STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

AC-061A301 / AC-061A302

Two multi-center, randomized, double-blind studies to compare the efficacy and safety of cadazolid versus vancomycin in subjects with *Clostridium difficile*-associated diarrhea (CDAD)

Purpose of Analysis	Clinical Study Report
Investigational Drug	Cadazolid
NCT Numbers	NCT01987895 & NCT01983683
Protocol Numbers	AC-061A301 / AC-061A302
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
ALT	Alanine aminotransferase
AMT	Antimicrobial treatment active against CDAD
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CC	Clinical Cure
CCR	Clinical Cure Rate
CCRc	Clinical Cure Rate for cadazolid
CCRv	Clinical Cure Rate for vancomycin
CDAD	*Clostridium difficile*-associated diarrhea
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
DBP	Diastolic blood pressure
ECC	Early Clinical Cure
ECG	Electrocardiogram/graphy
EIA	Enzyme immunoassay
EOS	End-of-Study
EOT	End-of-Treatment
ES	Re-treatment extension with cadazolid set
ETR	Early Treatment Response
FAS	Full analysis set
FDA	Food and Drug Administration
FMT	Fecal microbiota transplant

GDH	Glutamate dehydrogenase
HR	Heart rate
HVAS	Hypervirulent analysis set
ICF	Informed consent form
ICU	Intensive care unit
INR	International normalized ratio
ISR	Investigator's judgment of Sustained Response
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
LT	Liver test
LLN	Lower limit of normal
LOCF	Last observation carried forward
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC_{50}	Median of minimum inhibitory concentration
MIC_{90}	90% quantile of minimum inhibitory concentration
MNAR	Missing not at random
mITT	Modified intent-to-treat
MTF	Metronidazole treatment failure
NBM	Normalization of bowel movements
NED	New episode of diarrhea
NI	Non-inferiority
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PPS	Per-protocol analysis set
PRO	Patient reported outcome
PROAS	Patient reported outcome analysis set

QTc	Corrected QT
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
REA	Restriction endonuclease assay
ROD	Resolution of diarrhea
RTE	Re-treatment end
RTS	Re-treatment start
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis Software
SBP	Systolic blood pressure
SCR	Sustained Cure Rate
SCRAS	Screened analysis set
SCRc	Sustained Cure Rate for cadazolid
SCRv	Sustained Cure Rate for vancomycin
SDTM	Study Data Tabulation Model
SI	International system of units
SMQ	Standardised MedDRA Query
SOC	System organ class
SS	Safety set
STS	Study treatment start
UBM	Unformed bowel movement
ULN	Upper limit of normal
VRE	Vancomycin-resistant enterococci
WBC	White blood cells
WHO	World Health Organization
WPAI	Work productivity and activity impairment

1 INTRODUCTION

The studies AC-061A301 and AC-061A302 have identical designs, including study assessments and statistical methods. This statistical analysis plan (SAP) describes in detail the analyses and data presentation of the primary, secondary and exploratory endpoints for each final clinical study report (CSR).

Outputs are prepared separately for each study. All information about subjects in the respective trials, including that collected during the open-label re-treatment extension with cadazolid, are included in the database lock and statistical analysis for the CSR.

Separate SAPs (not described here) are developed for:

- The meta-analysis of Sustained Cure rate in the hypervirulent subgroup,
- Analysis of pharmacokinetic (PK) data,
- Statistical analysis on questionnaires for the blinded analysis of content validity and psychometric properties planned in the patient reported outcomes (PRO) sub-study protocol,
- Gut microbiome assessment,
- Fecal cadazolid concentrations, if required.

CDI-DaySyms PRO is a new PRO measure to assess *Clostridium difficile*-associated diarrhea (CDAD)-related symptoms in subjects with CDAD on a daily basis. The psychometric validation of the '*Clostridium difficile* infection (CDI) – Daily symptoms' (CDI-DaySyms) PRO, was completed on 18 January 2017. The CDI-DaySyms PRO was previously known as the CDAD-DaySyms PRO. In order to be consistent with the disease description used in current medical practice and the terminology used in publications, the name of the questionnaire has been updated to refer to CDI rather than CDAD.

This SAP has been updated to incorporate the changes to the endpoints for analyses of the CDI-DaySyms PRO based on the psychometric validation, as well as further refinements to the planned analyses of these endpoints. The algorithms for the PRO endpoints are described in Section 5.5.2.3.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM).

2 STUDY DESIGN AND FLOW

The two trials AC-061A301 and AC-061A302 have identical study designs. The only difference is the location of the centers participating in the studies. The protocol synopsis of AC-061A301 is included in Appendix A.

2.1 Study design

Each study is a prospective, multi-center, double-blind, double-dummy, randomized, parallel group, active controlled, Phase 3 study. In each study approximately 630 adult subjects are to be randomized to the two treatment groups: cadazolid and vancomycin using a 1:1 ratio, stratified by first occurrence / first recurrence of CDAD and by site (approximately 100 sites).

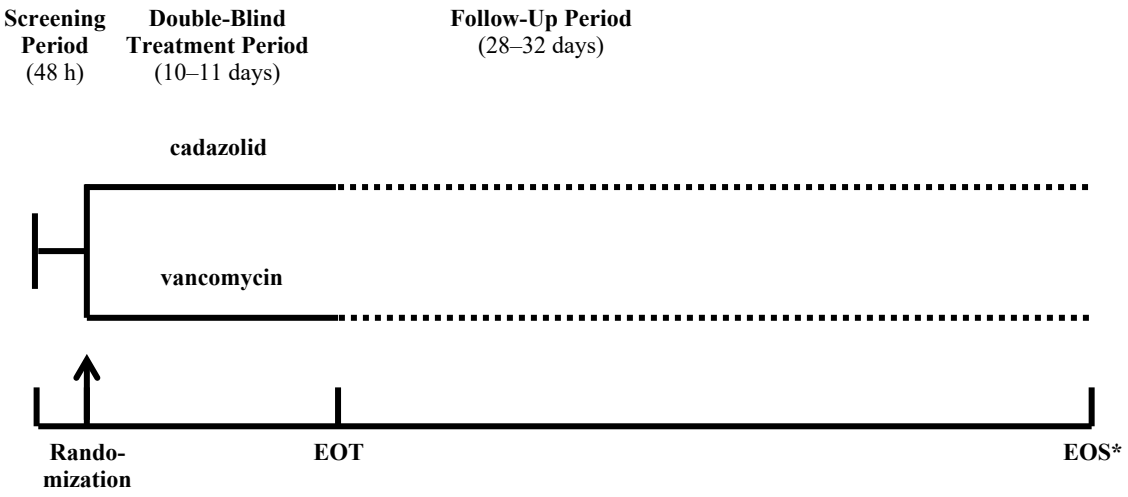
The study consists of the following study periods:

- **Screening period** lasts up to 48 hours, starting from signature of informed consent form (ICF) and ending with subject randomization.
- **Treatment period** starts immediately after randomization with the first dose of study drug at the end of Visit 1 (Day 1 of the study) and ends with End-of-Treatment (EOT) on the day of the last dose of study drug (which is either Day 10 or Day 11 of the study, to account for 10 complete days of treatment).
- **Follow-up period** starts immediately after the last dose of study drug and ends approximately 30 days after the last dose of the study drug, at Visit 5. The End-of-Study (EOS) is expected to occur together with Visit 5.

Unscheduled visits may also take place during the treatment and follow-up periods.

The study design of the main study is shown in Figure 1.

Figure 1 Study design



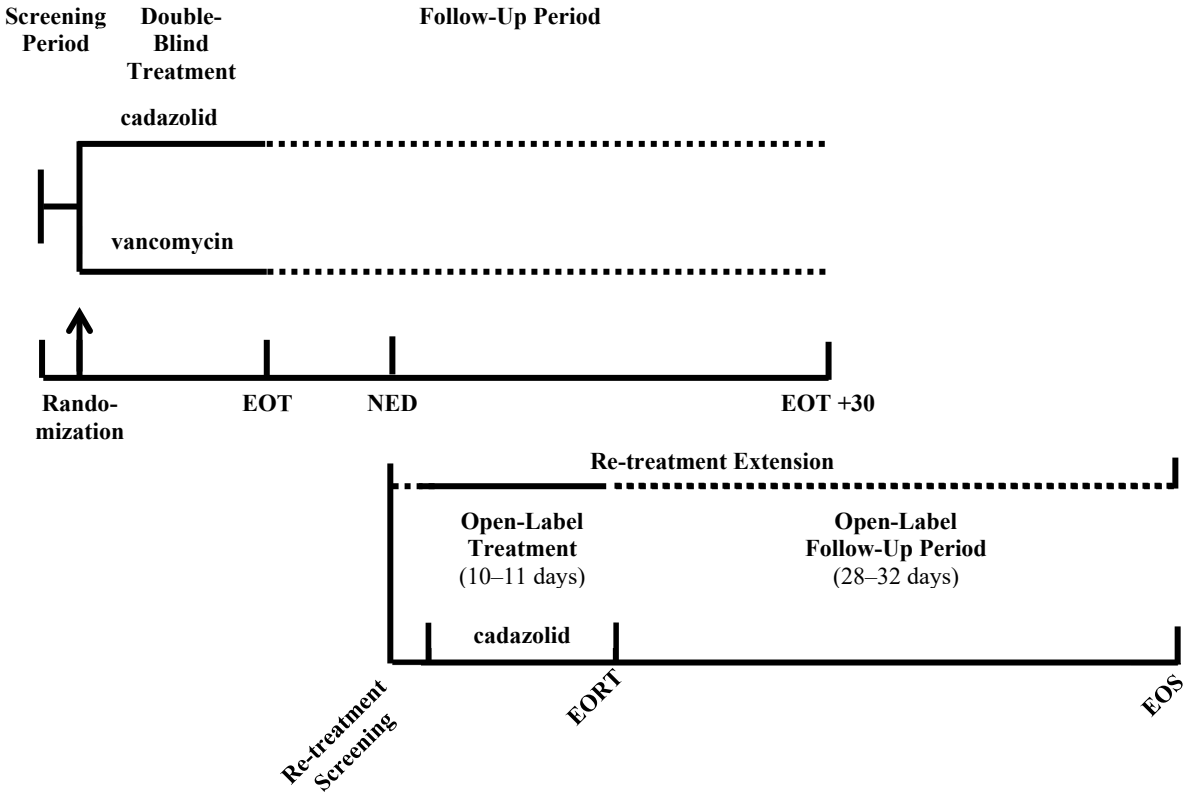
Randomization is stratified by (i) 1st occurrence or 1st recurrence of CDAD and (ii) by site.
*Unless subject enters the open-label re-treatment extension with cadazolid
EOS = End-of-Study; EOT = End-of-Treatment.

The study also includes an extension phase:

- **Re-treatment extension with cadazolid:** Subjects with first occurrence of CDAD at study entry who experience a recurrence during the study, whether they have been treated with cadazolid or vancomycin, may enter the re-treatment extension with cadazolid (after providing a specific informed consent) consisting of a 10-day treatment with cadazolid followed by an approximately 30-day follow-up.

The study design including re-treatment extension is shown in Figure 2. Subjects can start the re-treatment extension at any time during the follow-up period of the main study once they have experienced a recurrence (between EOT + 3 days and EOT + 32 days). At that moment, the follow-up period of the main study stops and the subject continues in the re-treatment extension.

Figure 2 Study design including re-treatment extension



EORT = End of Re-Treatment; EOS = End-of-Study; EOT = End-of-Treatment; NED = New episode of diarrhea Visit.

2.2 Study visit and assessment schedule

Table 1 shows a schematic representation of the assessments during the study. The schedule of assessments performed during the re-treatment extension with cadazolid is summarized in Table 2.

If a subject experiences a recurrence and participation in the re-treatment extension is confirmed (i.e., after the subject has signed the ICF for re-treatment and eligibility is confirmed), Visit 5 in the main study is not performed. Assessments that would have been performed as part of Visit 5 in the main study are performed as part of Re-treatment Visit 1 (Re-1).

Note: Visit 1 referred to in Table 1 covers the entire screening and randomization period (within 48 h of randomization), followed by randomization and study treatment start. Similarly, Visit Re-1 referred to in Table 2 covers the entire screening for re-treatment period, eligibility assessment for re-treatment and re-treatment kit delivery.

Table 1 Visit and assessment schedule

PERIODS	Name	SCREENING	TREATMENT			FOLLOW-UP			-
	Duration	**Up to 48 hours**	**10 to 11 days**			**28 to 32 days**			-
VISIT	**Number**	1		2	3	4	4.a, 4.b,…	5	U1, U2, …
	Name	**Screening**	**Randomization**				**NED**		**Unscheduled**
EVALUATION	**Time**	Day –2 to Day 1 (within 48 h)	Day 1	Day 5 or Day 6 *On site or by phone*	Day 8 to Day 10 *incl. Premature Disc.*	*EOT + 2 to 4 days On site or by phone*	*If applicable, in case of NED* [5, 6]	*EOT + 28 to 32 days or Study Withdrawal*	*If applicable*
Informed consent		X							
Fecal sampling for microbiology		X			X		X		
***C. difficile* GDH and toxin test**		within 72 h (MTF: 48 h)					X		
Demographics		X							
Medical history		X							X
Concomitant medications		X		X	X	X	X	X	X
Physical examination		X			X		X	X	X
Body weight/height		X[1]			X			X	X
Vital signs / Body temperature		X[1]			X		X	X	X
Hematology/coagulation/chemistry		X [2]			X		X	X	X
12-lead ECG		X			X			X	X
Randomization			X						
Study drug			X[3]	and Study Drug Journal completion					
Stool Diary			◄	———	———	———	———	►	
CDAD DaySyms PRO Diary		◄	———	———	———	———			
Interview (face to face or by phone)			Daily[7]				Twice weekly		
Investigator assessment				X		X		X	
Pharmacokinetic sample *Sub-study*					X				
WPAI:CDAD		X			X			X	
AEs/SAEs [4]		X	X	X	X	X	X	X	X

1. Height collected at Visit 1 only. **2.** Includes pregnancy test for women of childbearing potential. **3.** After randomization. **4.** All AEs and SAEs are reported after the first dose of study drug. Between informed consent and first dose of study drug, only SAEs are reported. **5.** Subject may enter re-treatment extension with cadazolid in case of recurrence. **6.** All assessments must be performed in the case of a recurrence. **7.** Interviews start from Day 2.

AE = adverse event, *C. difficile* = *Clostridium difficile*, CDAD = *Clostridium difficile*-associated diarrhea, ECG = electrocardiogram, EOT = End-of-Treatment, GDH = glutamate dehydrogenase, MTF = metronidazole treatment failure, NED = new episode of diarrhea, PRO = patient reported outcomes, SAE = serious adverse event, WPAI = work productivity and activity impairment.

Table 2 Visit and assessment schedule for the re-treatment extension with cadazolid

PERIODS	**Name**	**SCREENING**	**TREATMENT**			**FOLLOW-UP**			**-**
	Duration	**Up to 24 hours**	**10 to 11 days**			**28 to 32 days**			**-**
VISIT	**Number**	Re-1		Re-2	Re-3	Re-4	Re-4.a, Re-4.b,…	Re-5	Re-U1, Re-U2, …
	Name	**Eligibility**	**Re-treatment kit delivery**				**NED**		**Unscheduled**
EVALUATION	**Time**	Day –1 to 1 (within 24 h)	Day 1	Day 5 or 6 *On site or by phone*	Day 8 to 10 *incl. Premature Disc.*	*EOT + 2 to 4 days On site or by phone*	*If applicable, in case of NED*[4]	*EOT + 28 to 32 days or Study Withdrawal*	*If applicable*
Informed consent		X							
Fecal sampling for microbiology		X			X		X		
***C. difficile* GDH and toxin test**		within 72 h					X		
Concomitant medications		X		X	X	X	X	X	X
Physical examination		X			X		X	X	X
Body weight		X			X			X	X
Vital signs / Body temperature		X			X		X	X	X
Hematology/coagulation/ chemistry		X[1]			X		X	X	X
12-lead ECG		X			X			X	X
Re-treatment kit delivery			X						
Study drug intake			X[2]	and Study Drug Journal completion					
Stool Diary			←					→	
CDAD DaySyms PRO Diary		←				→			
Interview (face to face or by phone)			Daily[5]				Twice weekly		
Investigator assessment				X		X		X	
WPAI:CDAD		X			X			X	
AEs/SAEs[3]			X	X	X	X	X	X	X

1. Includes pregnancy test for women of childbearing potential. **2.**After re-treatment kit delivery. **3.** All AEs and SAEs are reported after the first dose of study drug. Between informed consent and first dose of study drug, AEs and SAEs are reported as part of the main study. **4.** All assessments must be performed in the case of a recurrence. **5.** Interviews start on Day 2.
AE = adverse event, *C. difficile* = *Clostridium difficile*, CDAD = *Clostridium difficile*-associated diarrhea, ECG = electrocardiogram, EOT = end-of-treatment, GDH = glutamate dehydrogenase, NED = new episode of diarrhea, PRO = patient reported outcomes, SAE = serious adverse event, WPAI = work productivity and activity impairment.

3 OBJECTIVES

3.1 Primary objective

To determine whether the clinical response after 10-day oral administration of cadazolid is non-inferior to oral vancomycin in subjects with CDAD.

3.2 Secondary objectives

To determine whether oral administration of cadazolid for 10 days is superior to oral vancomycin in the sustained clinical response of subjects with CDAD.

To determine whether the resolution of diarrhea (ROD) is more rapid with oral administration of cadazolid compared to vancomycin.

To determine whether CDAD symptoms as reported by the subject show larger improvements from baseline with oral administration of cadazolid compared to vancomycin.

3.3 Other objectives

3.3.1 Objective of the meta-analysis of AC-061A301 and AC-061A302

To determine through meta-analysis of both studies whether oral administration of cadazolid for 10 days is superior to vancomycin in the sustained clinical response of subjects with CDAD due to infection by hypervirulent *C. difficile* strains.

3.3.2 Exploratory objective

To evaluate the plasma cadazolid concentration at approximately 2 hours post-dose (PK sub-study).

3.3.3 Safety objective

To determine the safety and tolerability of an oral administration of cadazolid compared to vancomycin.

3.3.4 Objective of the re-treatment extension with cadazolid

To describe the clinical response, sustained clinical response and safety in subjects with a first occurrence of CDAD at study entry (cadazolid or vancomycin subjects) who experience a recurrence of CDAD and are re-treated with cadazolid for 10 days.

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes related to PRO validation

It was specified in section 7.2.4 of the protocols of studies AC-061A301 and AC-061A302 that the CDI-DaySyms PRO questionnaire comprises 13 items. Based on the psychometric validation of this tool, 3 out of the 13 items have been removed (passing gas, dizziness, and nausea). Absolute change from baseline in CDI-DaySyms PRO total daily score up to Day 12 derived from the daily CDI-DaySyms PRO items is described as one of the secondary endpoints in the study protocols. However, derivation of such a total score is not supported by the psychometric validation, and therefore three symptom domain scores are derived: Diarrhea Symptoms, Abdominal Symptoms, and Systemic/Other Symptoms. These three domains are tested hierarchically, starting with Diarrhea Symptoms, then Abdominal Symptoms, and finally Systemic/Other Symptoms. The figure in section 11.3.4.1 of the protocol describing the hierarchical testing strategy to control the experimentwise α level is updated in Section 10.1.1 of this SAP in order to include the hierarchical testing of the CDI-DaySyms domain scores.

Section 11.3.4.3 of the protocols specified that a repeated measurements ANCOVA for the absolute and percent change from baseline would be applied, including the baseline value as a covariate. In order to maximize the number of data points included in the analysis, an ANOVA model is fitted to all available absolute values (including baseline and post-baseline data up to Day 12), and treatment difference for the absolute change from baseline for each day is computed from the model using appropriate contrast statements. Consequently, the baseline value is not included as a covariate, and percent change from baseline analysis has been dropped.

The change from baseline to Day 3 is identified as the primary comparison of interest (and used for the hierarchical testing strategy); comparisons for all other days are considered exploratory. Day 3 is selected as the primary comparison of interest as the results from the Phase 2 trial showed that time to modified resolution of diarrhea was 48 hours after start of treatment in the cadazolid arm vs 72 hours in the vancomycin arm. Methods for handling missing data are further described in Section 10.7.3.2. Additional new responder endpoints for the CDI-DaySyms domains are also defined in Section 5.5.3.12. The corresponding supportive analysis of these endpoints is included in Section 10.8.1.11.

4.2 Changes to the analyses planned in the study protocol

A change in the definition of censoring for the variable ‘Time to return to usual bowel movements’ is applied: Subjects without a return to usual bowel movements are censored at the last date with known number of bowel movements. This represents a modification of the text included in the study protocol, which states they would be censored at Visit 5

or, for subjects without a Visit 5 assessment who either died, withdrew from the study or are lost to follow-up, would be censored at the date of death, study withdrawal or last contact, respectively. The rationale for this change is the following: A return to usual bowel movements cannot be achieved after the last recorded bowel movement information, i.e., the subject is no longer in the risk set. Censoring at the last recorded bowel movement information is therefore more appropriate and results in being more conservative in the assessment.

4.3 Changes in the conduct of the study / data collection

The following protocol amendments were performed:

Protocol Version 2, 11 December 2014

- Analysis of the primary endpoint (Clinical Cure) on two co-primary analysis sets (i.e., modified intent-to-treat [mITT] analysis set and Per-protocol analysis set [PPS]) instead of sequentially on PPS and mITT analysis set, following FDA advice.
- Derivation of the variable Sustained Cure was clarified.

Further changes included, e.g., the addition of an emerging hypervirulent *C. difficile* strain, the addition of endpoints related to susceptibility testing of *C. difficile* and vancomycin-resistant enterococci, and general clarifications of eligibility criteria.

Protocol Version 3, 22 October 2015

- Removal of planned interim analysis, which was to be performed after the randomization of the first 67% of subjects.

Additional changes were, for example, the following: a diagnostic test for *C. difficile* is required to detect both glutamate dehydrogenase (GDH) and toxin A/B; introduction a two-part ICF in order to improve efficiency of the informed consent procedure; change of the planned duration of the trial from 23 to 40 months; allowing routine / standard-of-care assessments performed prior to consenting.

Note: Only the main reasons for the protocol amendments are described.

4.3.1 Clarification on wording

Actelion's templates for SAP and CSR have been updated since protocol finalization. The terminology used in the SAP is the one of the revised template. Changes of terminology comprise "medications" replaced by "therapies", and "protocol violations" replaced by "protocol deviations."

5 DEFINITIONS OF VARIABLES

This section provides the definitions and sources for all variables used in the analyses, including specifications for the derivations.

General recurrent definitions (e.g., study treatment start date, baseline) or unit conversion are described in Section 11.

The description of re-treatment variables and analyses are organized in this document as follows: Re-treatment efficacy variables and analyses are separated from the main study efficacy variables [Section 5.5.5] and analyses [Section 10.8.1.13] as re-treatment efficacy variables are not part of the hierarchical statistical testing strategy. However, safety and subject characteristic variables and analyses for the re-treatment extension are described together with their corresponding main study counterparts [Section 5 and Section 10] to ease description of derivation and analyses.

5.1 Screening failures

A subject is considered a screening failure, if the subject is recorded as screened and never randomized in the Interactive Voice Response System (IVRS; subjects screened more than once and subsequently randomized are not counted as screening failures).

The primary reason for screening failure is documented in the randomization case report form (CRF; primary reason why the subject was not randomized) as 'subject not eligible', 'subject withdrew consent', 'adverse event' or 'other'. If a subject is considered a screening failure but no reason for screening failure is reported, the reason is categorized as 'Unknown'.

For the re-treatment extension, a subject is considered screened for re-treatment if the answer to the question 'Has the subject been screened for re-treatment?' in the CRF is 'Yes.' The subject is considered a screening failure for re-treatment if he/she has signed the informed consent to participate but then the answer to the question 'Has the subject been enrolled into the re-treatment?' is answered 'No.'

5.1.1 Unmet eligibility criteria

Unmet eligibility criteria are defined as:

- Inclusion criteria not met (reported as No in the CRF) and
- Exclusion criteria met (reported as Yes in the CRF).

The inclusion and exclusion criteria information is taken from the Screening and Randomization Visit. For re-screened subjects it is taken from the latest Re-screening and Randomization Visit. Unmet re-treatment extension eligibility criteria are defined in the same way and taken from the Re-1 Visit.

5.2 Subject characteristics

5.2.1 Demographics

Demographic data comprise age at screening (years; continuous and categorical), sex, ethnicity, race, height (cm), weight (kg) and body mass index (BMI; kg/m^2; continuous and categorical).

The following categories are defined for demographic variables:

- **Age (years):** 18–64; 65–74; ≥ 75
  In addition, EudraCT age categories are defined as 18–64; 65–84; ≥ 85.
- **BMI (kg/m^2):** < 18.5; ≥ 18.5 – ≤ 25; > 25 – ≤ 30; > 30 – ≤ 40; > 40.
- **Geographical region:** According to the recruitment plans, the following geographical regions are considered:

– United States (301 & 302).

– Canada (301 & 302).

