recurrence rate table as described above will be presented for subjects who were exposed to other concomitant antibiotic treatment to treatment infections other than CDI (i.e., not used to treat CDI) prior to their CDI recurrence for the FAS. This table will exclude any subject

who took an antibiotic other than fidaxomicin, metronidazole, or vancomycin prior to their recurrence.

Subgroup analysis of the primary efficacy endpoint will be presented by age group (18 to ≤64 years, 65 to ≤74 years, and ≥75 years), and by each of the randomization stratification factors using the FAS.

In addition, the number of subjects with CDI recurrences up to Week 8 presented by randomization stratification factor, a tabular summary of testing results (positive, negative, or unavailable) for all suspected CDI recurrences, a tabular summary of all diarrhea episodes treated with antibiotics, and a table summarizing the number of responders by randomization stratum will be presented by treatment group.

The start date of a CDI recurrence will be defined as follows:

- If the subject presents on Day X with 8 stools (Bristol type 7) and the central lab Day X stool sample is reported after Day X as positive, then the CDI recurrence date is the date of Day X
- If the Day X stool sample is reported as negative but a subsequent stool sample is reported as positive sometime after Day X, then the CDI recurrence date should be reported as the earliest date for the positive stool test.

In general, missing values will not be imputed for the primary analysis of the primary efficacy endpoint analysis. However, additional supportive analyses will be performed in which the following imputation rules will be applied, with dropouts treated as a failure (as having a recurrence at Week 8):

Put imputation rules here for dropouts treated as failures.

- Discontinuing early for any reason, including withdrawal of consent: For subjects who have not experienced a recurrence prior to Week 8 and who discontinued for any reason prior to the Week 8 visit, impute for these subjects a recurrence at Week 8. Per the current recurrence counting algorithm applied within the efficacy tables, this imputed recurrence at Week 8 will be carried forward to all subsequent weeks in the table.

8.1.1. Sensitivity Efficacy Analyses

Sensitivity analyses will be conducted on the following efficacy variables for the FAS and PPS:

- Sensitivity Analysis I: In addition to the CDI recurrence definition for the primary efficacy endpoint, the CDI recurrence definition for Sensitivity I will also include any recurrence that was diagnosed with a positive PCR test (including cytotoxicity assay) and treated with an antibiotic that targets *C. difficile*

- Sensitivity Analysis II: In addition to the CDI recurrence definition for the primary and Sensitivity I efficacy endpoints, the Sensitivity II CDI recurrence definition will include any recurrence, in the absence of laboratory confirmation, that is treated with an antibiotic that targets *C. difficile*.

In addition, Sensitivity I and II analyses will each be presented by age group and for the number of subjects with CDI recurrences up to Week 8 by randomization stratification factor for the FAS.

8.2. SECONDARY EFFICACY ANALYSES

8.2.1. Recurrence of CDI up to 4, 12, and 24 Weeks Post-Treatment

The number and percentage of subjects without recurrence of CDI before or at Week 4, 12, and 24 weeks after start of study drug will each be presented by treatment group for the FAS using the same method described for the primary analysis in Section 8.1.

8.2.2. Time to Recurrence of CDI

For the primary efficacy analysis, as well as for the Sensitivity I and Sensitivity II analyses, the time to CDI recurrence will be summarized by treatment group for the FAS only using the median and 25th and 75th percentiles from Kaplan-Meier (KM) analysis. The 90% confidence intervals (CIs) for the median will also be presented. Subjects who complete the study and do not experience a CDI recurrence by the end of the Follow-up Period will be censored on the date of last contact. Subjects who are lost to follow-up or who terminated the study prematurely before experiencing a CDI recurrence will be censored on the date of last contact. Subjects who die before having a CDI recurrence will be censored on the date of death.

The distributions of time to CDI recurrence for each treatment group will be plotted and the differences in these distributions between Placebo and each VE303 treatment group will be tested for significance using the stratified log-rank test. The number of subjects at risk and the number of subjects with a recurrence event will be presented graphically. The KM method will be applied to estimate the curves for each treatment group. Median time to recurrence and corresponding 90% CI's will be calculated and presented in a table.