– Europe: Belgium (302 only), Croatia (302 only), Czech Republic (302 only), France (301 only), Germany (301 only), Greece (302 only), Hungary (302 only), Italy (301 only), Netherlands (301 only), Poland (301 only), Romania (301 & 302), Slovakia (302 only), Spain (301 only), United Kingdom (302 only).

– Rest of the World: Argentina (302 only), Australia (301 only), Brazil (301 & 302), Chile (302 only), Israel (302 only), Peru (301 only), South Korea (302 only).

5.2.2 Baseline disease characteristics

Main baseline disease characteristics include:

- **CDAD episode type strata (from IVRS)** defined as baseline stratification factor 'First occurrence' or 'First recurrence' of CDAD as recorded in the IVRS at the time of subject randomization. The CDAD episode type together with randomization number and date and time of randomization information is transferred to the CRF via IVRS integration (Primary form).
- **CDAD episode type reported (CRF)** defined as 'First occurrence' or 'First recurrence' of CDAD as entered in the CRF (Demographics form).
- **Initial strain of *C. difficile*** identified in baseline stool sample* by polymerase chain reaction (PCR) performed by the central laboratory is categorized as:

– 'Hypervirulent' if the *C. difficile* strain belongs to either ribotype 027, 078 or 244 (initial type).

– 'Non-hypervirulent' if the *C. difficile* strain has a PCR ribotype which is different from 027, 078 or 244.

– 'Unable to determine' if PCR ribotype information of *C. difficile* at baseline is not available, e.g., due to missing baseline fecal sample or if *C. difficile* was not isolated in central laboratory.

* Baseline stool sample is the last sample collected up to treatment start date (inclusive) with available *C. difficile* culture result. The sampling date is recorded on the CDAD Diagnosis and Microbiology Sample CRF for subjects enrolled under protocol version 3 or later. For subjects enrolled under earlier protocol versions, the sampling date is collected on the Fecal Sampling CRF.

Note: Handling of multiple samples with identical fecal sampling date/time qualifying for baseline is detailed in Section 5.5.4.1.

If a new ribotype(s) is identified by external experts as a hypervirulent strain prior to unblinding of the data of any of the two studies, this SAP will be updated accordingly to include the new ribotype(s) in the hypervirulent strain definition.

- **CDAD severity at Baseline** is categorized according to the definition specified in the protocol [see sections 1.1.1 and 7.1 of the protocol] and derived as:

– 'Severe' if

  – baseline maximum core body temperature > 38.5 °C
  (Source: Vital Signs CRF), **or**

  – baseline white blood cell (WBC) counts > 15.0 10^9/L
  (Source: From central laboratory; if not available local result is used, see Section 5.6.9), **or**

  – rise in baseline serum creatinine > 50% compared to pre-CDAD diagnosis (Source: baseline serum creatinine is taken from central laboratory; if not available local result is used, see Section 5.6.9. Pre-CDAD serum creatinine is taken from the CDAD Related Medical History CRF at screening. Handling of missing pre-CDAD diagnosis is described below.)

– 'Mild-Moderate' if none of the 3 criteria above for severe are met, and all measurements required for derivation of severity have been performed.

– 'Unable to determine' if any of the measurements required for derivation of severity is missing for subjects not yet considered severe.

Pre-CDAD serum creatinine values will be converted to the same units as used for the baseline value and, where applicable, will be normalized using the method as specified in Section 5.6.9. If no pre-CDAD diagnosis assessment of creatinine is available for

subjects without chronic kidney disease (i.e., subjects whose medical history does not include selected preferred terms from the Standardised MedDRA Query [SMQ] Chronic kidney disease [Appendix C]), the CDAD is considered severe if the baseline serum creatinine > 1.5 × upper limit of normal (ULN).

Other main baseline characteristics include:

- **Time since diarrhea start date for current CDAD episode** (days) is defined as the randomization date minus the start date of current CDAD episode + 1.
- **Time since first occurrence for subjects with first recurrence** is defined as the randomization date minus the start date of first occurrence + 1.
- **Number of bowel movements within 24 hours prior to randomization**, as recorded in the CRF at Screening Visit (Bowel Movement Information form).
- **Number of unformed bowel movements (UBMs) within 24 hours prior to randomization**, as recorded in the CRF at Screening Visit (Bowel Movement Information form).

  Note: For the 2 variables above, the following categories are used: 0 to ≤ 3; > 3 to ≤ 5; > 5 to ≤ 9; and > 9.
- **Number of bowel movements per day reported as usual by the subject**, as recorded in the CRF at Screening Visit (Bowel Movement Information form).
- **Number of UBMs per day reported as usual by the subject**, as recorded in the CRF at Screening Visit (Bowel Movement Information form).

  Note: For the 2 variables above, the following categories are used: 0, 1, 2, 3, > 3.

Note: *For re-screened subjects, information for baseline characteristics is taken from the last Re-screening Visit instead of the Screening Visit.*

5.2.3 Other baseline characteristics

Other baseline disease characteristics include:

- **Endoscopy during current CDAD episode** (for subjects who have undergone endoscopy during the current CDAD episode as recorded at Screening Visit)

– Visible pseudomembranes (Yes/No)

– Histology consistent with pseudomembranous colitis (Yes/No)

- **Imaging during current CDAD episode** (for subjects who have undergone abdominal imaging during the current CDAD episode as recorded at Screening Visit)

– Distension of large intestine (Yes/No)

– Colonic wall thickening, including low attenuation mural thickening, pericolonic fat stranding (Yes/No)

– Ascites not explained by other causes (Yes/No)

- **Hospitalization status at baseline** categorized as:

– 'Outpatient' if the response to the question 'Is the subject an outpatient?' is 'Yes', as recorded on the Baseline Healthcare Setting CRF.

– 'Inpatient' if the response to the question 'Is the subject an outpatient?' is 'No'.

- **Healthcare settings in the past three months at baseline** categorized as:

– Hospitalization (Yes/No)

– Long-term care facility (Yes/No)

– Chronic outpatient exposure (Yes/No)

– Other (Yes/No)

Include all healthcare setting information as reported on the CDAD-related Medical History CRF.

- **Metronidazole treatment failure (MTF)** as reported on the CDAD-related Medical History CRF at Screening Visit (Yes/No).
- **Prior antimicrobial treatments active against CDAD within 1 week of study treatment start (Yes/No)** taken from the Concomitant Medication CRF, see definition in Section 5.2.5.3.
- **History of chemotherapy and immunosuppression** as reported on the CDAD-related Medical History CRF at Screening Visit (Yes/No).

Note: *For re-screened subjects, information for other baseline characteristics is taken from the last Re-screening Visit instead of the Screening Visit*

5.2.4 Medical history

Medical history includes previous and/or concomitant diseases or diagnoses recorded in the Medical History CRF. Reported terms are coded using MedDRA version 19.

Previous medical history are those diseases or diagnoses that are not ticked as ongoing (ongoing 'Yes' not ticked) on the CRF and with an end date before or equal to the study treatment start date. In the event of a partial end date that overlaps with first dose (e.g., May2013 and first dose occurred on 23May2013) or if an end date is missing, the medical history is considered as previous if ongoing is ticked 'No'. All other medical history terms are considered concomitant.

5.2.5 Previous and concomitant therapies

Therapies are collected in the Concomitant Medications CRF and terms are coded using the WHO drug code dictionary and the anatomical therapeutic chemical (ATC) classification code (version dated 1 March 2016).

5.2.5.1 Previous therapies

Previous therapies are those medications that were started prior to start date/time of study treatment with an end date/time prior to study treatment start date/time.

In the event of a partial end date that overlaps with study treatment start date (e.g., end date May2013 and study treatment start occurred on 23May2013) or if an end date is missing, then the therapy is considered as previous if 'Ongoing at start of treatment?' is ticked 'No'. All other therapies are considered concomitant.

5.2.5.2 Study concomitant therapies

Main study concomitant therapies are all the treatments that are ongoing at start of study treatment or initiated on or after the start date/time of study treatment first dose (from Study Drug Log CRF) and up to Visit 5, and prior to start of re-treatment with cadazolid (in the re-treatment extension).

Main study concomitant therapies are further split into (i) main study concomitant therapies with onset prior to study treatment start and (ii) main study concomitant therapies with onset on or after study treatment start up to EOT + 7 days.

Re-treatment concomitant therapies are all the treatments that are ongoing at start of re-treatment with cadazolid or initiated on or after the start date/time of first dose of re-treatment and up to Visit Re-5.

5.2.5.3 Specific therapies

Concomitant opiate treatments at baseline are those initiated before or at the first dose of study treatment, and with end date at or after the study treatment start date/time.

Opiates are defined as any therapy in the Standardised Drug Grouping 1: Analgesia producing opioids.

Antimicrobial treatments active against CDAD (AMT) comprise the therapies (standardized medication name) within the specified ATC codes (medication class code) and route as detailed in Table 3.

Table 3 Antimicrobial treatments active against CDAD

Medication (Standardized Name**)	Medication class code (ATC)	Route	Description of combinations
Vancomycin Vancomycin hydrochloride	A07AA, J01XA	Oral*	
Vanco Plus	J01RA	Oral*	with vancomycin
Metronidazole	P01AB, J01XD, A02BD	Any	
Metronidazole Benzoate	J01XD	Any	
Pylera Helidac /01327801/	A02BD	Any	with metronidazole
Bacitracin	J01XX, A07AX	Any	
Bacitracin w/polymyxin	J01XB	Any	with bacitracin
Nebacetin /00037701/	A07AA	Any	with bacitracin
Fusidic Acid	J01XC	Any	
Nitazoxanide	P01AX	Any	
Teicoplanin	J01XA	Oral*	
Tigecycline	J01AA	Any	
Fidaxomicin	A07AA	Any	
Rifampicin Rifamycin Rifabutin Rifapentine	J04AB	Any	
Rifaximin	A07AA	Any	
Rifaprim Rifinah Rifacept-3 Levofloripine Risorine Tisobrif Rifater Kombipak II	J04AM	Any	with rifampicin

* In addition to oral administration, the administration of these products via rectal and intragastric route (or in the event of missing route information) will be considered as antimicrobial treatment active against CDAD.
** Standardized medication name = Preferred name from WhoDrug Dictionary.
ATC = anatomical therapeutic chemical; CDAD = *Clostridium difficile*-associated diarrhea.

Prior antimicrobial treatments active against CDAD within 1 week of study treatment start are defined as any AMT taken in the 7 days prior to study treatment start. This is derived as previous medications with medication start date/time or end date/time between study treatment start date – 7 days (inclusive) up to study treatment start date/time; or main study concomitant medications with medication start date/time

prior to study treatment start. If start or end time is missing, evaluation is done using the date part only. Previous medications with missing end dates are not considered to have been taken within 1 week prior treatment start.

Main study concomitant antimicrobial treatments active against CDAD are defined as any main study concomitant therapies [see Section 5.2.5.2] with ATC codes as defined in Table 3.

Main study concomitant antibiotics for infections other than CDAD are defined as any main study concomitant therapies [see Section 5.2.5.2] with ATC codes equal to or starting with A07A, G01, J01, R02AB, S02A, with the exception of those reported as active against CDAD [see Table 3].

Main study concomitant proton pump inhibitors (PPIs) and H2 blockers are defined as any main study concomitant therapies [see Section 5.2.5.2] with ATC codes equal to or starting with A02BA (H2 blockers), A02BC (PPIs), or with the ATC codes A02BD, B01AC, M01AE for combination therapies that include omeprazole, esomeprazole, pantoprazole or lansoprazole.

Main study concomitant antimicrobial treatments active against CDAD, main study concomitant antibiotics for infections other than CDAD and concomitant PPIs and H2 blockers will be considered, in addition, for the two following periods: (i) starting between study treatment start and EOT + 2 days (inclusive), or (ii) starting between EOT + 3 days and Visit 5 (inclusive).

The following categories will be considered in addition for efficacy analyses:

- Concomitant antibiotics for infections other than CDAD taken from first dose to EOT + 2 days (yes/no)
- Concomitant antibiotics for infections other than CDAD taken from first dose to Visit 5 / re-treatment (yes/no)

Concomitant medication days: Several variables defining the number of days between a specific date and the start date of concomitant medication are derived using the definitions in Section 11.3: Concomitant medication days from first dose, from last dose, from first re-treatment dose, and from last re-treatment dose.

5.2.6 Procedures

Pre-specified CDAD-related procedures as well as any other procedures are collected in the Procedures CRF, where the date of procedure is reported.

CDAD-related procedures are defined as the following pre-specified CDAD-related procedures: Fecal microbiota transplant (FMT), colectomy, hemicolectomy, loop ileostomy with colonic lavage.

Other procedures are coded using MedDRA version 19.

Procedures performed before starting the study are reported in the Medical History CRF.

5.2.6.1 Concomitant procedures

Concomitant procedures are classified into main study procedures and re-treatment extension procedures.

- Main study concomitant procedures, if the date of the procedure is between the first dose of the study and Visit 5, inclusive (or prior to first dose of re-treatment, if applicable).
- Re-treatment extension concomitant procedures, if the date of the procedure is between the first dose of the re-treatment with cadazolid and Visit Re-5, inclusive.

Procedures performed after Visit 5 or after Visit Re-5 are presented chronologically in a listing and, thus, not classified into a period.

5.2.6.2 Endoscopy and imaging since first dose of study drug

For subjects who have undergone endoscopy or abdominal imaging since first dose of study drug, additional information is collected for these procedures on the Endoscopy and Imaging CRF at Visit 5 [see Section 5.2.3].

5.3 Study treatment exposure and compliance

Study treatment exposure (duration and mean daily dose) and compliance are all defined once for the main treatment period and again for the re-treatment period.

5.3.1 Exposure

Exposure to study drug is described in terms of duration and mean daily dose for active drug type (cadazolid or vancomycin) in the double-blind treatment period, and for cadazolid only for the re-treatment period (open-label treatment).

Duration of study treatment (days) is defined per active drug type: For cadazolid it is the time elapsing between first treatment start date/time and last treatment end date/time of sachets + 12 hours, and for vancomycin it is the time elapsing between first treatment start date/time and last treatment end date/time of capsules + 6 hours, all divided by 24 and rounded to the nearest 0.25 of a day.

In the event of missing treatment end time, duration of study treatment is calculated as:

Last treatment end date per drug type – treatment start date per drug type + 1

In the event of missing or partial treatment end date, duration is missing. Duration of re-treatment is defined in a similar way as for cadazolid above, but based on first

re-treatment start date/time and last re-treatment end date/time of open-label sachets + 6 hours.

Exposure (days), i.e., treatment duration adjusted for interruptions, is defined as:

Duration of study treatment (days) – Total Duration of Interruptions (days),

where Total Duration of Interruptions is defined as the sum of Duration of Interruption over all interruption periods, rounded to the nearest 0.25 of a day. For a single period the Duration of Interruption is defined as:

Duration of Interruption, cadazolid (h) = max{Interruption End Date/Time sachets – Interruption Start Date/Time sachets – 12 h , 0},

Duration of Interruption, vancomycin (h) = max{Interruption End Date/Time capsules – Interruption Start Date/Time capsules – 6 h , 0},

where Interruption Start Date/Time is the Study Drug Log End Date/Time with corresponding reason for treatment end being temporarily interrupted (due to an adverse event [AE] or not due to an AE). Interruption End Date/Time is the next chronological Study Drug Log Start Date/Time after Interruption Start Date/Time for the same medication type (capsules or sachets).

In the event of missing treatment start or end time, derivations are conducted based on days. In the event of partial or missing treatment start or end date, exposure is missing. If Interruption End Date/Time cannot be derived as there is no next chronological Study Drug Log entry the exposure is missing.

Mean daily dose (mg) per subject is defined as the total amount of active drug taken divided by the duration of study treatment.

The total number of doses taken is directly taken from the Drug Accountability CRF, expressed as the total number of sachets/capsules taken (as determined by the investigator).

The total amount of active drug taken is defined for cadazolid as the number of sachets taken multiplied by 250 mg. Similarly, the total amount of active drug taken is defined for vancomycin as the number of capsules taken multiplied by 125 mg. If total number of sachets/capsules taken or the duration of study treatment is missing then mean daily dose is set to missing.

Cumulative subject days exposure (days) is calculated by summing the duration of study treatment for all subjects having a duration of at least 0.25 days.

5.3.2 Compliance with study treatment

Compliance (%) is defined as the percentage of total number of sachets/capsules taken as recorded in the CRF out of total number of planned doses (20 sachets and 40 capsules) and is determined separately for sachets and for capsules (for both active study drug and matching placebo study drug). If the total number of sachets/capsules taken are missing, compliance is set to missing.

5.3.3 Study treatment discontinuation

Reasons for study treatment premature discontinuation are recorded on the Premature Permanent Discontinuation of Study Treatment CRF.

A subject is considered to have discontinued from the study treatment prematurely if at least one reason is reported, or the reason for treatment discontinuation on the Study Drug Log CRF is 'premature permanent discontinuation'.

Reasons for premature discontinuation have the following possible answers: 'Death', 'Lost to follow-up', 'Subject decision' (further split into 'Tolerability related', 'Efficacy related', or 'Other'), 'Physician decision' (further split into 'Adverse event', 'Lack of efficacy / Treatment failure' or 'Other') or 'Sponsor decision' (further split into 'Study termination by sponsor' or 'Other'). An additional category would be called 'Reason not provided' for subjects where the reason is missing.

Subjects who complete study treatment as per protocol are those with a record in the CRF Study Drug Log of 'Completed as per protocol' and who have not prematurely discontinued study treatment.

The duration of an interruption period is derived as described for derivation of exposure in Section 5.3.1.

Re-treatment discontinuation and corresponding reasons are recorded on the Re-treatment Study Drug Log CRF and are derived from this source in the same way as for the main study.

5.3.4 Study treatment interruptions

Study treatment interruptions are recorded on the Study Drug Log CRF.

A subject is considered to have had a study treatment interruption (Yes/No) if any reason for treatment end is either 'Temporarily interrupted due to an AE' or 'Temporarily interrupted not due to an AE' (Study Drug Log CRF).

For each subject, all study treatment interruptions with reason for interruption are considered.

Re-treatment interruptions are recorded on the Re-treatment Study Drug Log CRF and are derived from this source in the same way as for the main study.

5.4 Study withdrawal

Study withdrawal is recorded on the End of Study CRF.

A subject is considered to have completed the study if 'Did the subject complete the study?' has been ticked as 'Yes'. A subject is considered to have withdrawn from the study prematurely if 'Did the subject complete the study?' has been ticked as 'No'.

Possible reasons for withdrawal are 'Death', 'Lost to follow-up', 'Subject decision' (further split into 'Withdrawal of consent from study participation' or 'Other'), 'Physician decision' or 'Sponsor decision' (further split into 'Study termination by sponsor' or 'Other'). An additional category would be called 'Reason not provided' for cases where the reason is missing.

Study withdrawal is described separately for the main study and the re-treatment extension. Subjects are considered to have completed the main study if they have completed the study and were not enrolled in the re-treatment extension. Subjects are considered to have completed the re-treatment extension if they have completed the study and were enrolled in the re-treatment extension.

Study withdrawal days: Several variables defining the number of days between a specific date and the date of study withdrawal are derived according to the definitions in Section 11.3: Study withdrawal days from first dose, study withdrawal days from last dose, study withdrawal days from first re-treatment dose and study withdrawal days from last re-treatment dose.

5.5 Efficacy variables

Regarding subjects who enter the re-treatment extension, only data collected prior to starting re-treatment with cadazolid (first re-treatment dose) are considered for all main study analysis variables [up to Section 5.5.4.8, inclusive], unless otherwise specified.

For the re-treatment extension variables, only data collected after the start of re-treatment with cadazolid (first re-treatment dose) from subjects entering the re-treatment extension will be considered [see Section 5.5.5], unless otherwise specified.

5.5.1 Primary efficacy variable: Clinical Cure

Clinical Cure Rate (CCR; %) is the variable to be analyzed for the primary endpoint Clinical Cure, and is derived by the sponsor based on daily UBM information and concomitant medications recorded by the investigator in the CRF.

CCR is the proportion of subjects meeting both criteria for Clinical Cure described below [see also Figure 3]:

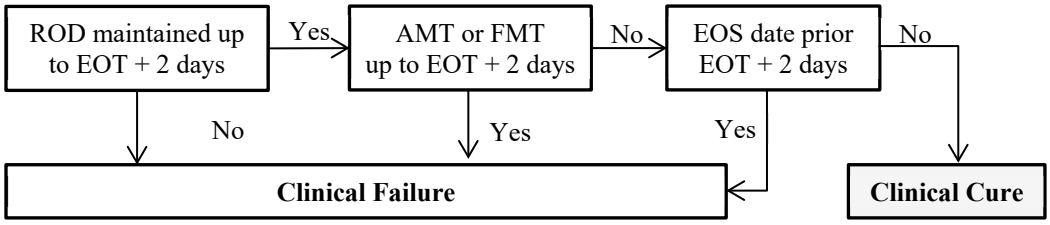
- Resolution of diarrhea (ROD; ≤ 3 UBMs per day for at least 2 consecutive days) on study treatment and maintained for 2 days after EOT

  AND

- No additional antimicrobial treatment active against CDAD (AMT) or fecal microbiota transplant (FMT) between first dose of study drug and 2 days after EOT (inclusive).

In the event of death by any cause, or being lost to follow-up, or study withdrawal prior to EOT + 2 days, the subject is considered a Clinical Failure.

Figure 3 Derivation of Clinical Cure: Schematic overview



AMT = antimicrobial treatment active against CDAD; FMT = fecal microbiota transplant; ROD = resolution of diarrhea.

5.5.1.1 Derivation details

Clinical Cure is assessed during the period from treatment start up to EOT + 2 days, i.e., starting after study treatment start date/time and ending on EOT + 2 days (inclusive).

Note: EOT is defined as the date of last double-blind drug intake. Therefore the duration of the assessment period varies with treatment duration.

ROD on treatment and ROD maintained up to EOT + 2 days: A subject is considered to have ROD on treatment and maintained up to EOT + 2 days if he has ≤ 3 UBMs for at least two consecutive days up to EOT date (inclusive) and subsequently ≤ 3 UBMs maintained up to EOT + 2 days.

Note: This condition is met if and only if the subject has ≤ 3 UBMs on each day within the 4-day interval from EOT – 1 day to EOT + 2 days.

≤ 3 UBMs per day (derived) is considered met if:

1. 'Daily number of UBMs' (Daily Stool Information CRF) is ≤ 3.
2. '≤ 3' is ticked for the question 'Daily number of UBMs, if exact number is not known' (Daily Stool Information CRF).

Where both 1 and 2 above are missing (investigator response of 'Not known' is not considered as missing):

3. 'Check if no bowel movement today' is ticked 'Yes' in the daily stool diary (Stool Log CRF), the number of UBMs per day is assigned 0.

Where both 1 and 2 above are missing or unknown:

4. 'Daily number of bowel movements' is ≤ 3 (Daily Stool Information CRF).

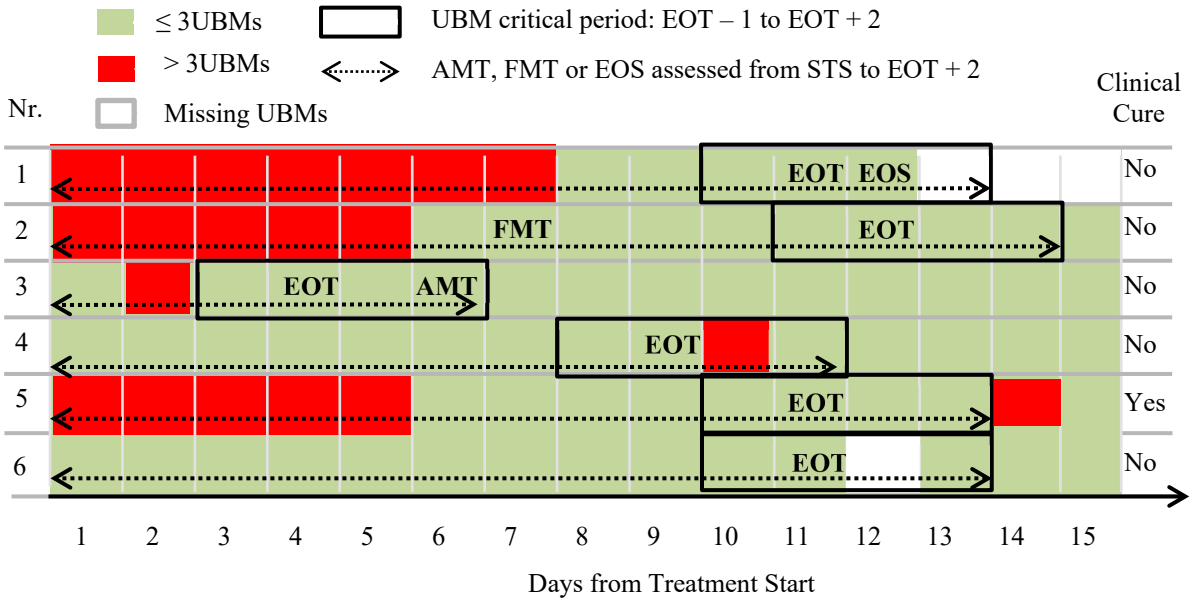
AMT up to EOT + 2 days: Derived as any antimicrobial treatment [as defined in Table 3] taken after treatment start date/time and up to EOT + 2 days (inclusive).

FMT up to EOT + 2 days: Derived as any FMT [as defined in Section 5.2.6] performed after study treatment start date/time and up to and including EOT + 2 days.

Study withdrawal (EOS date) prior to EOT + 2 days: A subject is considered to have withdrawn from the study prior to EOT + 2 days if the EOS date recorded on the EOS CRF (for any EOS reason, including death, lost to follow-up, or any other withdrawal) is prior to EOT + 2 days. For subjects that are lost to follow-up, the last contact date is used as the study withdrawal date instead of the EOS date (as the EOS date, in this case, represents an unsuccessful contact attempt per CRF completion guidelines).

Handling of missing data for daily number of UBMs is detailed in Section 10.6.2, treating subjects with missing UBM information on critical days as failures. Handling of missing or partial EOT date is detailed in Section 12, and Clinical Cure is then being evaluated based on the imputed EOT date.

Figure 4 Clinical Cure: Derivation examples



AMT = antimicrobial treatment active against CDAD; EOS = End-of-Study; EOT = End-of-Treatment; FMT = fecal microbiota transplant; STS = Study treatment start; UBM = unformed bowel movement.

5.5.1.2 Clinical Failure

Subjects who do not fulfill the requirements for Clinical Cure (including due to missing data) are considered a Clinical Failure. Reasons for Clinical Failure will be categorized as described in Table 4.

Table 4 Reasons for Clinical Failure

Short description	Derivation details
AMT or FMT up to EOT + 2 days	Any additional antimicrobial treatment active against CDAD taken or FMT received from treatment start up to EOT + 2 days.
No AMT or FMT up to EOT + 2 days:	
No ROD on treatment	Subject does not have ≤ 3 UBMs per day for at least 2 consecutive days on treatment (i.e., from treatment start date up to EOT day inclusive) and not classified as 'Missing UBMs without ROD'.*
ROD not maintained up to EOT + 2 days	≤ 3 UBMs per day for at least 2 consecutive days on treatment but ≤ 3 UBMs per day not maintained up to EOT + 2 days and not classified as 'Missing UBMs with ROD'.*
Missing UBMs without ROD	Any day with missing UBMs and no day with > 3 UBMs between EOT – 1 day and EOT + 2 days and no ≤ 3 UBMs per day for at least 2 consecutive days on treatment.*
Missing UBMs with ROD	Any day with missing UBMs and no day with > 3 UBMs between EOT – 1 day and EOT + 2 days and ROD, i.e., ≤ 3 UBMs per day for at least 2 consecutive days on treatment.*
Premature withdrawal prior to EOT + 2 days	Premature study withdrawal prior to EOT + 2 days and no AMT or FMT received up to date of withdrawal (EOS date).
ROD maintained up to withdrawal	≤ 3 UBMs per day for at least 2 consecutive days on treatment and ≤ 3 UBMs per day maintained up to date of withdrawal (EOS date).
No ROD / ROD not maintained up to withdrawal	Not classified as 'ROD maintained up to withdrawal' above.

* For subjects without AMT or FMT or premature withdrawal prior to EOT + 2 days.
AMT = antimicrobial treatment active against CDAD; EOS = End-of-Study; EOT = End-of-Treatment; FMT = fecal microbiota transplant; ROD = resolution of diarrhea; UBM = unformed bowel movement.

5.5.2 Secondary efficacy variables

5.5.2.1 Sustained Cure

Sustained Cure Rate (SCR, %) is the variable to be analyzed for the secondary endpoint Sustained Cure, and is derived by the sponsor based on daily UBM information, GDH and toxin test results and concomitant medications recorded by the investigator in the CRF. SCR is the proportion of subjects assessed as meeting the criteria for Sustained Cure up to Visit 5 (scheduled per protocol at EOT + 30 days, with protocol window of 28 to 32 days).

Sustained Cure is defined as Clinical Cure AND no recurrence.

Recurrence is defined for subjects with Clinical Cure as:

- New episode of diarrhea (NED): > 3 UBMs on any day between EOT + 3 days and Visit 5 (inclusive)

AND

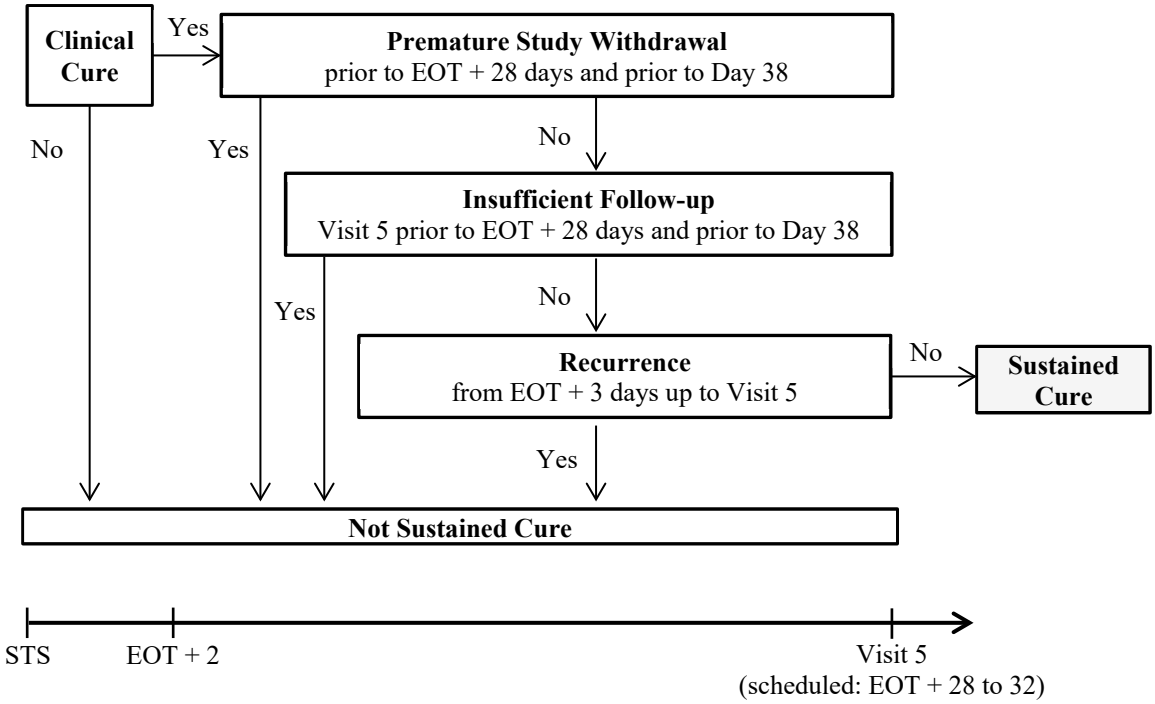
- Stool test showing positive *C. difficile* GDH and toxin test on the same stool sample (according to enzyme immunoassay [EIA] test approved by the sponsor)

AND

- Antimicrobial treatment active against CDAD (AMT) including participation in the re-treatment extension with cadazolid or fecal microbiota transplant (FMT) started between EOT + 3 days and Visit 5 (inclusive).

Subjects with Clinical Failure or with Clinical Cure followed by recurrence are considered not to have Sustained Cure [see Figure 5]. Thus, the denominator for rate estimation includes all subjects in the relevant analysis set (mITT analysis set or PPS) for each treatment group to ensure a comparison based on the randomized treatment group.

Figure 5 Derivation of Sustained Cure: Schematic overview



Clinical Cure is assessed up to EOT + 2 days. Sustained Cure is assessed up to Visit 5.
STS = Study treatment start; EOT = End of Treatment date.

5.5.2.1.1 Derivation details

Premature Study Withdrawal prior to EOT + 28 days and Day 38: Subjects with Premature Study Withdrawal according to EOS CRF, i.e., EOS reason of death by any cause, study withdrawal (subject decision, physician decision, sponsor decision) or being lost to follow-up, and with Study Withdrawal date prior to EOT + 28 days and Day 38. These subjects are considered not to have a Sustained Cure even if there is no recurrence determined.

Study Withdrawal date is defined as the EOS date unless the subject is lost to follow-up then it is defined as the last contact date [for definition see Section 11.3].

Note: The EOS date for subjects lost to follow-up relates to an unsuccessful contact attempt.

Insufficient Follow-Up: Subjects with Visit 5 conducted prior to EOT + 28 days and Day 38 are considered to have insufficient follow-up to evaluate Sustained Cure. These subjects are considered not to have a Sustained Cure even if there is no recurrence determined.

Recurrence: A subject is considered to have a recurrence between EOT + 3 days and Visit 5 if the subject satisfies all 3 criteria for recurrence in the period from EOT + 3 to Visit 5: (i) NED (> 3 UBMs per day), (ii) positive GDH and toxin test and (iii) AMT or FMT, and the criteria regarding temporal relationship of the 3 elements described below are met.

Temporal relationship between NED, positive GDH/toxin test and AMT/FMT for recurrence evaluation:

A NED should precede the positive *C. difficile* GDH and toxin test and AMT/FMT. Similarly the positive GDH and toxin test should precede AMT. To avoid temporal dissociation between a NED and a positive *C. difficile* GDH and toxin test and treatment of recurrence the following rules are implemented for evaluation of recurrence:

- A subject is only considered to have a recurrence if there is at least 1 day with > 3 UBMs within a window of 4 days prior to (and including) either the GDH and toxin test stool sample date or the AMT start date / FMT date (handling of missing UBMs: see below).
- GDH and toxin test results for stool samples taken prior to a NED are not considered.
- AMT/FMT with start date prior to a NED are not considered.
- GDH and toxin test results for stool samples taken after the AMT start date or FMT date are not considered.

- If multiple GDH and toxin tests are performed during a period with daily number of UBMs > 3, only the latest stool sample for the toxin test prior to (and including) AMT start date or FMT date is considered.
- Where > 3 UBMs occur on 1 or more days within the window 4 days prior to (and including) AMT start date (or FMT date) and the most recent GDH and toxin test is negative (or positive) but performed on a stool sample collected more than 4 days prior to AMT start date, the GDH and toxin test is not considered and the subject will be considered to have a recurrence in accordance with the missing data rules specified in Table 5.

NED (> 3 UBMs per day): A NED is derived from the daily number of UBMs between EOT + 3 and Visit 5. The number of UBMs per day is determined in the same way as for Clinical Cure [Section 5.5.1]. If there are several consecutive days with > 3 UBMs, NED is the first day.

Note: If Visit 5 occurs after EOT + 32 days, recurrence will be determined using NED information from EOT + 3 days up to EOT + 32 days.

AMT or FMT between EOT + 3 days and Visit 5: Derived as

- any AMT [as defined in Table 3] with start date between EOT + 3 days and Visit 5, inclusive, or if the subject participated in the re-treatment extension with cadazolid;

  or

- any FMT between EOT + 3 and Visit 5 with FMT recorded in the Procedures CRF with a date between EOT + 3 days and Visit 5, inclusive.

A subject is considered to participate in the re-treatment extension if at least one dose of open-label cadazolid has been taken, as recorded on the re-treatment study drug log CRF. AMT start date or FMT date is the start date of the AMT intake or re-treatment start date or the date FMT was performed.

Positive GDH and toxin test from EOT + 3 and Visit 5: Derived as any positive result of an approved GDH and toxin test (either Quik Chek Complete toxin test or any other pre-specified test for GDH as well as toxin) recorded in the CDAD Diagnosis and Microbiology Sample CRF (subjects enrolled under protocol Version 3) or Fecal Sampling CRF (subjects enrolled under protocol versions prior to Version 3) at Visit 4.x (unscheduled visit for a NED), where the corresponding stool sample has been taken between EOT + 3 and Visit 5, inclusive.

Similarly, a negative GDH and toxin test is derived as any negative result of an approved GDH and toxin test.

The relevant date of a GDH and toxin test is the date the corresponding stool sample was taken. It will be used to determine the temporal relationship between NED, toxin test and AMT/FMT.

Handling of missing data:

If a subject receives AMT or FMT, but any of the information to determine number of UBMs within the relevant time window, and a GDH and toxin test, is missing, the subject is still considered as having a recurrence and consequently does not have a Sustained Cure. Details are presented below in Table 5.

Table 5 Handling of missing data for the definition of recurrence

AMT or FMT	EIA GDH and toxin test approved by sponsor **	> 3 UBMs (window)	Recurrence
Yes	Missing or not done	> 3	Yes
No	Positive	> 3	No
No	Missing or not done	> 3	No
Yes	Positive	Missing*	Yes
Yes	Negative (current episode)	Missing*	No
Yes	Missing or not done	Missing*	Yes
No	Positive	Missing*	No
No	Negative	Missing*	No
No	Missing or not done	Missing*	No
Yes	Missing or not done	≤ 3	No
No	Positive	≤ 3	No
No	Missing or not done	≤ 3	No

* Missing includes subjects who have 1 or more days with 'unknown' or missing UBMs from EOT + 3 days to Visit 5/Re-1 or in the 4 days prior to (and including) the GDH and toxin test stool sample date or AMT start date or FMT.

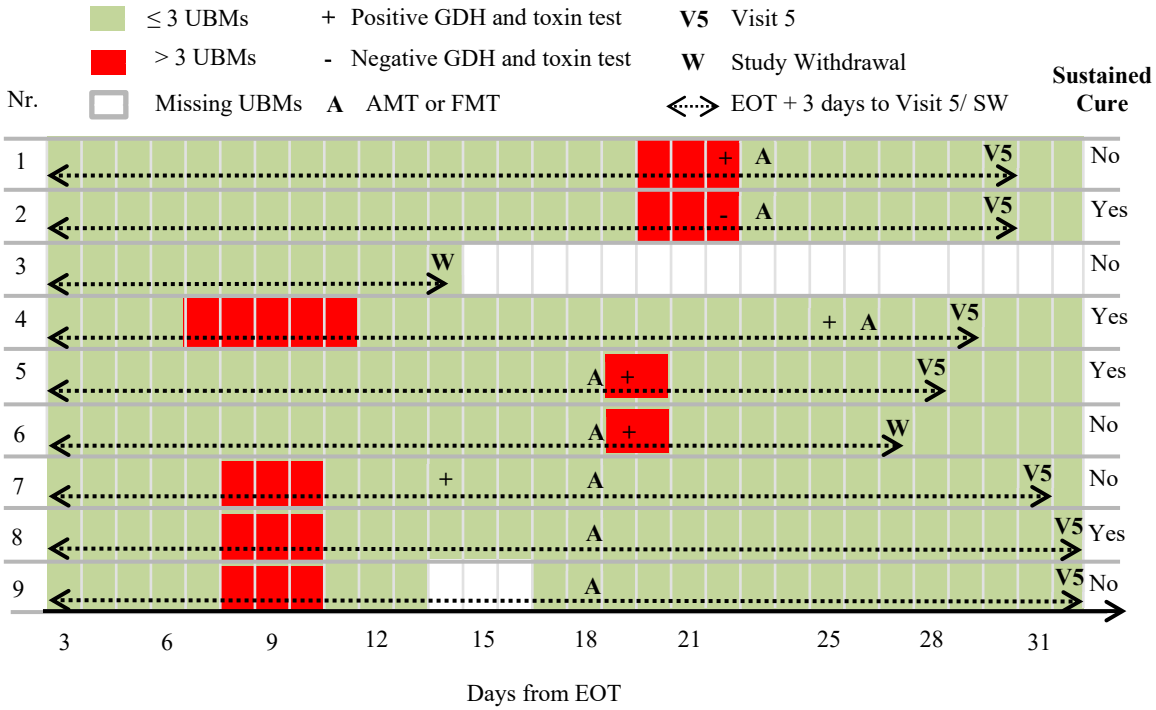
** Only GDH and toxin tests on stool samples taken prior to AMT intake or FMT are considered.

AMT = antimicrobial treatment active against CDAD; CDAD = *Clostridium difficile*-associated diarrhea; EIA = enzyme immunoassay; EOT = End-of-Treatment; FMT = fecal microbiota transplant; GDH = glutamate dehydrogenase; UBM = unformed bowel movement.

Handling of missing Visit 5: For subjects entering the re-treatment extension, Visit 5 is not performed and recurrence is assessed between EOT + 3 days and start of re-treatment. For subjects that have neither Visit 5 nor started re-treatment, the variables Recurrence and Sustained Cure are evaluated using Study Withdrawal date instead of Visit 5 date. If Study Withdrawal occurs after EOT + 32 days, recurrence will be determined using NED information from EOT + 3 days up to EOT + 32 days.

Handling of missing or partial EOT date is detailed in Section 12, and Sustained Cure will be evaluated based on the imputed EOT date (earliest between scheduled EOT date, EOS date, and death date).

Figure 6 Sustained Cure: Derivation examples



AMT = antimicrobial treatment active against CDAD; EOS = End-of-Study; EOT = End-of-Treatment; FMT = fecal microbiota transplant; SW = study withdrawal; UBM = unformed bowel movement.

Reasons for Not Sustained Cure:

Reasons for classifying subjects as Not Sustained Cure are further categorized as described in Table 6.

Table 6 Reasons for Not Sustained Cure

Short description	Derivation details
Not Sustained Cure	
Clinical Failure	All subjects with Clinical Failure.
Recurrence:	Clinical Cure with recurrence
AMT, Positive toxin test, > 3 UBMs (window)	Subjects with AMT (including re-treatment or FMT between EOT + 3 days and Visit 5), positive toxin test (i.e., approved GDH and toxin test with positive result between EOT + 3 days and the earliest of Visit 5 and AMT intake*), and at least one day with > 3 UBMs in the 4 days prior to (and including) AMT intake or sampling for GDH and toxin test.
AMT, Positive toxin test, missing UBM (window)	Subjects with AMT (as above), positive toxin test (as above), and at least one day with missing UBMs and no day with > 3 UBMs in the 4 days prior to (and including) AMT intake or sampling for GDH and toxin test.
AMT, No toxin test, > 3 UBMs (window)	Subjects with AMT (as above), no toxin test (i.e., no approved GDH and toxin test result between EOT + 3 days and the earliest of Visit 5 and AMT intake*), and at least one day with > 3 UBMs in the 4 days prior to (and including) AMT intake.
AMT, No toxin test, missing UBM (window)	Subjects with AMT (as above), no toxin test (as above), and at least one day with missing UBMs and no day with > 3 UBMs in the 4 days prior to (and including) AMT intake.
Premature Study Withdrawal prior to EOT + 28 days and Day 38	Premature Study Withdrawal prior to EOT + 28 and Day 38 for subjects without recurrence. [Note: Includes only subjects with Clinical Cure].
Insufficient follow-up	Visit 5 date prior to EOT + 28 days and Day 38 for subjects without recurrence and without premature study withdrawal prior to EOT + 28 days and Day 38 [Note: Includes only subjects with Clinical Cure].

* Toxin test results are considered if also within 4 days prior to and including AMT start date.
AMT = antimicrobial treatment active against CDAD; EOT = End-of-Treatment; FMT = fecal microbiota transplant; GDH = glutamate dehydrogenase; UBM = unformed bowel movement.

Reasons for classifying subjects with Clinical Cure with no Recurrence are further categorized as: subjects with no AMT taken; subjects with AMT and negative GDH or toxin test in window 4 days prior to (and including) AMT intake; and subjects with AMT, positive toxin test but ≤ 3 UBM on all days in the 4 days prior to (and including) AMT intake.

5.5.2.2 Time to ROD

Time to ROD is defined as the time (h) elapsed between the first dose of study drug and the time when ROD is considered achieved.

Time when ROD is considered achieved is the time of the last UBM prior to the first two consecutive 24 h periods with ≤ 3 UBM with subsequent maintenance of ≤ 3 UBMs per day up until EOT + 2. The condition of maintaining ≤ 3 UBMs per calendar day is determined based on the number of UBMs per day as derived for Clinical Cure [Section 5.5.1]. If this last UBM is prior to the first dose of study treatment, the time of ROD is considered equal to the date and time of first dose + 1 min and hence time to ROD is set to 1 min.

Using the above criteria, the date and time when ROD is achieved is defined for subjects with ROD on study treatment and maintained up to EOT + 2 days, using the information from the Stool Log CRF or, if missing, is taken from the presence of > 3 UBMs in the Daily Stool Information CRF.

If that daily UBM count is also missing or 'unknown' in the Daily Stool Information CRF, the subject is considered to have had > 3 UBMs on that day (i.e., ROD did not occur). If the timing of UBM is missing in the Stool Log CRF, the time when ROD is achieved is imputed as 23:59.

Subjects without Clinical Cure are censored at EOT. Similarly, subjects who have withdrawn from the study, died, or are lost to follow-up before EOT + 2 days or have prematurely discontinued treatment are censored at the expected EOT day, i.e., 10 days after starting medication. This constitutes a right-censored observation.

5.5.2.3 Change from baseline in CDI-DaySyms PRO domain scores at Day 3

The CDI-DaySyms PRO has 10 items, from which three domain scores are derived:

Table 7 Domains and items of the CDI-DaySyms® diary

Domain scores	Items
Diarrhea Symptoms	1. Diarrhea
	2. Feeling a need to empty bowels
	3. Needing to go to the bathroom
Abdominal Symptoms	4. Abdominal cramping
	5. Abdominal pain
	6. Feeling bloated
Systemic/Other Symptoms	7. Feeling tired
	8. Lack of Energy
	9. Lightheadedness
	10. Lack of appetite

Each item is scored on a 5-point Likert scale, with possible responses: "None", "Mild", "Moderate", "Severe" and "Very Severe". These responses are converted to numeric values, where None = 0, Mild = 1, Moderate = 2, Severe = 3 and Very Severe = 4.

The domain score for each day is calculated as the mean of the non-missing responses for that domain on that day.

If two adjacent responses (e.g., "mild", "moderate") are recorded by a subject for the same item on the same day, then the response is set to the worst case for this item, e.g., "moderate". Any other cases of multiple responses, such as more than two responses or non-adjacent responses (e.g., "none", "moderate"), are set to missing [see Appendix D].

For the Diarrhea Symptoms domain, a score is always calculated if item 1 "Diarrhea" is available. Otherwise, the domain scores are only calculated if more than 50% of items for a domain are available on a day. As a sensitivity analysis, the Diarrhea Symptoms domain score is re-derived using this 50% rule, i.e., the score is only calculated if more than 50% of the items are available.

The domain scores are calculated at each time point (i.e., for each day) from Day 1 (baseline) to Day 12. The three domains are evaluated in a hierarchical manner, starting with Diarrhea Symptoms, then Abdominal Symptoms, and finally Systemic/Other Symptoms.

5.5.3 Other efficacy variables

5.5.3.1 Investigator's assessment of Early Treatment Response at Visit 2

The variable Early Treatment Response (ETR) is the ETR as assessed by the investigator at Visit 2 as improved, unchanged or worsened compared to baseline. It is taken from the Investigator Assessment of Early Treatment Response CRF.

ETR rate (%) is the proportion of subjects considered to have ETR assessed as 'improved'. Subjects with missing assessment are considered as not improved for the analysis.

5.5.3.2 Investigator's judgment of Clinical Response at Visit 4

The variable Investigator's judgment of Clinical Response (ICR) is the ICR as assessed by the investigator at Visit 4 as Cure or Failure. It is taken from the CRF 'Investigator judgment of Clinical Response (ICR)'. Reasons for assessing the ICR as cure or failure are taken from the answers in the same CRF.

ICR rate (%) is the proportion of subjects with ICR assessed as cured. Subjects with missing assessment are considered as not cured for the analysis.

5.5.3.3 Investigator's evaluation of Clinical Cure per protocol definition

The variable Investigator's evaluation of Clinical Cure per protocol (ICC) definition is taken from the Investigator evaluation of Clinical Cure per protocol definition CRF.

5.5.3.4 Investigator's judgment of Sustained Response at Visit 5

The variable Investigator's judgment of Sustained Response (ISR) is defined as the ISR as assessed by the investigator at Visit 5/Re-1 as Sustained Cure or Not Sustained Cure. It is taken from the Investigator judgment of Sustained Response CRF. Reasons for assessing the ISR as sustained cure or not sustained cure are taken from the same CRF.

Subjects with missing assessment are considered as having 'Not Sustained Cure' for the analysis.

ISR rate (%) is the proportion of subjects with ISR assessed as Sustained Cure at Visit 5/Re-1.

5.5.3.5 Investigator's evaluation of Sustained Cure per protocol definition

The variable Investigator's evaluation of Sustained Cure per protocol definition is taken from the Investigator evaluation of Sustained Cure per protocol definition CRF.

5.5.3.6 Early Clinical Cure by Day 5

Early Clinical Cure (ECC) rate (%) is the proportion of subjects assessed as meeting the criteria for ECC by Day 5, where the criteria for ECC is defined for a subject meeting both the following criteria:

- ROD by Day 5: ≤ 3 UBMs per day for at least 2 consecutive days prior to or including Day 5 and maintained for 2 days after EOT

  AND

- No additional AMT or FMT between first dose of study drug and 2 days after EOT (inclusive).