8.3. EXPLORATORY ANALYSES

8.3.1. Microbiological Outcomes

Final analysis results from stool microbiota composition and VE303 detection analyses will be presented in by-subject listings and graphs and summarized by treatment group and study day. The atypical nature and complexity of these analyses requires the use of software tools developed by the Sponsor. Any exploratory microbiological analyses not included in the data outputs will be reported separately and will not be included in the main CSR.

Tabular and/or graphical summaries for the microbiome and VE303 detection analyses will be produced for VE303 strain presence, VE303 strain abundance, community diversity (Shannon Index, and Species Richness calculations), and relative abundance of all species detected in the sample. In addition, an analysis will be performed to evaluate the longitudinal microbiome changes within each subject and within each study arm, including changes in diversity over time, changes in microbiome species over time grouped by phylum, and changes in VE303 strains over time (both presence/absence and relative abundance).

The Sponsor will also collect serum and stool samples (for stool antibiotic concentrations, metabolomics, antibiotic-resistant bacteria other than *C. difficile* [e.g., carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactamase (ESBL), or vancomycin-resistant enterococci (VRE)], and culture) from clinical study participants and may analyze them for possible exploratory purposes and biomarkers.

8.4. INTERIM ANALYSIS

Three IAs are planned for administrative purposes only. These 3 administrative IAs will provide input to Vedanta management regarding business and development strategy outside of the context of this study. The administrative IAs will be performed after at least 24 subjects complete 8 weeks of the study, after at least 39 subjects complete 8 weeks of the study, and after at least 54 subjects complete 8 weeks of the study. Further details of these administrative IAs are described in Section 3.3.2.

No unblinded review of the efficacy and safety data will be conducted by the independent DMC members.

8.5. HANDLING OF MISSING DATA

In general, missing values for the primary efficacy endpoint will not be imputed. See additional details in Section 8.1 for imputation rules for treating dropouts as having a CDI recurrence at Week 8.

9. SAFETY

All safety analyses will be conducted for the SAS, unless otherwise specified. Subjects will be analyzed according to the treatment they actually received, rather than to that which they were randomized. Data for placebo subjects will be presented by combining the Placebo High and Placebo Low treatment groups.

9.1. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Exposure will be assessed by treatment group for the total number of capsules taken and for the number of days study drug was taken (Last Dose Date – First Dose Date + 1).

Compliance will be presented descriptively by treatment group for the percentage of subjects who were ≥90% in compliance, the percentage of subjects who were 100% in compliance, and for the number of missed doses. Compliance will be calculated as:

Compliance (%) = (Number of capsules taken / Number of expected capsules taken) x 100.

9.2. ADVERSE EVENTS

Adverse events will be coded using MedDRA V21.1. All treatment-emergent AEs (TEAEs) from the start of study drug dosing will be collected. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug up to Week 24. Serious TEAEs and adverse events of special interest (AESIs) that started on or after start of study drug dosing will be considered TEAEs and will be included in separate summary tables and listings.

The following AE summaries will be presented by treatment group:

- An overall summary table, including the number and percentage of
  - TEAEs
  - TEAEs associated with COVID-19
  - Subjects with at least one TEAE
  - Subjects with no TEAEs
  - Study drug-related TEAEs
  - Subjects with study drug-related TEAEs
  - Serious TEAEs
  - Subjects with serious TEAEs
  - Serious TEAEs related to study drug
  - Subjects with serious TEAEs related to study drug
  - Treatment-emergent AESIs
  - Subjects with treatment-emergent AESIs
  - Treatment-emergent AESIs related to study drug

  - Subjects with treatment-emergent AESIs related to study drug
  - Severe TEAEs
  - Subjects with severe TEAEs
  - TEAEs leading to study drug discontinuation
  - Subjects with TEAE leading to study drug discontinuation
  - TEAEs leading to death
  - Subjects with TEAEs leading to death

- TEAEs by SoC and PT
- Serious TEAEs by SoC and PT
- Treatment-emergent AESIs by SoC and PT
- TEAEs leading to study drug discontinuation by SoC and PT
- TEAEs by SoC, PT, and maximum reported Common Terminology Criteria for Adverse Events (CTCAE) Grade
- Related TEAEs by SoC and PT

The following subject listings will be provided as a table:

- Deaths
- Serious TEAEs
- AESIs
- TEAEs leading to study drug discontinuation
- TEAEs associated with COVID-19

For all TEAE tables summarized by SoC and PT, a subject contributes only once to the count for a given TEAE on the SoC level and on the PT level within SoC. TEAEs will be sorted alphabetically, first by SoC and then by PT within the SoC.