ROD by Day 5 is determined from the number of UBMs per day in the same way as for Clinical Cure [Section 5.5.1]. To be considered as having Early Clinical Cure the subject must have ≤ 3 UBMs per day from Day 4 up to EOT + 2 days. If the number of UBMs on one or more days is missing or 'unknown' then the subject is considered a Failure.

5.5.3.7 Normalization of bowel movements rate

Normalization of bowel movements (NBM) rate is the proportion of subjects with NBM, where NBM is defined as:

- ≤ 2 bowel movements per day and no UBM on at least 2 consecutive days up to EOT and maintained up to 2 days after last dose of study drug

AND

- No additional AMT or FMT between first dose of study drug and 2 days after EOT (inclusive).

The number of bowel movements and UBMs are determined from the Daily Stool Information CRF. Subjects with missing assessments are considered as not having had NBM for the analysis.

5.5.3.8 Time to return to usual stools

Time to return to usual stools is defined as the time (days) elapsed between the first dose of study drug and the first day where the stools have returned to usual for a subject, i.e., the number of bowel movements (including UBMs) per day ≤ number of bowel movements reported as usual by the subject and maintained for at least 3 calendar days. The number of usual bowel movements is reported by the subject at baseline and recorded in the CRF. Number of bowel movements per day is determined from the Daily Stool Information CRF (where days are measured according to calendar days) between date of first dose up to Visit 5 / re-treatment start date. If the number of bowel movements is missing but 'Check if no bowel movement today' is ticked 'Yes' (Stool Log CRF) the number of bowel movements per day is assigned 0 (unless 'Daily number of UBMs' entered by investigator is 'exact number not known').

For subjects that have neither Visit 5 nor started re-treatment, the Study Withdrawal date is used instead of Visit 5 date in the derivation.

Subjects without a return to usual stools are censored at the last date with known number of bowel movements (within Daily Stool Information CRF). Subjects without any day with known number of bowel movements are censored at study treatment start date.

5.5.3.9 Recurrence rate and adjusted recurrence rate

Recurrence rate (%) is the proportion of subjects assessed as having a recurrence [see definition in Section 5.5.2.1] out of subjects meeting the criteria for Clinical Cure. It is defined as:

$$\text{Recurrence rate (\%)} = 100 * \frac{\text{Number of subjects with Recurrence}}{\text{Number of subjects with Clinical Cure}}$$

The Adjusted Recurrence Rate is the proportion of subjects assessed as having a recurrence out of subjects in the analysis set. It is defined as:

$$\text{Adjusted Recurrence Rate (\%)} = 100 * \frac{\text{Number of subjects with Recurrence}}{\text{Number of subjects in analysis set}}$$

The following relationship exists between the two measures:

Adjusted Recurrence Rate (%) = Recurrence Rate (%) * Clinical Cure Rate (%).

Recurrence rate estimates are accompanied by the proportion of subjects with recurrence in the analysis set.

Recurrence is classified either as relapse or re-infection [Section 5.5.4.2].

5.5.3.10 Time to recurrence

If a subject meets the criteria for recurrence then time to recurrence is determined. It is defined as the period (h) between the time of the last dose of study drug and the onset of the NED determined to be a recurrence.

NED determined to be a recurrence is defined by a day with > 3 UBMs within the time window 4 days prior to (and including) AMT intake (or FMT date) or positive GDH and toxin test [see Section 5.5.2.1.1]. The date when the NED started is the first day with > 3 UBMs in the time window. If this falls on the first day of the window, previous days are assessed for > 3 UBMs to determine the onset date of that NED. The period of interest is between EOT + 3 days and Visit 5 / re-treatment start date.

Onset time of the NED is defined as the time of the first UBM recorded in the Stool Log CRF on the NED onset date.

If NED information is missing (no day with > 3 UBMs in the time window), onset date/time is defined as either the date and time of positive EIA GDH and toxin test approved by the sponsor, or the start of AMT or FMT, or the start of re-treatment, whichever is earliest, between EOT + 3 days and Visit 5. Days with missing or not known UBMs are not considered for determining the onset date in derivations above.

Subjects considered as having Sustained Cure, i.e., clinically cured and without establishment of recurrence or death, are censored at their Visit 5 date. Subjects who died after EOT + 3 days are censored at the date/time of death. Subjects without establishment of recurrence who are lost to follow-up without a Visit 5, are censored at the last contact date [see Section 11.3], and subjects without recurrence who have insufficient follow-up are censored at their Visit 5 date. If time (NED onset time or EOT time) is not available then time is imputed as 00:00.

Subjects not clinically cured (and therefore not at risk for a recurrence) are not considered for this endpoint.

If Visit 5 is missing it is replaced with the study withdrawal date in derivations (for subjects starting re-treatment it is replaced with the re-treatment start date).

5.5.3.11 Modified Sustained Cure

Modified Sustained Cure is defined using the following modified definition of recurrence (independent of a *C. difficile* stool positive GDH and toxin test) for subjects with Clinical Cure. Modified recurrence is defined as follows:

- NED (> 3 UBMs on any day between EOT + 3 days and Visit 5)

  AND

- AMT (including participation in the re-treatment extension with cadazolid) or FMT started between EOT + 3 days and Visit 5).

Subjects with Clinical Cure but without modified recurrence are considered to have a Modified Sustained Cure.

All rules, including the handling of insufficient follow-up and missing data as specified for the variable SCR [Section 5.5.2.1], will apply to this modified SCR.

5.5.3.12 CDI-DaySyms PRO response rate at Day 3

$$\text{Response Rate (\%)} = 100 * \frac{\text{Number of subjects meeting response threshold}}{\text{Number of subjects in analysis set}}$$

A responder to treatment is defined as a subject with an observed change from baseline in domain score below a predefined threshold for each domain, as described in Table 8. See the scoring and analysis guideline in Appendix D for more details of this definition.

Change from baseline is derived as [value post-baseline] – [value at baseline], where baseline is the value recorded at Day 1. A negative value for change from baseline corresponds to a reduction in domain score, i.e., an improvement. Subjects with missing values at baseline or at Day 3 are considered to be non-responders.

Table 8 Threshold for responders (response definition)

Domain Score	Threshold
Diarrhea Symptoms	−1.00
Abdominal Symptoms	−0.80
Other/Systemic Symptoms	−0.70

5.5.4 Microbiology variables

Baseline is defined for microbiology variables as the last sample taken up to treatment start date (inclusive) with available result.

5.5.4.1 Isolation of C. difficile

Isolation of *C. difficile* isolates by the central laboratory via culturing is planned to be performed per protocol at Visit 1, at Visit 3 for subjects considered Clinical Failure, and at Visit 4.x for subjects considered a Recurrence.

A subject is defined as presenting:

– a *C. difficile* isolate at the time point under consideration if *C. difficile* was isolated by the central laboratory from any stool sample corresponding to that time point (*C. difficile* culture result available with outcome 'Isolated'),

– no *C. difficile* isolate at that time point if *C. difficile* was not isolated by the central laboratory in all stool samples corresponding to that time point (*C. difficile* culture result available with outcome 'Not isolated').

It is defined at the following time points:

- **Baseline**, defined as the last sample taken (fecal sampling date/time) up to treatment start date (inclusive) with available *C. difficile* culture result,
- **Visit 3**,
- **Visit 4.x**, it is considered recovered if it was recovered in any stool sample collected at any Visit 4.a, 4.b, etc., or at Visit Re-1.

The following definitions are considered:

Baseline *C. difficile* isolate is defined as the *C. difficile* isolate from the baseline fecal sample (see baseline definition above for identifying the sample).

Handling of multiple *C. difficile* isolates: In the unplanned event that multiple *C. difficile* isolates from different stool samples are present with identical fecal sampling date/time (e.g., due to unplanned testing of back-up samples), the isolate cultured earliest is considered for determining baseline. The isolate cultured earliest is identified by the earliest test or plating date/time or, if identical, by the lowest laboratory identifier number (MBREFID). All isolates for a subject and time point with duplicated fecal sampling date/time but not cultured earliest are flagged as repeats.

Note: It is anticipated that the central laboratory may identify up to 2 phenotypically distinct C. difficile isolates from a small minority (i.e., < 1%) of stool specimens. Data on phenotypically distinct isolates from a single stool specimen (and single C. difficile culture) will be entered separately into the database. In these exceptional cases the results from isolate 2 will not be included in summary tables and figures, but will be included in listings. This applies also to all further C. difficile microbiology variables including typing and susceptibility variables. Isolate 2 data are identified in the data transfer specification by MBTEST variables ending with 'ISOLATE 2'.

5.5.4.2 Typing of C. difficile

C. difficile isolates are identified by using PCR ribotyping and restriction endonuclease assay (REA) typing information provided by the central laboratory.

5.5.4.2.1 Ribotyping of C. difficile

- **Ribotype** of a C. *difficile* isolate is the so-called 'ribotype initial type' provided by the central laboratory. Further ribotype information variables include the ribotype subtype and ribotype comments.
- **Hypervirulent ribotypes** are those ribotype initial types belonging to the hypervirulent strains [see also Section 5.2.2]: 027, 244, 078.
- **Baseline ribotype**, defined as the ribotyping result (initial type) from the baseline *C. difficile* isolate.
- **Ribotype as compared to baseline:** comparison of ribotype information from post-baseline isolate against the baseline *C. difficile* isolate. They are defined as having:
  - *Different ribotypes*, in the event of different ribotype information at baseline vs post-baseline, i.e., either different initial type or subtype.
  - *Identical ribotypes*, in the event of matching ribotype information at baseline and post-baseline, i.e., identical initial type or initial types "AC-UNK" with identical subtype.

5.5.4.2.2 REA typing of C. difficile

- **REA group** of a *C. difficile* isolate is the so-called 'REA initial group' provided by the central laboratory. Further REA type variables include the 'REA consistency' (to be interpreted together with laboratory isolate number) and 'REA comments'.
- **REA groups of special interest** of a *C. difficile* isolate are the following REA initial groups: BI and BK group. *Note: It is anticipated that BI group is equivalent to ribotypes 027 and 244, and BK group is equivalent to ribotype 078.*
- **Baseline REA group**, defined as the REA typing result (REA initial group) from the baseline *C. difficile* isolate.
- **REA type as compared to baseline:** comparison of REA type information from post-baseline isolate against the baseline isolate. They are defined as having:
  - *Identical REA groups*, in the event of identical REA profiles:

    REA initial group is identical and samples have been identified as matching by the laboratory (either REA consistency is "Matches xxx" where "xxx" laboratory sample number [MRL ID] of the baseline isolate; or REA consistency contains a subtype [e.g., "Y6"] that is identical to the baseline subtype).

– *Different REA groups*, in the event of different REA profiles:

Either REA initial group differs or REA consistency differs for subjects with identical REA initial group, i.e., samples have not been identified as matching by the laboratory (REA consistency is "Matches xxx, yyy, zzz, …" where none of "xxx", "yyy", "zzz", … match the laboratory sample number [MRL ID] of the baseline isolate; or REA consistency contains a subtype [e.g., Y6] that differs from the baseline subtype).

Notes: REA consistency of "None seen" does not reflect a subtype, and cannot be considered a confirmation that the REA profile differs from any other REA profile in the study. Therefore, the comparison of two isolates with identical REA initial group but REA consistency of "None seen" is considered undetermined.

5.5.4.2.3 Relapse and Re-infection

Subjects with Recurrence are classified either as:

- **Relapse:** Identical *C. difficile* strain identified either by REA typing or ribotyping at new episode of diarrhea and baseline, i.e., subjects with identical ribotypes and identical REA groups as per definitions above, at (all) new episode of diarrhea visit(s) as compared to baseline.

  OR

- **Re-infection:** Different *C. difficile* strains identified either by REA typing or ribotyping at (any) new episode of diarrhea and baseline, i.e., subjects with either different ribotype or different REA group at (any) new episode of diarrhea visit(s) as compared to baseline.

New episode of diarrhea visit(s), Visit 4.x, are defined as: Visit 4.a, 4.b, etc., and Visit Re-1. Repeat isolates with identical fecal sampling date/time as defined in Section 5.5.4.1 are included in the derivation of relapse and re-infection.

Handling of missing typing information: A subject with Recurrence is considered to be undetermined for Relapse and Re-infection if no *C. difficile* typing information is available at baseline or at (any) new episode of diarrhea visit(s). If typing information is missing for one of the two typing methods only, the classification is performed using the available typing information at baseline and at Visit 4.x, i.e., the subject is considered a Relapse if the available *C. difficile* typing information is identical, a Re-infection if the available typing information is different, and undetermined if the available typing comparison is undetermined.

5.5.4.3 Susceptibility of C. difficile

Susceptibility of *C. difficile* to different antibiotics is determined at the central laboratory for each *C. difficile* isolate by the minimum inhibitory concentration (MIC; in μg/mL) of

the test agent (i.e., cadazolid, vancomycin, linezolid, moxifloxacin, metronidazole and fidaxomicin) which inhibits bacterial growth. Per protocol it is planned to be evaluated at Visit 1, for Clinical Failures at Visit 3, and for Recurrences at Visit 4.x if *C. difficile* was isolated [see Section 5.5.4.1].

Susceptibility of *C. difficile* to each of the test agents is the MIC (µg/mL) reported by the central laboratory and is defined at the following time points:

- Baseline, defined as the MIC result from the baseline *C. difficile* isolate.
- Visit 3.
- Visit 4.x, the maximum MIC of *C. difficile* in stool samples collected at any Visit 4.a, 4.b, etc., or Visit Re-1.
- Maximum post-baseline result, maximum MIC of *C. difficile* during main study.

Handling of multiple C. difficile isolates: In the event of multiple post-baseline isolates at a time point, the highest MIC is considered for analysis. At baseline the MIC of the baseline *C. difficile* isolate is considered.

Note: The MIC values will be provided using categories such as: ≤ 0.03, 0.06, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, > 32. The range of tested MIC depends on the test agent.

5.5.4.4 Change from baseline in susceptibility of C. difficile

This variable is defined as the relative change in MIC of cadazolid, vancomycin, linezolid, fidaxomicin, metronidazole, and moxifloxacin at post-baseline compared to baseline using the following ratio: MIC at post-baseline / MIC at Baseline. MIC classified as > × µg/mL, will be treated as belonging to the next highest dilution, i.e., 2 × µg/mL (e.g., > 32 will be treated as 64), for the purpose of computing the ratio. The change from baseline is grouped into the categories described below in Table 9.

Table 9 Relative changes in minimum inhibitory concentration

Category	Example Changes (µg/mL)
≥ 4-fold decrease	e.g., decrease from 16 to 4, or from > 32 to 16, or 16 to 2, or > 32 to 8
2-fold decrease	e.g., decrease 8 to 4, or from > 32 to 32, or 0.06 to ≤ 0.03
No MIC change	No change, e.g., from 8 to 8
2-fold increase	e.g., increase from 4 to 8, or from 32 to > 32, or ≤ 0.03 to 0.06
≥ 4-fold increase	e.g., increase from 4 to 16, or from 16 to > 32, or ≤ 0.03 to 0.125

MIC = minimum inhibitory concentration.

5.5.4.4.1 Antibiogram comparison to baseline

Defined as antibiogram comparison of post-baseline isolate with the baseline isolate. Two *C. difficile* isolates are considered to have:

- *Different antibiograms*, in the event of a ≥ 4-fold MIC difference of *C. difficile* in two unrelated test agents, i.e.,
  - ≥ 4-fold MIC difference in at least one cadazolid related agent (cadazolid, linezolid, moxifloxacin)

    AND
  - ≥ 4-fold MIC difference in at least one cadazolid nonrelated agent (vancomycin, metronidazole, fidaxomicin)
- *Similar antibiograms*, if susceptibility of *C. difficile* information for both isolates is available (for at least one agent per group) and they are not considered to have different antibiograms.

5.5.4.5 Isolation of vancomycin-resistant enterococci

Isolation of vancomycin-resistant enterococci (VRE; central laboratory) is performed by the central laboratory at baseline and at Visit 3.

Baseline is defined as the last fecal sample (fecal sampling date/time) taken up to treatment start date (inclusive) with available VRE isolation result (i.e., VRE-positive or VRE-negative), see also note below.

A subject is defined at a time point to be:

- 'VRE-positive' where vancomycin-resistant enterococci were present in any test sample corresponding to that time point:

  Any VRE type (vancomycin-resistant *Enterococcus faecium,* vancomycin-resistant *Enterococcus faecium* 2^{nd} *colony morphology*, vancomycin-resistant *Enterococcus faecalis,* vancomycin-resistant *Enterococcus faecalis* 2^{nd} *colony morphology*, or vancomycin-resistant *Enterococcus* not *E. faecium* and not *E. faecalis*) with outcome "Isolated" or with recorded quantitative counts.
- 'VRE-negative' where vancomycin-resistant enterococci were not present in all test samples corresponding to that time point:

  Vancomycin-resistant *Enterococcus* with outcome "No isolated".

Handling of multiple test samples at a time point: If multiple test samples (different MBREFID) with identical fecal sampling date/time are available at a time point then the sample for analysis or determining the baseline VRE test sample is identified in the following hierarchy: (i) prefer VRE-positive samples over VRE-negative samples,

(ii) select earliest test sample (test sample with earliest testing date/time), or if identical testing date/time, use the lowest laboratory identifier number MBREFID. This approach also applies to all variables related to VRE defined in the following Sections 5.5.4.6 to 5.5.4.8.

Rationale: This situation is not expected as per protocol and may only arise in rare case of unplanned testing of e.g., back-up samples.

5.5.4.6 Vancomycin-resistant enterococci quantitative culture

The central laboratory provides the density of VRE counts (log10 cfu/mL) at baseline and Visit 3 for all subjects with quantifiable VRE counts by VRE type.

Total VRE counts (log10 cfu/mL) per test sample are defined as the log10 of the sum of counts (x cfu/mL = 10^{x log10 cfu/mL}) for isolates identified as: vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus* not *E. faecium* and not *E. faecalis*, including also second colony morphology counts.

Total VRE counts for subjects considered VRE-negative at a time point, i.e., with no VRE present, are imputed for the analysis with a Total VRE count of 0 log10 cfu/mL (= 1 cfu/mL). This approach allows allocation of a suitable VRE count value to subjects with no VRE present.

Total VRE counts and VRE counts per VRE type are considered at baseline and Visit 3. Baseline VRE count is defined as VRE count from the baseline VRE test sample [see Section 5.5.4.5]. *Note: A quantitative VRE assessment includes all VRE types assessed within the same test sample, i.e., for assessing total counts VRE types should not be selected from different test samples (different MBREFIDs).*

5.5.4.7 Change from baseline in vancomycin-resistant enterococci quantitative culture at Visit 3

This is defined as the difference between the Visit 3 and baseline total VRE counts (log10 cfu/mL). It is derived including imputed total VRE counts.

5.5.4.8 Susceptibility of vancomycin-resistant enterococci to different antibiotics

Susceptibility of VRE performed by the central laboratory is defined as the MIC (µg/mL) of the test agents (cadazolid, vancomycin, linezolid, moxifloxacin, fidaxomicin, daptomycin, tigecycline, ampicillin, gentamicin, and quinupristin-dalfopristin).

It is determined at baseline and by visit per isolate type: *VRE faecium* (first and second colony), *VRE faecalis* (first and second colony) and VRE not *faecium* not *faecalis*; and for any type (first colony) as the highest MIC of *VRE faecium*, *VRE faecalis,* or *VRE* not *faecium* not *faecalis* (first colony only). Change from baseline in susceptibility of VRE is defined as described in Table 9 for change from baseline in susceptibility of *C. difficile*.

5.5.5 Re-treatment extension variables

Primary and relevant secondary efficacy variables for the re-treatment extension with cadazolid are defined in the same way as the corresponding variables described above for the main double-blind part of the study with the appropriate change in dates or periods or interest.

Re-treatment Clinical Cure:

In the re-treatment extension, resolution of diarrhea is determined on re-treatment and maintained up to End of Re-treatment + 2 days. The algorithm is the same as the one described in Section 5.5.1, but using the information reported during the re-treatment with cadazolid.

Recurrence after re-treatment:

Recurrence is defined as for the main treatment period but using End of Re-treatment + 3 days and the Re-5 visit. For re-treated subjects with missing Re-5 visit, evaluation is based on Study Withdrawal date instead of Re-5 visit date.

Re-treatment Sustained Cure:

Sustained Cure is defined as Clinical Cure in the re-treatment extension period and no recurrence during the follow-up period up to Visit Re-5. For re-treated subjects with missing Re-5 visit, evaluation is based on Study Withdrawal date instead of Re-5 visit date.

In the event of death by any cause, premature study withdrawal or being lost to follow-up, from End of Re-treatment + 2 days and prior to End of Re-treatment + 28 days, and premature study withdrawal prior to 38 days from first re-treatment dose, the subject is considered not to have a Sustained Cure in the re-treatment extension period.

Re-treatment microbiology variables:

Microbiology variables during re-treatment are defined identically to those defined for the main study but using re-treatment baseline instead of baseline, and Visit Re-3 and Visit Re-4.x instead of Visit 3 and Visit 4.x respectively.

Re-treatment Baseline for microbiology variables is defined based on the last sample taken up to re-treatment start date (inclusive) with available result. Only samples after EOT are considered.

5.6 Safety variables

Safety variables are defined in this section for the main study (double-blind part and follow-up) and for the open-label re-treatment extension.

Main study safety variables for subjects who enter the re-treatment extension, are considering information from study treatment start up to re-treatment start. Re-treatment extension safety variables consider information collected after re-treatment start.

The period defining treatment-emergent events is defined for this study from study treatment start up to EOT + 7 days.

Similarly the period defining re-treatment emergent events is defined from open-label re-treatment start up to End of Re-treatment + 7 days.

In addition the period from study treatment start up to Visit 5 is used for main study safety displays. Visit 5 is planned to be conducted between EOT + 28 and EOT + 32 days. It is the last visit conducted during the main study follow-up period and is expected to be the EOS date. In the event of missing Visit 5, information up to EOS is considered.

Similar re-treatment extension displays are prepared from re-treatment start up to Visit Re-5, which is scheduled to be conducted between End of Re-treatment + 28 and + 32 days and is expected to be the EOS date for re-treated subjects.

5.6.1 Adverse events

An AE is any event reported by the investigator on the Adverse Event CRF. All AEs are coded using MedDRA version 19. Each preferred term is counted as an event.

AEs are classified according to the period of occurrence of the event. Events are considered to be:

- **Main study adverse events**: where the start date/time of the event is from the first dose date/time of intake of study treatment up until Visit 5 (inclusive) or prior to the first dose of re-treatment with cadazolid.
- **Treatment-emergent adverse events**: where the start date/time of the event is from the first dose date/time of intake of study treatment up to EOT + 7 days (inclusive) or prior to the first dose of the re-treatment period (if before EOT + 7 days).
- **Re-treatment extension adverse events**: where the start date/time of the event is from the first dose date/time of starting re-treatment with cadazolid up until Visit Re-5 (inclusive).
- **Re-treatment-emergent adverse events**: where the start date/time of the event is from the first dose intake of re-treatment up to the End of Re-treatment + 7 days (inclusive).

In the event of missing or incomplete dates/times, the rules described in Section 12 are applied.

Several variables defining the number of days between a specific date and the onset date of an AE are derived according to definitions in Section 11.3: AE days from first dose, AE days from last dose, AE days from first re-treatment dose, and AE days from last re-treatment dose. The AE duration is defined as AE end date minus AE onset date + 1.

5.6.1.1 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once for one subject within a specified time period are counted in the frequency table once.

5.6.1.2 Intensity of adverse events

The intensity of an AE is defined as mild, moderate or severe.

AEs reported more than once (as qualified by the same preferred term) for a subject within a specified time period but with different intensities are counted only once, with the worst reported intensity, in the corresponding analysis. If intensity is missing, the event is considered severe.

5.6.1.3 Relationship of adverse events

Relationship to study treatment is defined as 'related' or 'not related'. An event is considered related if the response to the question 'Is there a reasonable possibility that the Adverse Event was related to the use of study drug?' is answered 'Yes'.

For AEs reported more than once (as qualified by the same preferred term) for a subject within a specified time period, the worst relationship reported is taken. Adverse events with missing relationship are considered in any analysis as related.

5.6.2 Deaths

Death days from first dose and death days from last dose are derived using the definitions in Section 11.3 with respect to the date of the death.

5.6.2.1 All deaths

Death information is taken from the Death CRF. The primary cause of death is reported on the same form.

5.6.2.2 Adverse events with fatal outcome

AEs with an outcome reported as 'death' are considered as AEs with fatal outcome.

5.6.3 Serious adverse events

An AE is considered serious if the investigator ticked 'Yes' on the question 'Serious?' of the Adverse Event CRF. AEs with seriousness criteria missing are considered in any analysis as serious AEs.

5.6.4 Non-serious adverse events

An AE is considered non-serious if it is not a serious adverse event.

5.6.5 Adverse events leading to discontinuation of study treatment

These are AEs with 'Action taken with study drug' recorded as 'permanently discontinued' on the Adverse Event CRF.

5.6.6 Other significant adverse events

No other significant adverse events are defined. If, based on the safety reviews, a signal of a potential safety issue is identified, the SAP will either be amended or an addendum written to define the rules to identify the events of interest.