A related AE is defined as a relationship of Definitely Related, Probably Related, Possibly Related or missing, and a non-related AE is defined as a relationship of Unlikely, Probably Not Related, or Definitely Not Related.

The following are considered AESIs due to the CDI indication under study and the nature of the investigational product (live bacteria) and potential for gastrointestinal or extraintestinal AEs:

- Any clinically significant (Grade 2 or higher) gastrointestinal AE considered related to study drug.
- Any clinically significant (Grade 2 or higher) bacterial infection considered related to study drug.

In the summary by maximum severity, subjects reporting AEs at different severities will be counted only once at the highest severity reported within an AE level (SoC or PT). Severity categories will include mild, moderate, severe, or medically significant but not immediately life-threatening, life-threatening consequences, and death related to AE. Any missing severity will be imputed as severe, which as a result, a subject would be counted as severe due to a missing severity, even if the subject reported similar events at a lesser degree of severity. The same logic will be applied to the related AEs.

Partial start dates in AEs will be imputed with a conservative algorithm, to the first day of the month (if missing day) or the first month of the year (if missing month). Partial end dates in adverse events will be imputed to the last day of the month (if missing day) or the last month of the year (if missing month). All AEs will be assigned on a worse case basis to TEAEs. For example, if the start date of an AE is missing or incomplete, it will be assumed to be a TEAE, except if the partial start date, say with known year, confirms otherwise.

No statistical tests will be performed.

A listing of all TEAEs will be provided.

9.3. LABORATORY EVALUATIONS

Laboratory parameters include:

Hematology:

Absolute Basophils, Absolute Eosinophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Neutrophils, Absolute Neutrophil Count, Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Parasites Blood, Platelets, Red Blood Cells (RBCs), White Blood Cells (WBCs)

Clinical Chemistry:

Albumin, Alkaline Phosphatase, Alanine Aminotransferase, Amylase, Aspartate Aminotransferase, Blood Urea Nitrogen, Calcium, Chloride, Creatinine, Direct Bilirubin, Gamma-Glutamyl Transferase, Glucose Serum, Potassium, Lactate Dehydrogenase, Lipase, Sodium, Phosphorus, Total Bilirubin, Human Chorionic Gonadotropin Quantitative

Urinalysis:

Amorphous Phosphate Crystals, Amorphous Urate Crystals, Bacteria, Bilirubin Crystals, Bilirubin, Blood, Calcium Carbonate Crystals, Calcium Oxalae Crystals, Coarsely Granular Cast, Clarity, Clue Cells, Color, Cystine Crystals, Finely Granular Cast, Glucose, Hyaline Cast, Ketones, Leukocytes, Mucous, Nitrite, pH, Protein, RBC Cast, RBCs, Renal Epithelial Cells, Specific Gravity, Spermatozoa, Squamous Epithelial Cells, Sulfonamide Crystals, Transitional Epithelial Cells, Trichomonads, Triple Phosphate Crystals, Uric Acid Crystals, Urobilinogen, Waxy Cast, WBC Cast, WBC Clumps, WBCs, Yeast

Stool Analysis

C. difficile testing (EIA for Toxin A/B, PCR, CCNA, toxigenic culture assay) and for exploratory analyses (microbiota composition, VE303 component bacteria detection, antibiotic concentrations, metabolomics, culture, detection of antibiotic-resistant bacteria other than *C. difficile* (e.g., CRE, ESBL, or VRE)

All hematology, chemistry, blood screening, and pregnancy laboratory tests will be performed by a central laboratory or by local labs as applicable. Descriptive statistics of the laboratory parameters will be presented by treatment group for all study visits at which they were collected. The change from baseline of hematology and chemistry laboratory parameters to each post-baseline visit, including the early termination visit, and to the minimum and maximum post-baseline values will also be summarized by treatment group. Pregnancy laboratory tests will be listed only.

A shift table (low, normal, high) from baseline to each post-baseline visit where laboratory tests where assessed will be presented by treatment group for hematology. A shift table for clinical hematology tests will be presented only for Leukocytes, Absolute Neutrophil Count, Lipase, and Amylase as low/normal/high, and for Fecal Calprotectin as a separate shift table in categories of No Inflammation, Mild Inflammation, or Active Organic Disease where No Inflammation is defined as <50 µg/g, Mild Inflammation is defined as 50-200 µg/g, and Active Organic Disease is defined as >200 µg/g.