5.6.7 Vital signs and body weight

Vital signs, comprising systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature and body weight are collected on the Vital Signs CRF, scheduled at Visits 1, 3, 4.x (excluding body weight), 5, Re-1, Re-3 and Re-5.

The following variables are defined:

- **Baseline:** The last vital sign assessment (per type) before the date and time of first dose intake of double-blind treatment. (Assessment types: blood pressure and heart rate, temperature, body weight, height.)
- **Re-treatment Baseline:** The last vital sign assessment before the date and time of first dose intake of re-treatment with cadazolid. Only assessments after EOT are considered.
- **Change from baseline in SBP, DBP, HR, body weight and temperature:** Absolute difference in these measurements between the visit and the baseline.
- **Change from re-treatment baseline in SBP, DBP, HR, body weight and temperature:** Defined for visits during re-treatment extension as the absolute difference in these measurements between the visit and the re-treatment baseline.
- **Marked abnormalities in SBP and DBP:** Defined in Table 10.
- **Treatment-emergent marked abnormalities in SBP and DBP:** Any marked abnormality not present at baseline or if a worsening occurred, as compared to the corresponding value at baseline (e.g., change from no marked abnormality to any marked abnormality, from HH to LL or from HH to HHH). The worst abnormality is considered in each direction separately (Low and High). The time window of interest is from after the first intake of study treatment up to EOT + 7 days (inclusive) or first drug intake of the re-treatment period (if applicable), whichever occurs first.

- **Re-treatment-emergent marked abnormalities in SBP and DBP:** Defined as for treatment-emergent marked abnormalities, except the time window is from after the first drug intake of the re-treatment period up to End of Re-treatment + 7 days (inclusive). The re-treatment baseline is used to determine worsening during the re-treatment emergent period.
- **Main study marked abnormalities in SBP and DBP up to Visit 5:** Main study marked abnormalities are defined as for treatment-emergent marked abnormalities above, except the time window of interest is from after the first drug intake up to Visit 5 (inclusive) or first drug intake of the re-treatment period (if applicable).
- **Re-treatment extension marked abnormalities in SBP and DBP up to Visit Re-5:** Defined as above, except the time window of interest is after the first drug intake of re-treatment up to Visit Re-5. The re-treatment baseline is used for worsening during the re-treatment extension.
- **Vital signs days:** Vital signs days from first dose is derived according to definition in Section 11.3 with respect to the assessment date.

Position of the body at the moment of the vital signs measurement will not be taken into account in these definitions as the protocol allows measurement of BP in different positions. If SBP and DBP are taken in a different position at a post-baseline visit than at the baseline visit, the change from baseline will be derived irrespective of the position.

Body temperature may be measured in different locations (rectal, oral, ear, axilla) in °C or °F. Conversion rules are provided in Section 11.1.

Table 10 Marked abnormalities in blood pressure

Blood pressure	LL	LLL	HH	HHH
SBP (mmHg)	SBP < 90 or decrease > 20 from baseline	-	SBP 140–159 or increase > 20 from baseline	SBP ≥ 160
DBP (mmHg)	DBP < 50 or decrease > 10 from baseline	-	DBP 90–99 or increase > 10 from baseline	DBP ≥ 100

Normal limits: 90 ≤ SBP < 140, 50 ≤ DBP < 90
DBP = diastolic blood pressure, SBP = systolic blood pressure.

5.6.8 Electrocardiography

ECGs are scheduled at Visits 1, 3, 5, Re-1, Re-3 and Re-5, and outcomes are recorded either on the local ECG forms of the CRF if assessed at the site, or provided by the central ECG provider electronically.

The following ECG parameters are considered: PR (ms), QRS (ms), QT (ms), HR (bpm), RR (s), QTcB (ms) and QTcF (ms).

Local ECG parameters are recorded in the CRF, apart from the QTc parameters which are automatically derived in the CRF. If QTcB (ms) or QTcF (ms) for local ECG assessments are missing they are derived using the following formulae:

QTcB (ms) = QT (ms)/$RR_{der}^{1/2}$, where RR_{der} is 60/HR (bpm).

QTcF (ms) = QT (ms)/ $RR_{der}^{1/3}$, where RR_{der} is 60/HR (bpm).

Qualitative ECG abnormalities (findings) are recorded in the CRF or provided from the central ECG provider. The standardized coded terms (EGSTRESC) are considered.

The following variables are defined:

- **Baseline:** The last ECG assessment before date and time of first dose intake of double-blind treatment. (An ECG assessment includes all ECG parameters determined at the same collection date/time.)
- **Changes from baseline in ECG parameters:** The absolute difference between the visit and the baseline for each ECG parameter (HR, PR, QT, QRS, QTcB, QTcF).
- **Re-treatment baseline:** The last ECG assessment before date and time of first dose intake of re-treatment with cadazolid. Only assessments after EOT are considered.
- **Changes from re-treatment baseline in ECG parameters:** Defined for visits during re-treatment extension as the absolute difference between the visit and the re-treatment baseline for each ECG parameter (HR, PR, QT, QRS, QTcB, QTcF).
- **Treatment-emergent marked abnormalities (change) in QT/QTc:** A change is defined as an increase from baseline in QT, QTcB or QTcF, which is > 30 ms (HH), or by an increase from baseline > 60 ms (HHH). It is considered treatment-emergent if it occurred after first dose intake up until EOT + 7 days (inclusive) or first drug intake of the re-treatment period (if applicable), whichever occurs first.
- **Re-treatment-emergent marked abnormalities (change) in QT/QTc:** Defined as above except the time window is after the first drug intake of re-treatment up to End of Re-treatment + 7 days, and the increases are determined from the re-treatment baseline.

- **Treatment-emergent QT/QTc marked abnormalities (absolute):** There are three different categories of abnormalities for QT/QTc (QTcB or QTcF) values; they are defined as: QT/QTc > 450 ms (H), > 480 ms (HH), or > 500 ms (HHH). An abnormality is considered treatment-emergent if it occurred after first dose intake of study treatment up until EOT + 7 days (inclusive, or first drug intake of the re-treatment if applicable), and it worsened from baseline, i.e., a change from no marked abnormality to HH or HHH, or from HH to HHH. The worst abnormality is used for analysis. Examples for treatment-emergent abnormalities for QT/QTc are given in Table 12. In order to allow appropriate interpretation of overall incidence of abnormalities > 450 ms, the marked abnormalities are presented cumulatively, e.g., a QTc value of 501 ms is reported in > 450 ms (H), > 480 ms (HH) and > 500 ms (HHH) categories.
- **Re-treatment-emergent QT/QTc marked abnormalities (absolute):** Defined as above, except the time window is after the first drug intake of re-treatment up to End of Re-treatment + 7 days (inclusive). The re-treatment baseline is used to determine worsening during re-treatment.
- **Treatment-emergent qualitative ECG abnormalities (findings):** defined as a finding that was not present at baseline and where the ECG interpretation is abnormal. It is considered treatment-emergent if it occurred after first dose intake up until EOT + 7 days (inclusive) or first drug intake of re-treatment (if applicable), whichever occurs first.
- **Re-treatment-emergent qualitative ECG abnormalities (findings):** Defined as above, except the time window is after the first drug intake of re-treatment up to End of Re-treatment + 7 days, and the increases are determined from the re-treatment baseline.
- **Main study QT/QTc marked abnormalities (absolute and change):** Defined as for treatment-emergent QT/QTc marked abnormalities except the time window is after the first dose of treatment intake up until Visit 5 (or first dose of re-treatment if applicable).
- **Main study qualitative ECG abnormalities (findings):** Defined as for treatment-emergent qualitative ECG abnormalities except the time window is after first dose intake of treatment up until Visit 5 (or first dose of re-treatment if applicable).
- **Re-treatment QT/QTc marked abnormalities (absolute and change):** Defined as above, except the time window is after the first drug intake of the re-treatment up to Visit Re-5, and baseline is the re-treatment baseline.

- **Re-treatment qualitative ECG abnormalities (findings):** Defined as above, except the time window is after the first drug intake of the re-treatment up to Visit Re-5, and baseline is the re-treatment baseline.
- **ECG days:** ECG days from first dose is derived according to the definition in Section 11.3 with respect to the assessment date.

Note: If both central and local ECG readings are available at a time point, only the central ECG reading is taken into account for displays in tables and figures. All measurements will be displayed in listings.

Table 11 Marked abnormalities in ECG (absolute and change)

Parameter	LL	LLL	H	HH	HHH
QT/ QTc (ms) (absolute)			> 450	> 480	> 500
QT/ QTc (ms) (change)				> 30	> 60

QTc = corrected QT.

Table 12 Examples of treatment-emergent QT/QTc marked abnormalities

Treatment-emergent (Yes, No)				
		Category/Threshold		
Baseline	**Post-baseline**	**H**	**HH**	**HHH**
449 ms	451 ms	Yes	No	No
455 ms	469 ms	No	No	No
455 ms	481 ms	Yes	Yes	No
455 ms	501 ms	Yes	Yes	Yes

Note: Treatment-emergent QT/QTc marked abnormalities are presented in a cumulative way.

5.6.9 Laboratory

Laboratory parameters (hematology, coagulation and chemistry) are collected on the central or local laboratory CRF. Assessments are performed at Visits 1, 3, 4.x, 5, Re-1, Re-3, Re-5 and unscheduled visits.

The following parameters are considered:

- **Hematology:** Hemoglobin, hematocrit, platelets, erythrocytes, WBC counts (or leukocytes), neutrophils, lymphocytes, monocytes, eosinophils, basophils.
- **Coagulation:** Prothrombin time, international normalized ratio (INR), activated partial thromboplastin time.

- **Chemistry:** Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, creatinine, urea / blood urea nitrogen (BUN), sodium, potassium, chloride, calcium, protein, albumin.

All parameters are considered in SI units and results are taken from the central laboratory CRF. Manual differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils) are used where automated ones are not provided by the central laboratory. Pre-CDAD diagnosis assessment of creatinine is not included in the analyses of laboratory variables [Section 10.9.4] as this laboratory test is historical and not performed as part of the study.

If, for a visit, no central laboratory result is available, but a local laboratory result is recorded on the same date, the local laboratory result is used. If the normal ranges differ between local and central laboratory, only for graphics or tables with average values, the local laboratory value (Y_{loc}) and their normal ranges (LLN_{loc}, ULN_{loc}) are normalized as Y_{norm} using the central laboratory normal ranges (LLN, ULN) as follows:

$$Y_{norm} = LLN + \frac{(Y_{loc} - LLN_{loc})}{(ULN_{loc} - LLN_{loc})} * (ULN - LLN)$$

If the value is negative after normalization, zero will be assigned.

When determining marked abnormalities, all assessments, including unscheduled and local laboratory results, are considered. Marked abnormalities for local laboratory results are derived based on the non-normalized results except where change from baseline is used (hemoglobin when assessing HH and HHH, INR for subjects on anticoagulation, and creatinine when assessing if > multiple of baseline). The central laboratory provides BUN and not urea. However urea may be reported by the local laboratories in rare cases of unscheduled visits. For deriving marked abnormalities in BUN, local laboratory urea results are considered as BUN with conversion factor 1 (mmol/L).

The following variables are defined for each parameter separately:

- **Baseline:** The last assessment before date and time of first dose intake of study treatment.
- **Re-treatment Baseline:** The last assessment before date and time of first dose intake of study re-treatment. Only assessments after EOT are considered.
- **Change from baseline:** The absolute difference between the visit and the baseline values.
- **Change from re-treatment baseline:** Defined for visits during re-treatment extension as the absolute difference between the visit and the re-treatment baseline values.

- **Marked abnormalities** in laboratory parameters are defined in Table 13.
- **Treatment-emergent laboratory marked abnormalities:** Any marked abnormality not present at baseline if a worsening occurred as compared to the corresponding value at baseline (e.g., from no marked abnormality to any marked abnormality, from LL to LLL or from HH to HHH). The worst abnormality is considered in each direction separately (Low and High). The time window of interest is after the first drug intake up to EOT + 7 days (inclusive) or first drug intake of the re-treatment (if applicable), whichever occurs first.
- **Re-treatment-emergent laboratory marked abnormalities:** Defined as for treatment-emergent abnormalities, except the time window is after the first drug intake of the re-treatment period up to End of Re-treatment + 7 days (inclusive). Worsening is compared to the re-treatment baseline.
- **Main study marked abnormalities up to Visit 5:** Defined as for treatment-emergent marked abnormalities, except the time window of interest is from the first drug intake up to Visit 5 (or first drug intake of the re-treatment, whichever occurs first).
- **Re-treatment extension marked abnormalities up to Visit Re-5:** As above, except the time window is after the first drug intake of re-treatment up to Visit Re-5 (inclusive). Worsening is compared to the re-treatment baseline.
- **Laboratory days:** Laboratory days from first dose and laboratory days from last dose are derived according to the definition in Section 11.3 with respect to the assessment date.

Table 13 Marked abnormalities in laboratory parameters

Safety Parameter	LL	LLL	HH	HHH
Hematology				
Hemoglobin (g/L)	< 100	< 80	Increase (> 20 g/L) above ULN or above baseline if baseline is above ULN	Increase (> 40 g/L) above ULN or above baseline if baseline is above ULN
Hematocrit (%)	< 28% F < 32% M	< 20%	> 60% M > 55% F	> 65%
Platelet count (10^9/L)	< 75	< 50	> 600	> 999
Neutrophils (10^9/L)	< 1.5	< 1.0		
Eosinophils (10^9/L)			> 5.0	
Lymphocyte (10^9/L)	< 0.8	< 0.5	> 4.9	> 20
WBC count (10^9/L)	< 3.0	< 2.0	> 20.0	> 100.0
Coagulation				
INR			> 1.5 × ULN if not on anticoagulation or > 1.5 × above baseline if on anticoagulation	> 2.5 × ULN if not on anticoagulation or > 2.5 × above baseline if on anticoagulation
Chemistry				
AST (U/L)			> 3 × ULN	> 5 × ULN
ALT (U/L)			> 3 × ULN	> 5 × ULN
Alkaline phosphatase (U/L)			> 2.5 × ULN	> 5 × ULN
Total bilirubin (µmol/L)			> 2 × ULN	> 5 × ULN
BUN / UREA (mmol/L)			> 2.5 × ULN	> 5 × ULN
Creatinine (µmol/L)			> 1.5 × ULN or > 1.5 × baseline if baseline is above ULN	> 3 × ULN or > 3 × baseline if baseline is above ULN
Albumin (g/L)	< 30	< 20		
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)		< 130	> 150	> 155

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; ULN = upper limit of normal; WBC = white blood cell.

For INR, a subject is considered to be on anticoagulation if the subject took antithrombotic agent (ATC codes B01A) and date of INR assessment is on or after start of anticoagulation therapy.

- **Main study elevated liver test (LT):** Any LT abnormality occurring after the first drug intake up to Visit 5 (inclusive) or prior to first drug intake of the re-treatment (if applicable). The abnormalities are categorized as:

– ALT ≥ 3, 5, 8, 10 and 20 × ULN, and also for AST separately.

– ALT or AST ≥ 3, 5, 8, 10 and 20 × ULN.

– TBIL ≥ 2 × ULN.

– ALT or AST ≥ 3× ULN and TBIL ≥ 2× ULN (at the same time as ALT or AST).

– ALT or AST ≥ 3 × ULN and TBIL ≥ 2 × ULN and ALP < 2 × ULN (at the same time as ALT or AST).

LT abnormalities for local laboratory results are derived based on the non-normalized results.

Note: Laboratory results recorded as '< xxx' (or similar with ≤, >, or ≥) will be considered as 'xxx' for analysis, e.g., a result for ALT of '< 1' is considered as 1 for the analysis.

5.6.10 Other safety variables

Other safety variables include all physical examinations recorded on the Physical Examination CRF.

5.7 Quality of life variables

Not applicable.

5.8 Pharmacoeconomic variables

5.8.1 Hospitalizations

Hospitalizations data are collected in the Hospitalizations CRF. Hospitalization/hospital includes general ward, step-down/intermediate unit, or intensive care unit (ICU). The reason for hospitalization is collected ("CDAD" and "Other"). Duration and frequency of admissions are derived from study first dose up to Visit 5 (or re-treatment start date).

- **Length of stay in hospital (days)** is derived for each hospitalization as the period between the date of admission and the date of discharge, and is defined as Date of discharge – Date of admission + 1. The overall stay includes all hospitalizations for a subject, excluding hospitalization days prior to first dose.
- **Length of stay by ward unit** (general ward, step-down/intermediate unit, ICU [days]) is derived in the same way as the overall length of stay in hospital above but separately for each ward unit.
- **Frequency of re-admissions/admissions to hospital** after start of treatment is defined as the number of times that the subject has been admitted/re-admitted to hospital from first dose of study treatment until Visit 5 (or first dose of re-treatment for subject re-treated), as reported on the Hospitalization CRF. Re-admission is defined as a new admission to hospital following subject discharge home (where home includes 'home', 'rehab facility or nursing home' or 'other') for the previous

admission to hospital (i.e., admitted to general ward, step-down/intermediate unit or ICU). For subjects already hospitalized at first dose and discharged home during the study, the number of re-admissions are counted. For subjects not hospitalized at first dose, the first admission and later re-admissions are counted.

- **Frequency of emergency department visits** after start of treatment is defined as the number of times that the subject has been admitted to an emergency room in a hospital, from first dose of study treatment up until Visit 5, as reported on the Hospitalization CRF.

For hospitalizations with reason for hospitalization as 'CDAD' the endpoints above are derived in the same way.

Note: If the Visit 5 or re-treatment start date occurs during a hospitalization period the length of stay is derived up to Visit 5 date or up to re-treatment start date, respectively, instead of up to discharge date. If "Was the subject discharged" is answered "No" the EOS date is used instead of the discharge date for derivations.

The same endpoints for the re-treatment extension are produced, except the time window of interest is from first dose of re-treatment until Visit Re-5.

5.8.2 Change from baseline in Work Productivity and Activity Impairment: *Clostridium difficile*-associated diarrhea scores

Work productivity and activity impairment: *Clostridium difficile*-associated diarrhea (WPAI:CDAD) scores are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The four WPAI:CDAD scores are defined as follows, based on the scores Q1–Q6 of Questions 1–6:

- **Absenteeism**: Percent work time missed due to CDAD = Q2 / (Q2 + Q4) * 100
- **Presenteeism**: Percent impairment while working due to CDAD = Q5 / 10 *100
- **Work productivity loss**: Percent overall work impairment due to CDAD = {Q2 / (Q2 + Q4) + [(1–Q2 / (Q2 + Q4)) * (Q5 / 10)]} * 100
- **Activity impairment**: Percent activity impairment due to CDAD = Q6 / 10 * 100

Note: Questions 2–5 are only to be filled for subjects currently employed. Therefore the scores Absenteeism, Presenteeism, Work productivity loss are only defined for subjects currently employed (subjects with Question 1 "Are you currently employed" answered with "Yes").

Baseline is defined as the score at the screening visit. Change from baseline is the absolute difference between the visit and the baseline.

Note: For re-screened subjects baseline is defined as the last (highest visit label) screening/re-screening visit with at least one non-missing WPAI:CDAD question answered.

Re-treatment baseline is defined as the Re-1 visit score. Change from re-treatment baseline is the absolute difference between the visit and the re-treatment baseline.

Scoring: Handling of missing or inconsistent data
The following rules for handling of missing or inconsistent data are implemented as described in the section "Coding Rules for Self-Administration" by Reilly Associates [Reilly Associates 2002].

- *Employment status (Q1):*

  If Q1 = 'YES' or Q1 = 'NO' or 'missing' and hours missed (Q2) or hours worked (Q4) > 0, then subjects is considered employed.

  If Q1 = 'missing' and hours missed (Q2) and hours worked (Q4) = 0, then considered not employed (i.e., Q1 considered No).

- *Hours missed (Q2) and hours worked (Q4)*

  If hours worked (Q4) = 0, then productivity while at work (Q5) is not applicable and considered as missing.

  If subject enters a range of hours for (Q2 or Q4), use the midpoint.

  If a subject is considered employed but hours missed (Q2) is missing then impute as zero.

- *Productivity Questions (Q5 and Q6)*

  If for one question, two responses are provided, enter the midpoint and round to nearest integer.

Missing response after applying the above scoring
WPAI scores cannot be calculated if there is a missing response to one or more corresponding individual questions.

5.9 Pharmacokinetic variables

The definition of pharmacokinetic variables, including the definition of a valid PK sample is detailed in the PK SAP.

6 DEFINITION OF PROTOCOL DEVIATIONS

This section refers to all protocol deviations as recorded in the database following the specifications provided in the protocol violations code list.

Protocol deviation PV104 'Received kit different from kit assigned by IVRS' will be classified to 'Incorrect kit received: treatment received different from assigned treatment' (PV1041) or 'Incorrect kit received: assigned treatment received' (PV1042). Subsequently the codes PV1041 or PV1042 instead of PV104 will be considered as protocol deviation.

Protocol deviations are categorized while being entered into the database into the following categories as specified in the protocol violations code list:

- Main study, re-treatment extension or sub-study protocol deviations.

  Main study protocol deviations are those with protocol deviation code starting with 'PV' followed by a number. Re-treatment extension protocol deviations are those with protocol deviation code starting with 'PVR' followed by a number. Protocol deviations related to sub-studies are those with protocol deviation code starting with PVK (PK sub-study), PVM (microbiome sub-study) or PVP (PRO validation sub-study).

- Time point protocol deviation occurred.

  Main study (including sub-study) protocol deviations are classified as occurring before randomization, after randomization, or before or after randomization.

  Similarly, re-treatment extension protocol deviations are classified as occurring before enrollment, after enrollment, or before or after enrollment.

- Important protocol deviations (Yes/No).

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened analysis set

The Screened analysis set (SCRAS) includes all subjects screened even if they were not eligible.

7.1.2 Full analysis set

The Full analysis set (FAS) includes all subjects assigned to a study treatment based on the randomization-assigned treatment. Subjects are evaluated according to the study treatment to which they were assigned.

7.1.3 Modified intent-to-treat analysis set

The mITT analysis set includes subjects in the FAS who received at least one dose of study drug and had a confirmed diagnosis of CDAD.

Diagnosis of CDAD is confirmed if both the following conditions are met:

- More than 3 UBMs in the 24 h prior to randomization,
- Positive *C. difficile* GDH and toxin test (EIA approved by the sponsor) on the sample produced in the 72 h (48 h for MTFs) period prior to randomization.

More than 3 UBMs in the 24 h prior to randomization is determined from the Screening CRF as defined at the end of Section 5.2.2; if this is missing then the subject is considered to have more than 3 UBMs if the Inclusion Criteria CRF item 3a 'Diarrhea, defined as a change in bowel habits with > 3 UBM, in the 24 hours prior to randomization' is not equal to 'No'.

A positive GDH and toxin test is determined by a positive result of an approved GDH and toxin test (either the Quik Chek Complete toxin test or any other pre-specified test for GDH as well as toxin) recorded in the CDAD Diagnosis and Microbiology Sample CRF [older CRF versions: Fecal Sampling CRF] at screening. The positive *C. difficile* GDH and toxin A and/or B stool test should be performed on a sample collected within 72 h (48 h for MTFs) prior to or on randomization date.

Subjects are evaluated according to the study treatment to which they were assigned.

Reasons for exclusion from the mITT analysis set are classed into the following categories: (1) 'Study drug not taken'; (2) '≤ 3 UBMs within 24 h prior to Randomization'; (3) 'No approved positive diagnostic test', i.e., no positive GDH and toxin test (approved by the sponsor) within 72 h (48 h for MTFs) prior to or on randomization day.

7.1.4 Per-protocol analysis set

The PPS comprises all subjects from the mITT analysis set without conditions that might affect the evaluation of the effect of the study drug on the primary variable. The following conditions lead to the exclusion of a subject from the PPS:

At study entry:

- More than one previous episode of CDAD in the 3-month period prior to randomization (Protocol deviation code PV013).
- Fulminant or life-threatening CDAD (Protocol deviation code PV014).
- Concurrent immediately life-threatening disease or condition (Protocol deviation code PV015).
- History of inflammatory colitides, chronic abdominal pain, chronic diarrhea, or known positive diagnostic test for enteropathogens (Protocol deviation code PV016 or PV016_V2). Positive diagnostic test for enteropathogens at study entry for subjects enrolled under protocol Version 1 are determined by blinded clinical review and mapped to the DS SDTM domain.

- AMT > 24 h, except for MTFs (Protocol deviation code PV017).
- Any investigational drug to prevent or treat CDAD (Protocol deviation code PV018: FMT, intravenous immunoglobulin [IVIG] or any investigational drug to prevent or treat CDAD within 1 month prior to randomization; PV019: Monoclonal Ab against *C. difficile* within 6 months prior to randomization; and PV020: Vaccine against *C. difficile*).

During study:

- Any prohibited concomitant medication (except AMT or FMT or any investigational drug to treat CDAD) after randomization up to EOT + 2 days inclusive. Prohibited medications active against CDAD will lead to exclusion of a subject from the PPS as follows:
  1. Any use of IVIG or any investigational drug, antibodies or vaccine to prevent CDAD (PV119A).
  2. Other medication active against CDAD including probiotics and binding agents (e.g., cholestyramine) where duration is > 24 h, or consecutive or non-consecutive number of doses greater than what would be used in a 24 h period (PV119B).
  3. Initiation of treatment with opiates or a change in dose/regimen resulting in an increased opiate effect where duration is > 24 h, or initiation or increase in dose of opiates corresponding to a consecutive or non-consecutive number of doses greater than what would be used in a 24-h period, between randomization and EOT + 2 days inclusive (PV118B). Initiation or increase in dose of opiates for ≤ 24 h from EOT –1 day to EOT + 2 days (PV118A).
  4. Anti-peristaltic medications (e.g., loperamide), kaolin or related products, pectin or charcoal-containing anti-diarrheals where duration is > 24 h, or consecutive or non-consecutive number of doses greater than what would be used in a 24 h period (PV121B). Any anti-peristaltic medications (e.g., loperamide), kaolin or related products, pectin or charcoal-containing anti-diarrheals taken from EOT –1 day to EOT + 2 days (PV121A).
  5. Use of one or more doses for more than one prohibited medication (PV122B: Use of ≥ 1 dose of > 1 forbidden medication [opiates, probiotics, IVIG, binding agents, anti-peristaltic medications, kaolin, pectin, or charcoal]).
- Insufficient course of therapy: Subjects classified as a Clinical Failure with fewer than 6 doses of cadazolid or 12 doses of vancomycin taken. Subjects classified as a Clinical Cure with fewer than 16 doses of cadazolid or 32 doses of vancomycin taken (from Drug Accountability CRF).

- Positive diagnostic test for enteropathogens during treatment period. Positive diagnostic test for enteropathogens during treatment period is determined by blinded clinical review and mapped to the Subject Status SDTM domain.
- Received study treatment differed from randomized study treatment (PV1041). [Note: PV104 is classified according to whether the received treatment is different from (PV1041) or the same as (PV1042) treatment assigned. This is determined after unblinding.]
- Subject was unblinded before Database Lock (Source: PV103 [Unblinding for a reason not related to managing a clinical event] or from the DS SDTM domain [Unblinding of investigator or clinical trial team]; Note: Does not include unblinding as per process for managing SUSARs).
- Insufficient information to determine Clinical Cure, i.e., subjects
  - with missing daily stool information on any day between EOT –1 and EOT + 2 days, not otherwise documented as Clinical Failures (without information about AMT or FMT between Day 1 and EOT + 2 days, no day with > 3 UBMs between EOT –1 and EOT + 2 days).
  - lost to follow-up or study withdrawal prior to EOT + 2 days, not otherwise documented as Clinical Failures (no AMT or FMT between Day 1 and EOT + 2 days, no day with > 3 UBMs between EOT –1 and EOT + 2 days).

Subjects are evaluated according to the study drug to which they were assigned.

The protocol deviation codes listed above are based on the most recent version of the PV code list.

7.1.5 Hypervirulent analysis set

The Hypervirulent analysis set (HVAS) comprises subjects in the mITT analysis set who are confirmed to have CDAD due to an infection by a hypervirulent strain at baseline, as defined in Section 5.2.2.

7.1.6 Patient reported outcome analysis set

The PRO analysis set (PROAS) includes all subjects from the mITT analysis set who have signed the ICF themselves (as recorded in Informed Consent CRF for the main study).

It is based on the assigned treatment rather than the actual treatment received.

7.1.7 Safety analysis set

The Safety set (SS) includes all randomized subjects who received at least one dose of study drug (as recorded on the Study Drug Log CRF) and is analyzed based on the actual treatment received.

7.1.8 Re-treatment extension with cadazolid analysis set

The re-treatment extension with cadazolid set (ES) includes all subjects enrolled in the re-treatment extension who received at least one dose of re-treatment study drug (open-label cadazolid) as recorded on the re-treatment Study Drug Log CRF.

Tables on the re-treatment extension set will display results overall (Total cadazolid open-label) as well as by treatment arm during double-blind treatment (based on the actual treatment received, unless otherwise mentioned).

7.1.9 Other analysis sets

The definition of the Pharmacokinetic analysis set is detailed in the PK SAP.

The number of subjects from the FAS that participate in the PK sub-study, the PRO psychometric sub-study and in the microbiome sub-study is determined from the CRF 'Sub-studies'.

7.2 Usage of the analysis sets

Screening failures, including reasons for screening failure, are summarized using the SCRAS.

Subject disposition and study completion/withdrawal, including reason for withdrawal, and protocol deviations are summarized using the FAS.

Baseline demographics and disease characteristics are summarized using the mITT and PPS. Previous/concomitant medications and medical history are summarized for the mITT. Treatment exposure is summarized using the SS and mITT.

For efficacy, the main, supportive, sensitivity and subgroup analyses of Clinical Cure are performed on the PPS and on the mITT. All other efficacy analyses are performed on the mITT and on the PPS for the most relevant secondary endpoints, except:

- Meta-analysis, performed on the HVAS.
- CDI DaySyms analysis, performed on the PROAS (excluding subjects participating in the PRO sub-study).
- WPAI:CDAD analysis, performed on the PROAS.

The SS is used for the analyses of all safety variables (main study).

Listings are prepared using the FAS, unless otherwise specified.

All analysis of re-treatment period data are performed using the ES.

Table 14 below provides an overview of the analysis set usage for the main variables of the study.

Table 14 Overview of the different analysis sets and their usage

Analyses/Data Displays	SCRAS	FAS	mITT	PPS	SS	ES
Inclusion/exclusion criteria	✓					
Disposition		✓				✓
Demographic characteristics			✓	✓		✓
Baseline disease characteristics			✓	✓		
Medical history			✓			
Previous and concomitant therapies			✓			
Subgroup analyses			✓	✓		
Treatment exposure & compliance			✓		✓	✓
Protocol deviations		✓				
Efficacy: Primary endpoint			✓	✓		
Efficacy: Secondary endpoints			✓	✓*		
Efficacy: Other endpoints (unless otherwise specified)			✓	✓**		✓
Safety endpoints					✓	✓
Subject listings		✓				
Screening failures listing of reasons for failure	✓					

* Only on the most relevant secondary endpoints. ** Investigator's judgment of Clinical Cure only.
ES = Re-treatment extension with cadazolid set; FAS = Full analysis set; mITT = modified intent-to-treat; PPS = Per-protocol analysis set; SCRAS = Screened analysis set; SS = Safety set.

8 DEFINITION OF SUBGROUPS

Subgroups based on the following variables are considered for the analysis of Clinical Cure (primary endpoint) and Sustained Cure (secondary endpoint):

Baseline subgroups:

- CDAD episode type strata (from IVRS): first occurrence / first recurrence
- Geographical region (US, Canada, Europe, Rest of the World)
- Sex: female versus male
- Race: white, black or african american, other
- Age categories (years): 18–64; 65–74; ≥ 75
- Baseline frequency of UBMs: > 3 to ≤ 5; > 5 to ≤ 9; and > 9

- Inpatient/outpatient status
- CDAD severity at baseline: Mild-Moderate or Severe
- Prior AMT within 1 week of study treatment start: yes/no [see Section 5.2.5.3]
- Initial strain of *C. difficile*: hypervirulent versus non-hypervirulent
- BMI categories: < 18.5; ≥ 18.5 – ≤ 25; > 25 – ≤ 30; > 30 – ≤ 40; > 40
- MTF at baseline: yes/no

If the number of subjects in a category is small, the category might be combined with a contiguous category e.g., if the number of subjects with BMI > 40 is small, the category is combined with the BMI > 30 to ≤ 40 category, or e.g., if number of subjects for a geographical region is small, then US and Canada is combined to North America and Europe and Rest of the World to Non North America.

9 GENERAL STATISTICAL METHODOLOGY

This section describes in general terms the statistical models and methods applied.

9.1 Statistical methods for binary data

9.1.1 Confidence interval

Confidence intervals (CIs) for single proportions are estimated using the Wilson score method using the following SAS code:

```
proc freq data=;
tables resp /binomial(Wilson) alpha=0.05; run;
```

CIs for the difference between two proportions are estimated using the Wilson score method.

For the Wilson score method, the confidence intervals of the differences in proportions are derived by adding the following statement CL=(NEWCOMBE).

9.1.2 Stratified Cochran-Mantel-Haenszel

Stratified differences in proportions are estimated by weighted average of the stratum-specific differences in proportions. Using similar notation as above, if ‘s’ is the total number of stratum and ‘j’ a subscript representing the stratum, we have:

$$d_{adj} = \frac{\sum_{j=1}^{s} w_j \times d_j}{\sum_{j=1}^{s} w_j}$$

Where d_j is the difference in proportions in stratum j, and w_j is the weight assigned to stratum j.

The variance of the stratified difference in proportions is:

$$\mathrm{Var}(d_{adj}) = \frac{\sum_{j=1}^{s} w_j^2 \times \mathrm{Var}(d_j)}{(\sum_{j=1}^{s} w_j)^2}$$

The confidence interval is obtained as $d_{adj} \pm z_{\alpha/2} * se(d_{adj})$.

Cochran-Mantel-Haenszel (CMH) weights are used: $w_j = (n_{1j} * n_{2j} / (n_{1j} + n_{2j})$ where n represents the number of subjects in each treatment group within each stratum 'j'.

9.1.3 Logistic regression

For a binary outcome, a logistic regression model including treatment, a baseline covariate, and the interaction between the treatment and the covariate is considered. Specifically, the model with the structure below is used:

$$logit(p) \sim \beta_0 + \beta_1 \times TREAT + \beta_2 \times COVAR + \beta_3 \times TREAT \times COVAR + \varepsilon$$

The SAS code for this model is as follows:

```
proc logistic data=aa order=data;
 class treat(ref='Vancomycin') covar(ref="reference category");
model resp(event='1') = covar treat covar*treat /alpha=0.05;
oddsratio "Treatment" treat /cl=wald;
run;
```

9.2 Statistical methods for time-to-event data

The analysis of time-to-event data are conducted using Kaplan-Meier estimates of events over time (including graphical representation), stratified log-rank test and Cox proportional hazard model.

9.2.1 Time to Event and log-rank test

Estimates of the event rate are obtained for each treatment group using the Kaplan-Meier method as implemented in SAS Proc Lifetest. The graphical representation follows the recommendations from Pocock [Pocock 2002]. Two-sided CIs at specific time points are constructed, with confidence limits calculated using Greenwood's formula for the estimate of the standard error. Median time to event (as well as 25th and 75th percentiles) for each group are provided with the corresponding two-sided CIs calculated using the method of Brookmeyer [Brookmeyer 1982].

The stratified log-rank test is conducted with SAS Proc Lifetest where the STRATA statement includes the strata variables (CDAD type and geographical region) and the GROUP option includes the treatment variable (treat). The TIME statement includes a variable with times to event (time) and an indicator variable for right censoring (censor) with 1 representing censoring.

```
Proc lifetest data= method=KM;
  time survtime*censor(1);
  strata CDADTYPE  REGION / group=treat diff=control("Vancomycin");
run;
```

9.2.2 Cox proportional hazard model

SAS Proc Phreg is used to estimate the hazard ratio, the p-value associated with the treatment effect hazard ratio and the CI of the hazard ratio (using Wald-based methods). The Cox regression model can be implemented using the following code:

```
Proc phreg data =;
 class treat (ref='Vancomycin')
      strat_1 (ref = 'reference category')…;
 model TimeTo*censor(1)= treat /risklimits ties=exact;
 strata CDADTYPE  REGION;
run;
```

An investigation into the assumption of proportional hazards for treatment is performed informally using a plot of the complementary log-log of the survival against the log of time (for each group). If the hazards are proportional, the lines should be approximately parallel. A plot of the Schoenfeld residuals against time and log(time) is also constructed, including a Loess curve [Collett 1994]. Departure from a horizontal line indicates violations of the proportional hazard assumption. A test of a non-zero slope is also derived based on traditional linear regression model. Since certain types of non-proportionality are not detected by the test, both the test and the plot are used to assess the non-proportionality assumption.

9.3 ANOVA model for repeated measurements

A general mixed analysis of variance (ANOVA) model for repeated measurements (linear mixed effects model) with unstructured covariance structure is considered. The model is applied to absolute values from Day 1 (baseline) to Day 12 during the main study. The model includes fixed effects for treatment, time, and the interaction between treatment and time, and subject as a random effect. The comparisons between treatments for the change from baseline to Days 2–12 are computed using estimate statements. The change from baseline to Day 3 is the primary comparison of interest and that considered for the hierarchical testing strategy [see Section 10.1]. The SAS code below includes examples for Day 3 and Day 12.

The SAS code for this model is as follows:

```
Proc mixed data=;
  class subject treatment time;
  model score = treatment*time / noint DDFM = KR solution;
  repeated time /subject=subject type=un;
  lsmeans treatment*time;
example for Day 3
 estimate "Treatment effect at Day 3" treatment * time -1 0 1 0 0 0 0 0 0 0 0 0
                                                        1 0  -1 0 0 0 0 0 0 0 0 0/CL;
example for Day 12
  estimate "Treatment effect at Day 12" treatment * time -1 0 0 0 0 0 0 0 0 0 0 1
                                                          1 0 0 0 0 0 0 0 0 0 0  -1/CL;
run;
```

Sensitivity analyses for missing data imputation is performed using a standard multiple imputation approach under the Missing At Random (MAR) assumption. The robustness of the MAR assumption is further investigated via a tipping point approach. See Section 10.7.3 and Appendix E.

A similar model is applied for the comparison of absolute values of CDI-DaySyms domain scores versus Clinical Cure. The model includes fixed effects for Clinical Cure (CC) response, time, and the interaction between CC response and time, and subject as a random effect. The comparisons between CC response for the absolute values at Days 1–12 are computed using estimate statements.

Example SAS code for this model is as follows:

```
Proc mixed data=;
  class subject cc time;
  model score = cc*time / noint DDFM = KR solution;
  repeated time /subject=subject type=un;
  lsmeans cc*time;
example for Day 3
  estimate "Clinical Cure effect at Day 3" cc * time 0 0 1 0 0 0 0 0 0 0 0 0
                                                     0 0 -1 0 0 0 0 0 0 0 0 0/CL;
run;
```

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

This section describes the overall testing strategy and the statistical techniques used to deal with multiplicity issues related to:

- Multiple endpoints including primary endpoint of Clinical Cure and secondary variables which may become additional claims.

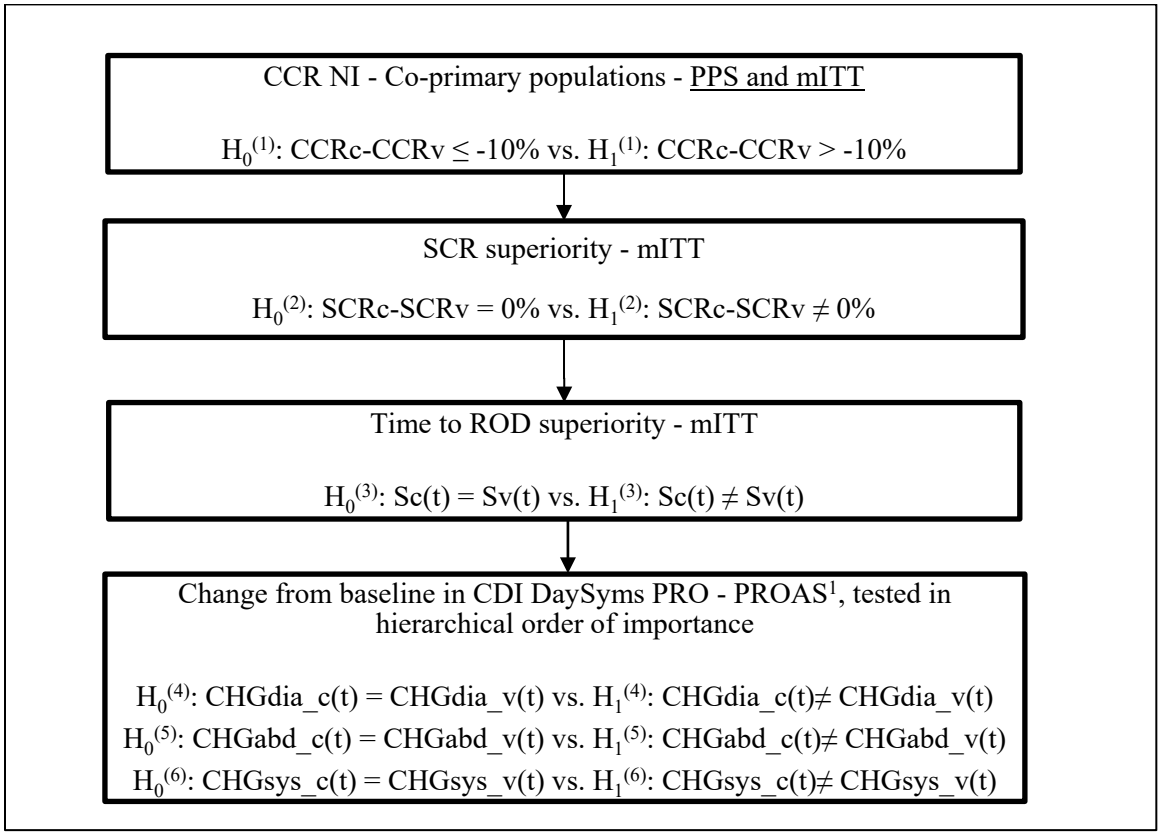
10.1.1 Statistical considerations

The overall α is at 0.05 two-sided level (or 0.025 one-sided).

No interim analysis is conducted: The analysis of the primary endpoint is conducted at the overall α level of 0.05 two-sided level (or 0.025 one-sided).

The analyses of the secondary endpoints are performed by implementing a hierarchical strategy to control the experiment-wise α level [Dmitrienko 2010] [see Figure 7] with overall two-sided α = 0.05. The secondary efficacy endpoints are tested in a sequential conditional manner, starting with SCR.

Figure 7 Hierarchical testing strategy



CCR = Clinical Cure Rate; CCRc = Clinical Cure Rate for cadazolid; CCRv = Clinical Cure Rate for vancomycin; SCR= Sustained Cure Rate; SCRc = Sustained Cure Rate for cadazolid; SCRv = Sustained Cure Rate for vancomycin; ROD = Resolution of diarrhea; S(t) = ROD survival function; CHGdia(t) = Change from baseline in CDI-DaySyms Diarrhea Domain Score; CHGabd(t) = Change from baseline in CDI-DaySyms Abdominal Domain Score; CHGsys(t) = Change from baseline in CDI-DaySyms Systemic/Other Domain Score; mITT = modified

intent-to-treat; NI = Non-inferiority; PPS = Per-protocol analysis set; PROAS1= Patient reported outcome analysis set (excluding subjects participating in the PRO sub-study).

10.2 General rules for data presentations

This section describes the general rules applied for all data displays, unless otherwise specified in each corresponding section. Standard Guiding Rules and Principles and standard outputs are followed where applicable.

SAS version 9.3 is used for the preparation of all tables, listings and figures. Listings are sorted by treatment group, subject number (includes sorting by country and center) and timing (dates and/or visits as applicable). For analyses performed on multiple analysis sets, only one listing containing all analyzed subjects is presented. Names of outputs have a suffix that indicates the analysis set (e.g., _SAF for Safety set).

Data are listed and summarized using appropriate descriptive statistics:

- Number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous variables.
- Number of events, number of censored observations and Kaplan-Meier estimates of the survival function for time-to-event variables.
- Number of non-missing observations, and frequency with percentage per category for categorical variables. Denominators for percentages are the number of subjects in the pertinent analysis set and treatment group, unless otherwise specified.
- For susceptibility data: number of non-missing observations, geometric mean, MIC_{50} (concentration which inhibits growth of ≥ 50% of isolates, i.e., median of MICs), MIC_{90} (concentration which inhibits growth of ≥ 90% of isolates, i.e., 90% quantile of MICs), minimum and maximum.

Absolute changes from baseline are defined as: post-baseline value minus baseline value, i.e., a positive sign indicates an increase compared to baseline.

A percentage change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

For susceptibility (MIC) endpoints, change from baseline is defined as described in Table 9.

In tables, column labels are ‘Cadazolid’ and ‘Vancomycin’. The cadazolid group is displayed in the first column, vancomycin in the second and a total column (including both treatment groups) is added in some tables as specified later on.

In tables for the re-treatment extension column labels are ‘Cadazolid / Cadazolid OL’, ‘Vancomycin / Cadazolid OL’, and ‘Total Cadazolid OL’.

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Screening failures

The number of subjects screened, re-screened and reasons for screening failure are summarized for the SCRAS in a table and in a listing. For subjects that fail screening more than once, only the reason of the last failure is reported in the summary table. All reasons for screening failure are included in the listing.

The number and percentage of subjects with 1 or more unmet eligibility criterion are presented overall and per criterion for the subjects failing screening.

All subjects with unmet eligibility criteria are listed. Subjects randomized with unmet criteria are flagged in the listing.

10.3.2 Subject disposition

The number of subjects randomized, treated, completed treatment, completed the main study enrolled in re-treatment extension, re-treated, completed re-treatment, completed the re-treatment extension are all summarized by treatment group and overall for the FAS.

Subjects prematurely withdrawn from study with reasons for premature study withdrawal are summarized separately. Disposition is presented overall and separately by study withdrawal occurring during the main study and the re-treatment extension for the FAS.

Subject disposition variables are listed.

Subjects randomization is also summarized by geographical region, country and site.

10.3.3 Protocol deviations

All main study protocol deviations as well as important main study protocol deviations are summarized by categories, per treatment group and overall.

Similar summaries are prepared for all re-treatment extension protocol deviations and important re-treatment extension protocol deviations.

Protocol deviations coded to “Other—Not considered a protocol violation by Actelion” (PV 298 and PVR298) are not included in the summaries. Also protocol deviations coded to sub-categories (e.g., PV118A and PV118B) are not included in the summaries as only the high level codes (PV with number and no letter suffix, e.g., PV118) are included to avoid double-counting.

Main study protocol deviations occurring before or after randomization are summarized together with the protocol deviations after randomization. Similarly for the re-treatment extension protocol deviations occurring before or after enrollment are summarized together with protocol deviations after enrollment.

A listing of all main study and re-treatment protocol deviations is provided.

10.3.4 Analysis sets

The number and percentage of subjects in each analysis set as well as the number of subjects in the PROAS excluding subjects in the PRO validation sub-study are summarized in a table, per treatment group and overall.

Reasons for excluding subjects from the mITT analysis set and PPS are listed and summarized in a table.

Subjects participating in the PRO validation sub-study, the PK sub-study and the microbiome sub-study are summarized by treatment group and overall.

10.4 Analyses of subject characteristics

10.4.1 Demographics

Demographic characteristics [defined in Section 5.2.1] are summarized using descriptive statistics for continuous and categorical data using the mITT, PPS and the ES. EudraCT age categories are summarized separately for the SS. One listing is produced, for the FAS. Tables are presented by treatment group and overall.

10.4.2 Baseline disease characteristics

Main baseline disease characteristics [defined in Section 5.2.2] are summarized by treatment group and overall using descriptive statistics for categorical data for the mITT and PPS. Listings are presented for the FAS. Separate tables are presented on the mITT and PPS for main disease characteristics.

CDAD episode type strata (from IVRS) and CDAD episode type reported in the CRF are cross-tabulated using frequencies and percentages on the mITT.

10.4.3 Other baseline characteristics

Other baseline diseases characteristics [defined in Section 5.2.3] are summarized similarly to baseline disease characteristics for the mITT and PPS.

10.4.4 Medical history

Previous and concomitant medical histories [defined in Section 5.2.4] are summarized separately, by treatment group and overall, by tabulating the number and percentages of subjects who had/have each disease/diagnosis (by system organ class [SOC] and preferred term) using the mITT. One listing is produced for the FAS including the variable ‘Days from first dose of treatment’. Number and percentages of subjects having had at least one medical history term are presented by SOC and individual preferred term within each SOC.

SOCs are sorted by descending order of frequency. If the frequencies of SOCs are the same, alphabetical order is used. The same rule applies for preferred terms within SOC.

10.4.5 Previous and concomitant therapies

Number and percentages of subjects having taken at least one treatment are presented by ATC class (level 4) and individual preferred term within each ATC class. All summaries are tabulated by ATC class, and individual preferred terms within each ATC class, for the mITT. ATC classes are sorted by descending order of frequency. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for preferred terms within ATC class. For study reporting purposes, all previous and study-concomitant therapies are reported in the subject listings.

Previous therapies [Section 5.2.5.1], main study concomitant therapies [Section 5.2.5.2], main study concomitant therapies with onset prior to study treatment start and main study concomitant therapies with onset on or after study treatment start up to EOT + 7 days [Section 5.2.5.2] are summarized separately, by treatment group and overall, using descriptive statistics for categorical data. A subject listing of previous and concomitant medications is provided. A separate listing of re-treatment concomitant therapies on the ES is provided.

Specific therapies are summarized per treatment group and overall, by type of therapy and preferred term. Specific main study concomitant therapies starting on or after study treatment start and up to EOT + 2 days and on or after EOT + 3 days and up to Visit 5 are summarized in a similar way. Specific therapies are flagged in the listing of all therapies.