All laboratory evaluations will be included in a subject data listing.

9.3.1. Stool Assessment

Stool pathogens assessment status (i.e., positive/negative/indeterminate) will be summarized at the screening visit. *C. difficile* toxin assessment status will be presented by visit and treatment group.

Stool vancomycin levels over time will be summarized by treatment group using descriptive statistics.

In addition, stool microbiota composition over time, stool VE303 detection over time, stool metabolomics evaluation over time, as well as stool calprotectin levels over time will also be summarized by treatment group using descriptive statistics.

The number and percentage of subjects with either a presence (yes/no) of stool culture will be presented by visit and by treatment group.

Stacked bar charts of the VE303 detection panel will be presented by treatment group and by timepoint.

Box and whisker plots of VE303 strain estimated abundance over time will be presented by treatment group. In addition, box-and-whisker plots of the microbiome – alpha diversity over time will also be illustrated by treatment group.

Scatter plots showing the correlated by-subject between abundance of each of the 8 component bacteria of VE303 versus vancomycin levels, as well as VE303 strain abundance versus diversity will also be presented by sample, by treatment group, and by timepoint.

Stool parameters will be included in a subject data listing.

9.4. VITAL SIGNS

As per the protocol, vital signs data include measurements of systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), pulse (beats/minute), and body temperature (Celsius). Descriptive statistics of the vital signs will be presented by treatment group for all study visits, including the early termination visit, at which they were collected. The change from baseline to each post-baseline visit, including the early termination visit, and to the minimum and maximum post-baseline value will also be summarized by treatment group.

All vital signs data will be included in a subject data listing.

9.5. ECG

The overall interpretation of ECGs will be recorded as “Normal”, “Abnormal, not clinically significant”, “Abnormal, clinically significant”, or “ECG not readable”. Shifts from baseline to Day 28 and to Early Termination in these ECG interpretation categories will be presented by treatment group. All ECGs will be listed.

9.6. PHYSICAL EXAMINATION

A by-subject listing with physical examination findings will be provided.

9.7. GASTROINTESTINAL SYMPTOMS SELF-ADMINISTERED QUESTIONNAIRE - PROMIS®

Subjects will be evaluated for gastrointestinal symptoms using the self-administered Patient-Reported Outcomes Measurement Information System (PROMIS®) scale questionnaire (v1.0, dated 01 September 2016) in order to assess 8 gastrointestinal symptoms (see the following table for the number of questions and grading for belly pain, bowel incontinence, constipation, diarrhea, disrupted swallowing, gas/bloating, nausea/vomiting, and gastroesophageal reflux). To obtain an adequate baseline, questionnaires must be completed before the first dose of study drug on Day 1. Post-baseline questionnaires should be completed prior to study drug administration on Days 7 and 14. All attempts must be made to have questionnaires completed at approximately the same time of day at every time point.

Row	GI symptoms	# of Questions	Each Question Grading	Total Grading
1	Belly Pain (Tier 1)	5	1 to 5	5 to 25
2	Diarrhea (Tier 1)	6	1 to 5	6 to 30
3	Nausea and vomiting (Tier 1)	4	1 to 5	4 to 20
4	GI incontinence	4	1 to 5	4 to 20
5	Constipation	9	1 to 5	9 to 45
6	Disrupted swallowing	7	1 to 5	7 to 35
7	Gas and bloating	13	1 to 5	13 to 65
8	Reflux	13	1 to 5	13 to 65

Two "Tier" domains will be used to summarize the PROMIS questionnaire data. Tier-1 will include grades from the GI symptom domains of Belly Pain, Diarrhea, and Nausea and Vomiting. These 3 domains have been selected for Tier-1 because they pertain to common clinical manifestations and symptoms of *C. difficile* infection and are often reported as AEs in association with *C. difficile* recurrences. Tier-2 domains will include grades from the other 5 GI symptom domains.

For Tier-1 domains, both the total grading and grades for each individual question within each domain will be summarized descriptively as continuous variables at baseline and at Day 7 and Day 14 by treatment group for the SAS. For Tier-2 domains, grading will be summarized only for total grading and not presented for each individual question within each domain.