10.4.6 Procedures

Main study concomitant procedures [described in Section 5.2.6.1] separated into CDAD-related procedures and other procedures are summarized using descriptive statistics for categorical data using the mITT. One listing for all procedures is produced for the FAS and one listing for endoscopy and imaging.

10.5 Analysis of study treatment exposure and compliance

10.5.1 Exposure

Exposure characteristics for active double-blind treatment [defined in Section 5.3.1] are summarized per treatment group using descriptive statistics for continuous and categorical data, for the mITT analysis set and the SS for the main treatment period. The cumulative distribution of double-blind treatment exposure time by class intervals (1 day) is tabulated. Exposure to open-label re-treatment is summarized using the ES. One listing is produced for the FAS.

10.5.2 Compliance with study treatment

Compliance for double-blind treatment [defined in Section 5.3.2] is summarized for both active study drug and placebo matching study drug per treatment group using descriptive statistics for continuous and categorical data, for the mITT analysis set for the double-blind treatment period. Compliance for open-label treatment is summarized using the ES. Compliance is listed in the exposure listing.

10.5.3 Study treatment discontinuation

Study treatment discontinuation variables [defined in Section 5.3.3] are summarized per treatment group, for the main study treatment using the SS and the mITT analysis set using number and percentages of subjects. Summaries for the mITT are performed only if more than 5% of subjects in the SS in any treatment group do not qualify for the mITT analysis set. Summaries on the SS are repeated using planned treatment instead of actual treatment received if actual treatment received differs from planned treatment for at least one subject. A listing is produced for the FAS. A separate listing of study treatment discontinuation variables for re-treatment are listed for the ES.

10.5.4 Study treatment interruptions

Subjects with study treatment interruption and corresponding reasons for interruption(s) [defined in Section 5.3.4] are summarized per treatment group for the main study treatment period using the number and percentages of subjects with at least one interruption on the SS. Multiple reasons for interruptions of the same type are only counted once per subject. One listing is produced using the FAS, also including data for re-treatment period interruptions.

10.6 Analysis of the primary efficacy variable

This section describes the analysis of the primary efficacy endpoint (i.e., CCR), as defined in Section 5.5.1.

The objective is to demonstrate that the CCR for cadazolid (CCRc) is not inferior to the CCR of vancomycin (CCRv), accounting for a non-inferiority (NI) margin of 10%.

The justification for the choice of 10% as NI is detailed in the study protocol.

10.6.1 Hypothesis and statistical model

The null hypothesis is: H_0: CCRc–CCRv $\leq -10\%$

and the alternative is: H_1: CCRc–CCRv $> -10\%$

10.6.2 Handling of missing data

Main analyses

As described in Section 5.5.1, all subjects who do not fulfill the requirements for Clinical Cure are considered as Clinical Failure.

If one or more days between EOT –1 day to EOT + 2 days have missing or 'unknown' UBM information then the subject is considered a Clinical Failure.

Sensitivity analyses

A sensitivity analysis of handling missing or 'unknown' UBM information for Clinical Cure in the mITT analyses set will be conducted using the following:

- If the number of UBMs on any one day between EOT –1 day to EOT + 2 days is missing or 'unknown' and the subject has ≤ 3 UBMs on all other days between EOT –1 day to EOT + 2 days, then it will be imputed with ≤ 3 UBMs, otherwise it will be considered > 3 UBMs. Clinical Cure is then derived as described in Section 5.5.1 based on this imputation.

10.6.3 Main analysis

Two main analyses are performed on the primary endpoint, one using the PPS and one using the mITT analysis set ('co-primary populations'). No statistical model is defined; the main analyses are based on CI of the crude difference in proportions.

A one-sided 0.025 significance level (equivalent to two-sided alpha of 0.05) is applied to test the primary hypothesis in both analysis sets.

The NI assessment on the mITT analysis set and the PPS compose the first part of the hierarchical testing procedure [see Figure 7].

If the lower limit of the 95% CI is above –10%, for **both** the mITT population and the PP population, the NI of cadazolid versus vancomycin for CCR is claimed.

The CCR is summarized by treatment group, including the number of subjects with and without a Clinical Cure. The CI for the difference in CCR is estimated using the Wilson score CI for the difference in proportions [Newcombe 1998] as described in Section 9.1.1. Imputation methods for the substitution of incomplete or missing data are defined in Section 10.6.2.

For the mITT analysis set and the PPS separately, the number and percentage of subjects not being classified as Clinical Cure (i.e., Clinical Failure) and the reason(s) for Clinical Failure [as listed in Section 5.5.1] are summarized descriptively. A subject may have more than one reason for Clinical Failure, therefore the reasons and combination of reasons are summarized so that they are mutually exclusive.

10.6.4 Supportive/sensitivity analyses

10.6.4.1 Stratified Cochran-Mantel-Haenszel analysis of Clinical Cure rate

A stratified CMH analysis of CCR is applied as a supportive analysis, stratified by first occurrence / first recurrence (IVRS) and geographical region using the PPS and mITT analysis set. In addition, the stratified analysis is repeated for each stratification factor

separately. For the average risk difference, the CMH estimate and corresponding CI is derived using normal approximation.

If there are small numbers per strata, the categories for geographical region (US, Canada, Europe, Rest of the World) are pooled, e.g., combining US and Canada to North America, and Europe and Rest of the World to Non-North America.

10.6.4.2 Analysis of Clinical Cure rate with imputation for a single missing day

A sensitivity analysis is conducted as for the main analysis [Section 10.6.3], applying imputation for a single missing day in the Daily Stool Information CRF between EOT –1 day to EOT + 2 days, as described in Section 10.6.2.

10.6.5 Subgroup analyses

Consistency of CCR results is explored over the different subgroups defined in Section 8. A table will summarize the frequency of subjects per treatment group in each subgroup category for the mITT analysis set and the PPS.

The CCR is summarized by treatment group per subgroup, with 95% CI of the difference in cure rates estimated using the Wilson Score method [Newcombe 1998]. Homogeneity per subgroup variable of the differences in proportions of CCR is assessed based on a Cochran's type homogeneity chi-square test. Treatment effects (difference in proportion) overall and within subgroups are presented in a Forest plot.

For each subgroup, a logistic regression is applied on the CCR, including the treatment group, the baseline characteristic and the interaction of both of them. Treatment effects in each subgroup are reported with odds ratios (cadazolid/vancomycin) and corresponding 95% Wald CI. An exploratory test of interaction is performed comparing against two-sided 1% level to adjust for multiplicity. Treatment effects (odds ratios) overall and within subgroups are presented in a Forest plot [Cuzick 2005].

10.6.6 Other analyses

Clinical Cure by concomitant therapy will be assessed as follows:

A table will summarize the frequency of subjects with Clinical Cure per treatment group by 'concomitant antibiotics for infections other than CDAD taken from first dose to EOT + 2 days' (yes/no) for the mITT analysis set together with difference in proportions and corresponding 95% Wilson score CIs.

Clinical Cure by country is summarized descriptively by treatment group in the mITT analysis set using frequencies and percentages and corresponding 95% Wilson score CIs.

Clinical Cure rates by MIC level are summarized descriptively as detailed in Section 10.8.2.3.

10.7 Analysis of the secondary efficacy variables

The analyses for the secondary variables are conducted using the mITT analysis set.

10.7.1 Sustained Cure Rate

10.7.1.1 Hypothesis and statistical model

If NI for CCR is demonstrated in both the PPS and the mITT analysis set, the SCR is hierarchically tested on the mITT analysis set [see Figure 7] at the two-sided 5% alpha level.

The objective is to demonstrate that the SCR for cadazolid (SCRc) is superior to the SCR for vancomycin (SCRv).

The null hypothesis is: H_0: SCRc – SCRv = 0%

and the alternative is: H_1: SCRc – SCRv ≠ 0%.

10.7.1.2 Handling of missing data

Main analyses

As described in Section 5.5.2.1, all subjects who do not fulfill the requirements for Sustained Cure are considered as not having Sustained Cure. Handling of missing UBMs and EIA GDH and toxin test approved by the sponsor is described in Section 5.5.2.1 and Table 5.

Sensitivity analyses

A sensitivity analysis will be conducted considering subjects with Visit 5 prior to EOT + 25 days and Day 35 as not sustained cure due to insufficient follow-up. The definition of Sustained Cure and handling of missing data as described Section 5.5.2.1 is used, apart from the following:

- Subjects with Clinical Cure and no recurrence according to the definition in Section 5.5.2.1 that have a Visit 5 prior to EOT + 25 days and Day 35 are considered not Sustained Cure for this sensitivity analysis (as opposed to the definition in Section 5.5.2.1 considering subjects sustained cure if Visit 5 is after or on EOT + 28 days or Day 38). If Visit 5 is missing and the subject was not re-treated the Study Withdrawal date instead of the Visit 5 date is used in the definition above.

10.7.1.3 Statistical analysis

The main statistical analysis of SCR is conducted on the mITT analysis set using the definition of SCR as in Section 5.5.2.1.

Data are summarized in a similar way as for the primary endpoint analysis. The CI for the difference in SCR is estimated using the Wilson score CI method for difference in proportions.

If the lower limit of the CI is greater than zero, the superiority of cadazolid versus vancomycin in SCR is claimed.

The number and percentage of subjects not classified as having Sustained Cure and the reasons for not being classified as having Sustained Cure [as listed in Table 6] are summarized descriptively.

10.7.1.4 Supportive/sensitivity analyses of Sustained Cure rate

The following sensitivity/exploratory analyses will be performed:

The analysis of SCR described above [Section 10.7.1.3] is repeated on the PPS for sensitivity.

A sensitivity analysis of Sustained Cure, applying handling of insufficient follow-up according to Section 10.7.1.2 (considering subjects with Visit 5 prior to EOT + 25 days or Day 35 as not having Sustained Cure due to insufficient follow-up), is conducted as for the main analysis [Section 10.7.1.3].

An exploratory analysis of Modified Sustained Cure [Section 5.5.3.11] will be performed on the mITT analysis set. The statistical analysis for this modified SCR will use the same methods as for SCR [Section 10.7.1.3].

10.7.1.5 Subgroup analyses

The same subgroup analysis performed for the primary endpoint CCR [see Section 10.6.5] is conducted for SCR.

Of note, the hypervirulent subgroup is primarily assessed in a meta-analysis involving both AC-061A301 and AC-061A302 studies, as described in the separate meta-analysis SAP.

10.7.1.6 Other analyses

Sustained Cure by concomitant therapy will be assessed as follows:

A table will summarize the frequency of subjects with Sustained Cure per treatment group by ‘concomitant antibiotics for infections other than CDAD taken from first dose to Visit 5 / re-treatment’ (yes/no) for the mITT analysis set.

Sustained Cure by country is summarized descriptively by treatment group in the mITT analysis set using frequencies and percentages and corresponding 95% Wilson score CIs.

10.7.2 Time to resolution of diarrhea

Time to ROD is hierarchically tested on the mITT analysis set [see Figure 7] at the two-sided 5% alpha level.

The objective is to demonstrate that the time to ROD for cadazolid is shorter than the time to ROD for vancomycin.

10.7.2.1 Hypothesis test and statistical model

The null hypothesis is: H_0: $Sc(t) = Sv(t)$

and the alternative is: H_1: $Sc(t) \neq Sv(t)$

10.7.2.2 Handling of missing data

See Section 5.5.2.2.

10.7.2.3 Statistical analysis

Analysis of time to ROD is conducted using a two-sided stratified log-rank test, including the strata first occurrence / first recurrence and geographical region (or region variable with pooled categories as described in Section 10.6.4.1 in the event of too small strata). Kaplan-Meier estimates of the survival functions are produced using upward estimates.

Data are summarized in a table including Kaplan-Meier estimates at each day up to Day 10 (including CIs), median (as well as 25^{th} and 75^{th} percentiles) together with CIs and the log-rank summary statistics.

A graphical display presenting a plot going upward is also presented overall and within each stratum including CIs at specific time points.

10.7.2.4 Supportive/sensitivity analysis

The statistical analyses for time to ROD [Section 10.7.2.3] are repeated on the PPS for sensitivity. An additional sensitivity analysis is conducted on the mITT analysis set using a stratified Cox proportional hazard model stratified by CDAD episode type (following strata assignation from the IVRS) and geographical region (or region variable with collapsed categories as described in Section 10.6.4.1 in the event of too small strata).

10.7.3 Absolute change from baseline to Day 3 in CDI-DaySyms PRO domain scores

The CDI-DaySyms PRO domain scores can be considered as quasi-continuous, and are therefore analyzed using methods for continuous data.

The three CDI-DaySyms PRO domain scores are hierarchically tested on the PROAS (excluding subjects participating in the PRO validation sub-study) as described in Figure 7, at the two-sided 5% alpha level. The three domains are evaluated in a hierarchical manner, starting with Diarrhea Symptoms, then Abdominal Symptoms, and finally Systemic/Other Symptoms. The absolute change from baseline to Day 3 is the primary comparison of interest and that considered for the hierarchical testing strategy. Comparisons for other time points from Days 2–12 are also presented as exploratory analyses.

The objective is to demonstrate that the change (improvement) from baseline at Day 3 in each domain score is greater in the cadazolid group compared to the vancomycin group.

10.7.3.1 Hypothesis test and statistical model

The null hypothesis is: H_0: CHGc(t) = CHGv(t)

and the alternative is: H_1: CHGc(t) ≠ CHGv(t)

An ANOVA model for repeated measurements is applied to absolute values from Day 1 (baseline) to Day 12 during the main study. The model includes fixed effects for treatment, time, and the interaction between treatment and time, and subject as a random effect. Assumption for this model is that missing data are MAR. The comparisons between treatments for the change from baseline at each time point are estimated from this model.

10.7.3.2 Handling of missing data

The main analysis models the CDI-DaySyms PRO domain scores over time using all available data from baseline (Day 1) to Day 12 as described in Section 9.3 under the MAR assumption. No imputation of missing values is performed.

Possible reasons for missing data:

- Early dropout (Premature study withdrawal with reason other than death – data missing from EOS date or last contact date onwards);
- Death (Premature study withdrawal with reason death – data missing from EOS date onwards);
- Other reasons (Not classified in any of the two categories above).

To assess the pattern of missing data, the number and proportion of subjects with missing data for each domain score at each time point will be summarized overall, and by reason for missing data as defined above.

Two sensitivity analyses for handling of missing data are performed using imputation methods:

<u>Multiple Imputation Method</u>

First, standard multiple imputation of the outcome variables (CDI-DaySyms PRO domain scores) under the MAR assumption is applied using PROC MI, using covariates constructed from the corresponding sets of preceding variables (treatment). Imputation of intermittent missing values is applied in a first step. In a second step, missing values after dropout are imputed. The resulting imputed datasets are analyzed using the model described in Section 9.3, and the results of these analyses are pooled using PROC MIANALYZE.

Second, to assess the robustness of the MAR assumption, a tipping point approach is applied, whereby the impact of missing data on the conclusions is assessed. The tipping points are defined to be the particular setting for the missing data values that would change the study's conclusions. Multiple imputation under the Missing Not At Random (MNAR) assumption is applied by searching for a tipping point by using "shift" approaches until the MAR inferences change from significance to non-significance, or vice-versa. The shifts are applied to the mean for the non-completers in the cadazolid treatment arm.

These analyses are performed in SAS 9.4 by an independent expert consultant [redacted]. Full details can be found in Appendix E.

Single Imputation Method

All missing post-baseline values are imputed with the last non-missing value available (last observation carried forward [LOCF] approach). As CDI-DaySyms symptoms are expected to improve over time in both active treatment groups when subjects achieve clinical cure, LOCF could be considered as a conservative single imputation method in that situation.

The latest available value prior to the missing value is imputed for any given missing data point. For example, if a subject has missing values at Day 4 and Day 7, but all other values are present, then the Day 4 value will be imputed with the Day 3 value, and the Day 7 value will be imputed with the Day 6 value. Missing baseline values are not imputed.

The results imputed are analyzed using the same model as described in Section 9.3.

10.7.3.3 Statistical analysis

For each CDI-DaySyms PRO domain score, the absolute values and changes from baseline are summarized descriptively by treatment group and time point. A box-plot is created for each domain score by treatment group and time point, displaying mean, median, Q1, Q3, and minimum and maximum.

Analysis of absolute change from baseline in each CDI-DaySyms PRO domain score at Day 3 is conducted using the PROAS (excluding subjects participating in the PRO validation sub-study) based on a general mixed ANOVA model for repeated measurements modeling the absolute CDI-DaySyms PRO domain score values using all available data up to Day 12. The model is described in Section 9.3.

The main comparison between treatment groups (cadazolid – vancomycin) is made for change from baseline to Day 3. If the upper limit of the two-sided 95% CI for treatment difference for change from baseline in CDI-DaySyms PRO domain score at Day 3 is

below zero, then statistically significant superiority of cadazolid versus vancomycin is claimed.

The treatment difference for change from baseline to all other days up to Day 12, derived from the model as described above is also presented. These comparisons are considered exploratory.

The least square means model estimates and associated 95% CI for all time points are plotted by treatment group and time point for each domain score.

10.8 Analysis of other efficacy variables

Analyses for the exploratory variables are conducted on the mITT analysis set unless otherwise specified. Statistical comparisons are performed at the two-sided alpha 5% level for exploratory purposes.

10.8.1 Efficacy variables

10.8.1.1 Investigator's assessment of Early Treatment Response at Visit 2

Summaries are presented per treatment, with difference in rates and corresponding CIs estimated using the Wilson score method.

10.8.1.2 Investigator's judgment of Clinical Response at Visit 4

Summaries are presented per treatment group, with difference in rates and corresponding CIs estimated using the Wilson score method.

This analysis is performed on the mITT analysis set and the PPS.

The reasons for assessing the subject as cure or failure are summarized using frequencies and percentages on the mITT analysis set.

10.8.1.3 Investigator's evaluation of Clinical Cure per protocol definition

The information is listed.

10.8.1.4 Investigator's judgment of Sustained Response at Visit 5

Summaries are presented per treatment group, with difference in rates and corresponding CIs estimated using the Wilson score method.

The reasons for assessing the subject as cure and failure are summarized using frequencies and percentages on the mITT analysis set.

10.8.1.5 Investigator's evaluation of Sustained Cure per protocol definition

The information is listed.

10.8.1.6 Early Clinical Cure by Day 5

Summaries are presented per treatment group, with difference in rates and corresponding CIs estimated using the Wilson score method.

10.8.1.7 Normalization of Bowel Movements rate

Summaries are presented per treatment group, with difference in rates and corresponding CIs estimated using the Wilson score method.

10.8.1.8 Time to return to usual stools

Summaries are presented per treatment group using the Kaplan-Meier method.

10.8.1.9 Recurrence rate and adjusted recurrence rate

Recurrence rates (recurrence out of subjects with Clinical Cure) are summarized descriptively with 95% CI of individual treatment group rates estimated using the Wilson method. No CI of the difference is provided. This endpoint is not statistically compared because it would be a biased comparison since the numbers of cured subjects in both treatment groups are expected to be different, and these populations could not have the same characteristics in both treatment groups. Summaries are accompanied by summaries of subjects with recurrence out of the analysis set using frequencies, proportions and 95% Wilson CI of proportions.

Adjusted recurrence rate (recurrence out of subjects in the analysis set) will be summarized with identical methods as for the recurrence rate.

Recurrence classifications (Relapse and Re-infection) are summarized descriptively. Recurrence is also summarized by subgroups.

10.8.1.10 Time to recurrence

This endpoint is analyzed using the same statistical methods as for the main statistical analysis of time to ROD [see Section 10.7.2.3]. Only subjects with Clinical Cure are considered in the analysis. It is summarized per treatment group, but not statistically compared because it would be a biased comparison.

10.8.1.11 CDI-DaySyms PRO response rates

CDI-DaySyms response status is computed for each domain using data as entered [see Section 5.5.3.12]. No imputation of missing scores is performed prior to deriving response status. Subjects with missing values at baseline or at Day 3 are considered to be non-responders. Response rates at Day 3 are summarized descriptively for each domain together with 95% CI of individual treatment group rates estimated using the Wilson method [Newcombe 1998] as described in Section 9.1.1. The treatment difference in proportions and corresponding 95% Wilson score CIs are also presented.

10.8.1.12 Comparison of absolute values of CDI-DaySyms domain scores versus Clinical Cure

To compare the CDI-DaySyms PRO to CC response (Clinical Cure vs Clinical Failure), a general mixed ANOVA model for repeated measurements is applied to the absolute CDI-DaySyms PRO values for each domain score using all available data up to Day 12. The model includes CC response, time and the interaction between CC response and time as fixed effects, and subject as a random effect. The model is as described in Section 9.3. The difference in absolute values of the domain score between subjects with CC and clinical failure for each time point at Days 1 (Baseline), 3, 7 and 12 is presented, together with the corresponding 95% CIs.

Example of estimate statements for the SAS code (to be done for Days 1 (Baseline), 3, 7 and 12):

```
/*Day 3:*/
  estimate "CC Effect at Day 3" CC * time  0 0 –1 0 0 0 0 0 0 0 0 0
                                           0 0   1 0 0 0 0 0 0 0 0 0/CL;
…
/*Day 12:*/
  estimate "CC effect at Day 12" CC * time   0 0 0 0 0 0 0 0 0 0 0 –1
                                             0 0 0 0 0 0 0 0 0 0 0   1/CL;
```

Descriptive statistics for absolute values of each domain score are presented in a summary table by CC response and time point. A box-plot is created by CC response, displaying mean, median, Q1, Q3, and minimum and maximum.

The same analysis is repeated for each treatment group separately.

10.8.1.13 Re-treatment extension variables

Unless otherwise specified, all summaries are provided by randomized treatment group and overall, using the ES.

Clinical Cure, Sustained Cure:

The number and percentage of subjects with the event of interest are summarized together with the 95% CI of the estimates of the difference using the Wilson score method.

Recurrence Rate:

The number and percentage of subjects with the event of interest, out of the re-treated subjects who presented clinical cure during the re-treatment period, is summarized per treatment group together with the respective 95% CI.

Adjusted Recurrence Rate:

The number and percentage of subjects with the event of interest, out of the re-treated subjects, is summarized per treatment group together with the respective 95% CI.

10.8.2 Analysis of microbiology variables

10.8.2.1 Isolation of C. difficile

Subjects with *C. difficile* isolate are summarized using frequencies and percentages. Denominator for percentages are number of subjects with any sample analyzed for *C. difficile* in central laboratory at the time point. The following displays will be prepared:

- Subjects with *C. difficile* isolate at baseline. Overall, by geographical region, and by Clinical Cure outcome in the mITT and PPS; by treatment group and overall.
- Subjects with *C. difficile* isolate by visit (Baseline, Visit 3 and Visit 4.x) in the mITT, by treatment group.
- Subjects with *C. difficile* isolate for Clinical Failures (Baseline and Visit 3) and Recurrences (Baseline and Visit 4.x) in the mITT and PPS by treatment group.

As described in Section 5.5.3.12, subjects with multiple new episode of diarrhea visits (i.e., Visit 4.a, 4.b, etc.) are considered to have a *C. difficile* isolate at Visit 4.x if *C. difficile* was isolated at any of these visits.

10.8.2.2 Typing of C. difficile

C. difficile strains are summarized using frequencies and percentages on the mITT and PPS. The denominator for deriving percentages is the number of subjects with non-missing result. The following displays will be prepared:

- *C. difficile* strains for baseline isolates based on PCR ribotyping (i.e., ribotype initial type) by treatment group and overall.
- *C. difficile* strains for baseline isolates based on REA typing (i.e., REA initial group) by treatment group and overall.
- Hypervirulent ribotypes [see definition in Section 5.5.4.2.1] and REA groups of specific interest [see definition in Section 5.5.4.2.2] for baseline isolates are summarized overall, by geographical region (by treatment group and overall), by country and are cross tabulated.

Furthermore, subjects with Relapse or Re-infection are summarized by treatment group using frequencies and percentages. The denominator for deriving percentages is the number of subjects with Clinical Cure, but also the percentages out of subjects in the mITT analysis set will be presented.

Typing information for all *C. difficile* isolates are listed.

10.8.2.3 Susceptibility of C. difficile

Susceptibility test results for *C. difficile* isolates will be summarized using MIC summary statistics (MIC range, MIC_{50}, MIC_{90}) and MIC frequency distribution (frequency of isolates at each MIC test concentration). The following displays will be prepared:

- Susceptibility of *C. difficile* to each test agent (i.e., cadazolid, vancomycin, linezolid, moxifloxacin, metronidazole and fidaxomicin) at baseline and post-baseline (highest MIC) using MIC summary statistics and MIC frequency distribution by treatment group and overall in the mITT and PPS.
- Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid and moxifloxacin for Clinical Failures at baseline and Visit 3 and for Recurrences at baseline and Visit 4.x using MIC summary statistics and MIC frequency distribution by treatment group in the mITT and PPS.
- Susceptibility of *C. difficile* to each test agent at baseline. Overall and by Clinical Cure Outcome using MIC summary statistics by treatment group in the mITT and PPS.
- Susceptibility of *C. difficile* to each test agent at baseline in subjects with hypervirulent strain. Overall and by Clinical Cure Outcome using MIC summary statistics and overall using MIC frequency distribution by treatment group in the mITT and PPS.
- Susceptibility of *C. difficile* to each test agent at baseline in subjects with REA group of special interest. Overall and by Clinical Cure Outcome using MIC summary statistics by treatment group in the mITT and PPS.
- Susceptibility of *C. difficile* to each test agent at baseline by geographical region using MIC summary statistics by treatment group in the mITT and PPS.