For the Tier-1 domains only, a shift table from baseline grade to worst post-baseline grade for each question within a domain will be presented by treatment group. Baseline will be defined as the last non-missing assessment prior to the administration of study drug. Worst post-baseline grade will be defined as the highest grade observed at any post-baseline visit. Grading will be based on the response provided to each question.

Box-and-whisker plots of the total grading for Belly Pain, Diarrhea, and Nausea and Vomiting over time will be presented by treatment group, presenting mean and +/- SD.

If a response to any of the individual questions within a domain is missing, then the total grading for this domain will not be calculated and set to missing. The amount of missed PROMIS questionnaire data will be summarized over time by treatment group.

All subject PROMIS questionnaire responses will be listed.

10. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

Any changes from the SAP will be provided in the CSR.

11. PROGRAMMING CONSIDERATIONS

All TLFs, and statistical analyses will be generated using SAS, Release 9.4 or later (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

11.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs, or a separate SAS program can be created for each output at the statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format / rtf format.
- Numbering of TLFs will follow ICH E3 guidance.

11.2. TABLE, LISTING, AND FIGURE FORMAT

11.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape
- oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

11.2.2. Headers

- All output should have the following header at the top left of each page:

  Vedanta Biosciences, Inc.
  Protocol: VE303-002 Version #7
  Draft/Final

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

11.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Analysis Set

11.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

11.2.5. Body of the Data Display

11.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified
- whole numbers (e.g., counts) are right-justified
- numbers containing fractional portions are decimal aligned

11.2.5.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
Severe	0
Moderate	8
Mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then it will be presented as >0.999.
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Values that round down to 0.0 will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%.
- Unless otherwise specified, tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SoC in alphabetical order, assuming all terms are coded. Within the body system, drug class and SoC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. If applicable, denominator details will be described in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will describe if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) needs to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

11.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates should be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values should be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

11.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

11.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left-justified with single line spacing immediately below the solid line underneath the data display.
- Footnotes should begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used as needed, however, it must add value to the table, listing, or figure. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last 2 lines of the footnote section will be a standard source that indicates the name of the program used to produce the data display, date the program was run, and the listing source (or data source for a listing) (i.e., 'Program: myprogram.sas Listing source: 16.x.y.z').

12. QUALITY CONTROL

Validation of analysis datasets and tables/listings/plots are conducted through independent parallel programming of the statistical output according to the agreed upon specifications defined in the protocol, SAP, table shells, and dataset specifications. In this process, two programmers working independently (i.e., without input from one another), program the same output and compare results (via SAS PROC COMPARE). Any discrepancies are discussed and resolved, and the validation cycle is repeated until no further differences are noted between the two outputs. Once the validation cycle is complete, the output is subjected to senior review by the statistician. All programs are submitted in batch mode to document the results of the PROC COMPARE indicating no unequal observations. In addition, tracking logs will be maintained which document all Quality Control and validation findings and their resolution.

13. ADMINISTRATIVE INTERIM ANALYSES

Since the estimate of the true underlying treatment effect is unknown, and since enrolment has been slow, the decision was made to change Study VE303-002 to a non-pivotal trial after the sponsor's careful assessment. Consequently, the study objective to enroll up to 146 patients (124 evaluable), to increase the sample size as a result of the SSR, and the IA stated in the original protocol will not be performed.

Instead, 3 administrative IAs will be performed to inform business decisions by the sponsor on whether to continue development of VE303 in the CDI indication. The administrative IAs will be performed after at least 24 randomized subjects complete 8 weeks of the study, after at least 39 randomized subjects complete 8 weeks of the study, and after at least 54 randomized subjects complete 8 weeks of the study. The number of subjects selected for each of the administrative IA were selected based on the number of subjects possibly randomized on each of the 3 treatment arms. The total number of approximately 60 to 80 subjects was assessed to allow at least 20 subjects per arm.

13.1. EFFICACY ANALYSIS

The administrative IAs will be performed on the FAS analysis set for efficacy endpoints. The PPS population might be included as a supportive analysis, if there is a sufficient number of patients in PPS population.

13.1.1. Primary Variable: Recurrence Rate before or at Week 8

The Bayesian posterior probability will be evaluated at each administrative IA, for each of the following 6 conditions of true underlying treatment difference in recurrence rate,

1. TRUE underlying treatment effect is better than placebo, i.e., recurrence rates difference >0% reduction associated with VE303

2. TRUE underlying treatment effect is at least 5% better than placebo, i.e., recurrence rates difference >5% reduction associated with VE303

3. TRUE underlying treatment effect is at least 10% better than placebo, i.e., recurrence rates difference >10% reduction associated with VE303

4. TRUE underlying treatment effect is at least 15% better than placebo, i.e., recurrence rates difference >15% reduction associated with VE303

5. TRUE underlying treatment effect is at least 20% better than placebo (i.e., recurrence rates difference >20% reduction associated with VE303

6. TRUE underlying treatment effect is at least 30% better than placebo (i.e. recurrence rates difference >30% reduction associated with VE303)

The number and percentage of subjects with CDI recurrence will be presented by treatment group, and the treatment difference from placebo group will be presented along with the odds ratio (treatment/placebo) of recurrence rates. The 80% CI (i.e., α= 0.2, 2-sided) and the 90% CI (i.e., α= 0.10, 2-sided) based on the asymptotic Wald CI will be constructed for the difference of the proportions of 2 treatments and associated 1-sided exact p-value. Bayesian posterior probability for each of the above conditions will be calculated by using [redacted] Go/No-Go software.

The number of subjects and the number of subjects with recurrence by treatment by randomization stratum at each administrative IA will be summarized for demonstrating the degree of balance of number of subjects between treatments by stratum.

The comparison between each treatment group and placebo will be analyzed using a stratified CMH method for treatment stratified by the stratification factors used in randomization at α= 0.05, 1-sided. The 90% CI based on the asymptotic Wald CI will be constructed for the difference of the proportions of 2 treatments. P-value from CMH test will be presented. The Breslow-Day chi-square test for homogeneity of the odds ratios across strata will also be used to check the assumption. If the assumption test fails, the nature of the difference may be further explored.

13.1.2. Sensitivity Efficacy Analysis on Primary Variable

The same analysis method that will be performed on the primary endpoint as described above will be repeated on 2 additional efficacy variables, which are defined as follows (see also Section 8.1.1):

- CDI recurrences using PCR-positive (with no confirmation using toxin positive) diarrhea episodes treated with an antibiotic that targets *C. difficile*
- Diarrhea episodes treated with an antibiotic that targets *C. difficile* in the absence of a positive toxin assay or a positive PCR result

13.1.3. Secondary Variable: Time to CDI Recurrence Before or at Week 8

Time to CDI recurrence will be summarized by treatment group using the median and 25th and 75^{th} percentiles from the KM analysis. The 2-sided 90% CIs by using Greenwood's formula for the median will also be presented. Subjects who are lost to follow-up or who terminated the study prematurely before experiencing a CDI recurrence will be censored on the date of last contact. Subjects who die before having a CDI recurrence will be censored on the date of death. The percentage of censored observations will also be presented.

Kaplan-Meier plots of Time to CDI recurrence will be presented by treatment group.

13.2. SAFETY ANALYSIS

Safety data are reviewed over the course of the study on an ongoing basis in blinded manner. There are no safety concerns expected; however, a safety summary might be presented if needed.

13.3. UNBLINDING AND BLINDING

The IA analyses will be performed according the Unblinding Plan v1.0 by a separate set of unblinded statisticians and programmers at [redacted], who will have access to individual treatment assignments and will not be involved in subsequent trial conduct. The delegated members at Vedanta will have access to the group level unblinded results and will remain blinded to the individual treatment assignments. The remaining personnel (not mentioned before) involved in the conduct of the trial, including those at Vedanta, the CRO, and the trial sites, will remain blinded to the individual subject treatment assignment until unblinding after trial completion.

13.4. STOPPING RULE

The study enrollment may be stopped after each of the 3 IAs if the VE303 High-dose arm recurrence rate is ≥ 50%.

At the 3rd administrative IA, when approximately 60 to 80 evaluable subjects complete 8 weeks of the study, the study may be stopped for futility if the reduction of the recurrence rate in the High-dose arm compared to the placebo arm either has a relative reduction of <33% (e.g., the odds ratio of treatment/control), or if the absolute reduction of recurrence rate is <10% (placebo minus high-dose arm).