Note: MIC_{50} and MIC_{90} values are derived and presented when MICs for at least 10 isolates are present.

Graphical displays of MIC frequency distributions of susceptibility of *C. difficile* to each test agent at baseline in the mITT will be presented.

Clinical Cure (frequencies and percentages) will be summarized by baseline *C. difficile* MIC level to cadazolid, vancomycin, linezolid, moxifloxacin, overall and separately for subjects with hypervirulent and non-hypervirulent strain at baseline using the mITT and PPS.

A listing of susceptibility of *C. difficile* will be prepared on the FAS.

10.8.2.4 Change from baseline in susceptibility of C. difficile

Frequencies (number of subjects and percentages) are displayed by treatment group, using the mITT analysis set and PPS, for the categories of change from baseline [see Table 9] in the susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid, fidaxomicin, metronidazole and moxifloxacin for Clinical Failures at Visit 3 and for Recurrences at Visit 4.x. A similar display will be prepared on change from baseline to highest post-baseline result.

For subjects with ≥ 4-fold increase in *C. difficile*, MIC from baseline for any post-baseline isolate for cadazolid, linezolid or moxifloxacin separate sub-listings of *C. difficile* susceptibility information by antibiotic (cadazolid, linezolid, moxifloxacin) will be prepared. Samples with different ribotypes, different REA types and different antibiogram as compared to baseline as well as Clinical Response (Clinical Failure, Recurrence) will be flagged.

10.8.2.5 Vancomycin-resistant enterococci

Frequencies and percentages of subjects considered VRE-positive and VRE-negative at each visit as well as the following shifts from baseline to Visit 3 are displayed:

- VRE Gain (or Colonization) = Visit 1 VRE-negative to Visit 3 VRE-positive
- VRE Loss (or De-colonization) = Visit 1 VRE-positive to Visit 3 VRE-negative
- VRE Uncolonized = Visit 1 VRE-negative and Visit 3 VRE-negative
- VRE Colonized = Visit 1 VRE-positive and Visit 3 VRE-positive

Summaries are presented using the mITT.

10.8.2.6 Vancomycin-resistant enterococci quantitative culture

Total VRE counts (cfu/mL) at baseline and Visit 3, as well as changes from baseline to Visit 3, are summarized by treatment group with descriptive statistics for subjects in whom VRE results at baseline are VRE-positive.

Note: For VRE-positive subjects at baseline who are VRE-negative at Visit 3, the imputed Total VRE count of 0 log10 cfu/mL is used for analysis at Visit 3 [see Section 5.5.4.6].

10.8.2.7 Susceptibility of vancomycin-resistant enterococci

Susceptibility test results for VRE (*E. faecium*; *E. faecalis*; Not *E. faecium,* not *E. faecalis)* isolates at baseline and Visit 3 will be summarized by VRE species (i.e., separately for *E. faecium* [first colony], and *E. faecalis* [first colony]) using MIC summary statistics (MIC range, MIC_{50}, MIC_{90}) to each test agent in the mITT.

Change from baseline in susceptibility of VRE for cadazolid, linezolid and moxifloxacin will be summarized by VRE species (i.e., separately for *E. faecium* [first colony] and *E. faecalis* [first colony]) with frequencies and percentages of subjects using the mITT.

MIC_{50} and MIC_{90} values are derived and presented when MICs for at least 10 isolates are present.

VRE isolation, quantitative culture and susceptibility are also listed.

10.9 Analysis of safety variables

Safety summaries are prepared using the SS or ES according to the period of interest (main study or re-treatment extension, respectively).

10.9.1 Adverse events

All AEs captured in the database are reported in the subject listings.

AEs are summarized by presenting, per treatment group, the number and percentage of subjects having any AE, having an AE in each primary SOC, and having each individual AE (preferred term).

The following summaries are considered:

- Treatment-emergent AEs (up to EOT + 7)
- Main study AEs (up to Visit 5)
- Re-treatment-emergent AEs (up to End of Re-treatment + 7)
- Re-treatment extension AEs (up to Visit Re-5)

In addition, treatment-emergent AEs and re-treatment-emergent AEs are also tabulated by maximum intensity. Treatment-emergent AEs are also tabulated for those related to study treatment. One summary table of treatment-emergent AEs by preferred term together sorted by absolute percent different between cadazolid and vancomycin is prepared.

Treatment-emergent AEs are also summarized using preferred terms only, ordered by incidence of subjects with events in the cadazolid group.

Non-serious AEs are summarized separately as:

- Non-serious frequent treatment-emergent AEs
- Non-serious frequent re-treatment-emergent AEs

Frequent AEs are those occurring in ≥ 5% of subjects in at least one treatment group.

Non-serious frequent treatment-emergent AEs and non-serious frequent re-treatment AEs are summarized by treatment group presenting the number and percentage of subjects having any such AE and having each individual AE (preferred term), together with the number of events overall and per individual AE (preferred term) with the event rate (number of events out of total events).

A separate listing is provided comprising all AEs per treatment group.

10.9.2 Deaths, other serious adverse events

10.9.2.1 Deaths

AEs with fatal outcome are summarized in a similar manner as described for AEs.

The number and percentage of subjects who died are summarized per treatment group, including the reported causes of death. A summary table is provided for all deaths overall and split by time windows after the first treatment intake up to Visit 5 (inclusive), after first treatment intake up to EOT + 7 days, after the first re-treatment intake up to Visit Re-5 (inclusive) out of subjects in the ES. A separate listing including all deaths is provided.

10.9.2.2 Serious adverse events

Serious adverse events (SAEs) are summarized separately by SOC and preferred term as:

- Treatment-emergent SAEs (up to EOT + 7)
- Main study SAEs (up to Visit 5)
- Treatment-emergent SAEs related to study drug (up to EOT + 7)
- Treatment-emergent SAEs with fatal outcome (up to EOT + 7)
- Re-treatment-emergent SAEs (up to End of Re-treatment + 7)
- Re-treatment extension SAEs (up to Visit Re-5)

A separate listing is provided comprising all SAEs per treatment group for the FAS, and listing of re-treatment emergent SAEs for the ES.

In addition, treatment-emergent SAEs are summarized using preferred terms only, ordered by incidence of subjects with events in the cadazolid group.

For treatment-emergent SAEs, the number of events, and event rate overall and per preferred term will be summarized in addition.

10.9.2.3 Adverse events leading to study treatment discontinuations

AEs leading to study treatment discontinuation are summarized for the main study (by SOC and PT, and by PT) and re-treatment extension (by SOC and PT).

A separate listing including all AEs leading to study treatment discontinuation and re-treatment discontinuation is provided.

10.9.2.4 Other significant adverse events

Not applicable.

10.9.3 Electrocardiography

Descriptive summary statistics by visit and study treatment are provided for observed values and absolute changes from baseline (changes from re-treatment baseline during the re-treatment extension). Values from unscheduled visits, and from Visits 4.a, 4.b, etc. [exception, see Section 11.5] are not included in these summaries, but are included in the listings and in the summaries for marked abnormalities and treatment-emergent marked abnormalities.

The number and percentage of subjects with at least one study QT or QTc marked abnormality (absolute and change) or treatment-emergent QT or QTc marked abnormality (absolute and change) are summarized by treatment group together with 95% CIs for proportions (Wilson score method). The number and percent of subjects with at least one marked abnormality are also presented separately for each parameter by category together with 95% CIs. If a subject assessment qualifies for more than one category of a marked abnormality then the worst case is taken into account.

The number and percentage of subjects with ECG qualitative abnormalities (findings) and treatment-emergent finding are summarized by treatment group.

The denominator for percentages is the number of subjects with at least one post-baseline assessment.

Re-treatment-emergent QT or QTc marked abnormalities up to End of Re-treatment + 7 days and Re-treatment-emergent qualitative ECG abnormalities up to End of Re-treatment + 7 days are presented in a similar way.

Summary statistics are calculated for ECG parameters for absolute values and changes from baseline to each visit (changes from re-treatment baseline during the re-treatment extension).

All ECG data including QTc parameters are listed by treatment group and subject. All marked abnormalities are flagged and qualitative abnormalities (as reported by the investigator on the CRF ECG pages) are listed.

All ECG data are also presented in one single listing.

10.9.4 Laboratory tests

Descriptive summary statistics by visit and study treatment group are provided for observed values and absolute changes from baseline (changes from re-treatment baseline during the re-treatment extension). Data are displayed in SI units as provided by the central laboratory (local laboratory data are normalized if no central laboratory data are available for the same time point). Values from unscheduled visits, and from Visits 4.a, 4.b, etc. [exception, see Section 11.5] are not included in these summaries, but are included in the listings and in the summaries for marked abnormalities and treatment-emergent marked abnormalities.

Summaries for WBC differential count are performed only on the absolute counts and not on the percentages.

The number of subjects with at least one marked laboratory abnormality is summarized by treatment group.

In addition, the number of subjects with treatment-emergent marked laboratory abnormalities is summarized by treatment group.

Shifts from baseline to worst post-baseline abnormality category up to Visit 5 are summarized with frequencies of subjects and percentages per category of shift. Categories considered are LLL, LL, L (L = below LLN), normal (between LLN and ULN), H (H = above ULN), HH, HHH. For baseline the category Missing is considered as well. Subjects experiencing a worsening from baseline in two different directions (e.g., going from normal at baseline once to H and once to L post-baseline) are counted in both directions.

The denominator for percentages is the number of subjects with at least one post-baseline assessment.

Re-treatment-emergent marked abnormalities up to End of Re-treatment + 7 days are presented in a similar way.

All data are also presented in one single listing. All abnormalities and marked abnormalities including those at baseline are flagged in the listings.

10.9.5 Vital signs and body weight

Descriptive summary statistics by visit and study treatment group are provided for observed values and changes from baseline (changes from re-treatment baseline during the re-treatment extension) for SBP and DBP, for HR, for body weight, and for core body temperature. Values from unscheduled visits, and from Visits 4.a, 4.b, etc. [exception, see Section 11.5] are not included in these summaries, but are included in the listings and in the summaries for marked abnormalities and treatment-emergent marked abnormalities.

The number and percent of subjects with at least one blood pressure marked abnormality is summarized by treatment group.

In addition, the number of subjects with treatment-emergent blood pressure marked abnormalities is summarized by treatment group.

The denominator for percentages is the number of subjects with at least one post-baseline vital sign assessment.

Re-treatment-emergent marked abnormalities up to End of Re-treatment + 7 days are presented in a similar way.

All data are also presented in one single listing, all marked abnormalities including those at baseline are flagged in the listings.

10.9.6 Other safety variables

Physical abnormalities including abdominal examination abnormalities are presented in one single listing.

10.10 Analysis of quality of life variables

Not applicable, analyses related to CDI-DaySyms PRO are described in Section 10.7.3, and Sections 10.8.1.11 and 10.8.1.12.

10.11 Analysis of pharmacoeconomic variables

WPAI scores and number of subjects currently employed by visit during the main study are summarized per treatment group. Hospitalizations are summarized by treatment group overall and separately for hospitalization situation (yes/no) at the time of first dose and separately for those with reason for hospitalization recorded as CDAD.

Number and percentage of subjects by frequency of admissions/re-admissions are summarized by treatment group and by reason for hospitalization.

Descriptive summary statistics by visit and study treatment group are provided for observed values for the treatment period. All data are also presented in one single listing.

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Unit conversion

Height (cm) = height (in) * 2.54

Weight (kg) = weight (lbs) * 0.4536

Temperature (°C) = (Temperature (°F) – 32) * 5 / 9

Core Temperature (°C) = Temperature (rectal; °C)

Core Temperature (°C) = Temperature (oral; °C) + 0.6

Core Temperature (°C) = Temperature (ear; °C)

Core Temperature (°C) = Temperature (axilla; °C) + 1.2

Core Temperature (°C) = Temperature (forehead[temporal]; °C) + 1.2

11.2 Variable derivation

BMI (kg/m^2) = weight (kg) / (height (cm) / 100)^2

Absolute change from baseline is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

A percentage (relative) change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

For susceptibility (MIC) endpoints, change from baseline is defined as post-baseline value divided by baseline value.

11.3 Dates, times and days

Baseline is defined as the last non-missing assessment before date and time of first dose intake of double-blind treatment.

Randomization date/time is taken directly from the primary form of the CRF (integrated from IVRS system).

Study treatment start (STS) is defined as the date/time of first (double-blind) study drug intake. It is the earliest treatment start date/time recorded on the Study Drug Log CRF.

Study treatment end (STE) is defined as the date/time of last (double-blind) study drug intake. It is the latest treatment end date/time recorded on the Study Drug Log CRF.

Re-treatment Baseline is defined as the last non-missing assessment before date and time of first dose intake of open-label re-treatment with cadazolid. Only assessments after EOT are considered.

Re-treatment start (RTS) is defined as the date/time of the first open-label study drug intake. It is the earliest treatment start date/time recorded on the re-treatment Study Drug Log CRF.

End-of-Treatment (EOT / Main period) is the date of last double-blind drug intake. It is the latest treatment end date recorded on the Study Drug Log CRF.

Re-treatment end (RTE) is defined as the date/time of last open-label drug intake. It is the latest treatment end date/time recorded on the re-treatment Study Drug Log CRF.

End of Re-treatment (EORT) is the date of last open-label drug intake. It is the latest treatment end date recorded on the re-treatment Study Drug Log CRF.

End-of-Study (EOS) date is taken directly from the End of Study page of the CRF.

Last contact date for subjects lost to follow up is defined as the latest date up to the end of study date amongst the following dates: visit dates, dates of laboratory blood samples taken, stool samples, physical examination / vital signs / ECG assessment date, AE onset and end dates, therapies start and stop dates, treatment intake, and dates with daily stool information. The end of study date itself is not considered as the date relates to an unsuccessful contact attempt. Dates completed by subjects, i.e., for patient-reported outcomes, are also not considered as it may contain impossible, spurious or partial dates and are not subject to cleaning.

Study Day (Day) refers to the number of days elapsed since STS date plus 1 (e.g., Day 1 is the day of STS). For dates prior to STS, study day is the negative number of days elapsed between the date under consideration and the day of STS. Therefore, the study day is always different from 0.

Days from first dose are estimated for several assessments, including AE onset, AE end, study withdrawal, treatment interruptions, End-of-Treatment, concomitant medication start day and concomitant medication end day. It refers to the number of days between the occurrence of the specific event and the STS and plus 1 if the event occurs from the day of STS onwards, and plus 0 otherwise. It is a negative value if the event occurred up until the day before STS, and a positive value if occurs from the day of STS.

Days from last dose are estimated for several assessments, including AE onset, concomitant medication start day, and study withdrawal. It refers to the number of days between the occurrence of the specific event and the date of EOT. It is a positive value if it occurs from the day after EOT and not defined otherwise.

Days from first re-treatment dose are estimated for several assessments, including AE onset, AE end, study withdrawal, re-treatment interruptions, End of Re-treatment, concomitant medication start day and concomitant medication end day. It refers to the number of days between the occurrence of the specific event and the RTS plus 1. It is a positive value if it occurs from the day of RTS onwards.

Days from last re-treatment dose are estimated for several assessments, including AE onset, concomitant medication start day, and study withdrawal. It refers to the number of days between the occurrence of the specific event and the date of RTE. It is a positive value if occurs from the day after RTE and not defined otherwise.

11.4 Periods

For variables assessed up to Visit 5 use the date of Visit 5 as upper limit for the considered period. In the event of missing Visit 5, use the re-treatment start date (if available) otherwise the EOS date in the main study as the upper limit for the considered period.

Similarly, for variables assessed in time periods up to Visit Re-5 use the date of Visit Re-5 as upper limit for the considered period. In the event of missing Visit Re-5 use the EOS date in the re-treatment extension as the upper limit for the considered period.

11.5 Summaries by visit

Summaries by visit are presented for Baseline, Visit 3, Visit 5 (or Visit Re-1 for subjects re-treated), Visit Re-1, Visit Re-3 and Visit Re-5. For subjects re-treated who do not have the assessment performed at Visit Re-1, the last Visit 4.x assessment performed prior to re-treatment are included in the summaries for the Re-1 visit if Visit 4.x is within 24 hours of re-treatment. Otherwise it is considered to be missing for Visit Re-1.

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

Missing parts for specific dates/times are imputed with acceptable non-missing values as described in Table 15.

In the following, ‘lower limit’ and ‘upper limit’ refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. The earliest and the latest dates refer to the first or last date, respectively, when ordered in sequence.

In addition, a review of the available data is performed, and if the classification of an AE or a medication cannot be performed programmatically (e.g., partial start date of event, with treatment and re-treatment start date occurring the same month as the event), a query is raised for the investigator to provide more details on the timing of the event. Based on the response of the investigator, a flag ‘Assigned to re-treatment’ might then be filled in by Actelion in the database (flag is hidden to the investigator).

The imputed EOT date is used in assigning safety events and assessments to the treatment-emergent period and used for deriving efficacy endpoints with definitions requiring EOT date. It is not considered for derivation of exposure variables.

Table 15 Handling of missing date and time

Type of date/time	Date/time is incomplete	Date/time is missing
AE resolution date	Use the upper limit.	No approximation made; the AE is considered as ongoing in the analysis.
AE resolution time	A partially entered time is not allowed. Value is considered to be missing.	Taken as '23:59' if the corresponding AE resolution date is not missing, otherwise no replacement.
AE onset date	If the end date of the AE is before start of study treatment, then the earliest between study treatment start date –1 and the end date of AE is used. If the end date of the AE is not before the start of study treatment, and if the study treatment start falls in the range of possible dates, and if 'Assign to re-treatment' is not ticked, then the study treatment start date is used. If the end date of the AE is not before re-treatment start, and if the re-treatment start falls in the range of possible dates, and if 'Assign to re-treatment' is ticked, then the re-treatment start date is used. In all the other cases, the lower limit is used.	If 'Assign to re-treatment' is not ticked, use the date of resolution of the AE or the date of start of study treatment, whichever is earlier. If 'Assign to re-treatment' is ticked, use the date of resolution of the AE or the date of re-treatment start, whichever is earlier.
AE onset time	A partially entered time is not allowed. Value is considered to be missing.	If the AE onset date is equal to the study treatment start date, then the study treatment start time is used. If the AE onset date is equal to the re-treatment start date, then the study re-treatment start time is used. Otherwise, it is taken as '00:00'
AE onset time	A partially entered time is not allowed. Value is considered to be missing.	If the AE onset date is equal to the study treatment start date, then the study treatment start time is used. If the AE onset date is equal to the re-treatment start date, then the study re-treatment start time is used. Otherwise, it is taken as '00:00'
Concomitant medication start date	If the end date of the concomitant medication is not before re-treatment start, and the re-treatment start date falls in the range of possible dates, and 'Assign to retreatment' has been ticked in the CRF, then the re-treatment start date is used (e.g., conmed start date May2014 and re-treatment start date 15May2014). In all other cases, the lower limit is used.	No replacement is made. If 'Assign to re-treatment' has not been ticked in the CRF then the medication is considered to have started before the screening. If 'Assign to re-treatment' has been ticked in the CRF then the re-treatment start date is used.

Type of date/time	Date/time is incomplete	Date/time is missing
Concomitant medication start time	A partially entered time is not allowed. Value is considered to be missing.	If the medication start date is equal to the study treatment start date and 'Ongoing at treatment start' is ticked 'No' and the medication end is after study treatment start then study treatment start time + 1 is used. If 'Assign to re-treatment' has been ticked the re-treatment start time is used. Otherwise '00:00' is used.
Concomitant medication end date	The upper limit unless the medication started prior to study treatment start and 'Ongoing at start of treatment?' is ticked 'No' or the medication was recorded on the First Occurrence CRF, and the study treatment start falls in the range of possible dates then it is not replaced but considered a previous medication.	No replacement; the treatment is considered as ongoing unless the medication started prior to study treatment start and 'Ongoing at start of treatment?' is ticked 'No' or the medication was recorded on the First Occurrence CRF, then it is considered a previous medication.
Lab, ECG, vital signs assessment start time	Partial time is not allowed. Value will be considered to be missing.	Replace with '00:00'
Treatment start time missing	Partial time is not allowed. Value will be considered to be missing.	Replace with randomization time + 1 min if randomization occurred on the same day, otherwise impute 00:00.
Re-treatment start time missing	Partial time is not allowed. Value will be considered to be missing.	Replace with 00:00.
EOT date	Earliest between treatment start date + 10 days (Day 11), the upper limit, EOS date and Death date.	Earliest between treatment start date + 10 days (Day 11), EOS date and Death date.
End of Re-treatment date	Earliest between re-treatment start date + 10 days (Re-treatment Day 11), the upper limit, EOS date and Death date.	Earliest between re-treatment start date + 10 days (Day 11), EOS date and Death date.

AE = adverse event, ECG = electrocardiogram, EOT = end-of-treatment date

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES (TLFS)

13.1 Subject disposition

Number	Dis-play*	Title (Description)	Analysis set(s)
T 1.1	T	Reasons for screening failures (including unmet eligibility criteria)	SCRAS
L 1.1a	L	Screening failures	SCRAS
L 1.1b	L	Re-treatment extension screening failures	FAS
L 1.2a	L	Unmet eligibility criteria	SCRAS
L 1.2b	L	Unmet re-treatment extension eligibility criteria	FAS
T 1.2a	T	Disposition of subjects	FAS
T 1.2b	T	Disposition of subjects in re-treatment extension [FAS subset of subjects enrolled in re-treatment extension]	FAS
L 1.3	L	Disposition of subjects	FAS
T 1.3	T	Subjects by geographical region, country and site	FAS
T 1.4	T	Subjects by geographical region, country and site	mITT
T 1.5	T	Overview of analysis sets	FAS
T 1.6	T	Reasons for exclusion from the mITT and Per-protocol analysis sets	FAS
T 1.7	T	Participation in PRO validation, PK and gut microbiome sub-studies	FAS
L 1.4	L	Exclusion from mITT analysis set	FAS
L 1.5	L	Exclusion from Per-protocol analysis set	FAS
L 1.6	L	Listing of randomized subjects and participation in analysis sets	FAS
L 1.7	L	Listing of subject unblinding	FAS

* T = Summary table, L = Listing, F = Figure.

13.2 Protocol deviations

Number	Dis-play*	Title (Description)	Analysis set(s)
T 2.1	T	All main study protocol deviations	FAS
T 2.2	T	Important main study protocol deviations	FAS
T 2.3	T	All re-treatment extension protocol deviations	ES
T 2.4	T	Important re-treatment extension protocol deviations	ES
L 2.1	L	All protocol deviations	SCRAS
L 2.2	L	Listing of other protocol deviations	SCRAS

* T = Summary table, L = Listing.

13.3 Subject characteristics

13.3.1 Demographics

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.1	T	Demographic characteristics	mITT
T 3.2	T	Demographic characteristics	PPS
T 3.3	T	Demographic characteristics of subjects who entered the re-treatment extension	ES
T 3.4	T	EudraCT age categories	SS
L 3.1	L	Demographics	FAS

* T = Summary table, L = Listing, F = Figure.

13.3.2 Baseline disease characteristics

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.5	T	Main baseline disease characteristics	mITT
T 3.6	T	Main baseline disease characteristics	PPS
T 3.7	T	Other main baseline disease characteristics	mITT
T 3.8	T	Other main baseline disease characteristics	PPS
T 3.9	T	CDAD episode type IVRS stratification vs CRF actual type	mITT
L 3.2a	L	Baseline disease characteristics	FAS
L 3.2b	L	Baseline disease severity	FAS

* T = Summary table, L = Listing, F = Figure.

13.3.3 Other baseline characteristics

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.10	T	Other baseline disease characteristics	mITT
T 3.11	T	Other baseline disease characteristics	PPS
L 3.3	L	Other baseline disease characteristics	FAS

* T = Summary table, L = Listing.

13.3.4 Medical history

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.12	T	Previous medical history by system organ class and preferred term	mITT
T 3.13	T	Ongoing medical conditions by system organ class and preferred term	mITT
L 3.4	L	Medical history	FAS

* T = Summary table, L = Listing.

13.3.5 Previous and concomitant therapies

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.14	T	Previous therapies by anatomical therapeutic chemical class and preferred term	mITT
T 3.15a	T	Main study concomitant therapies by anatomical therapeutic chemical class and preferred term	mITT
T 3.15b	T	Main study concomitant therapies with onset prior to study treatment start by anatomical therapeutic chemical class (ATC) and preferred term	mITT
T 3.15c	T	Main study concomitant therapies starting between study treatment start and EOT + 7 days by anatomical therapeutic chemical class (ATC) and preferred term	mITT
L 3.5	L	Previous and concomitant therapies	FAS
L 3.6	L	Re-treatment concomitant therapies	ES

* T = Summary table, L = Listing.

13.3.6 Specific previous and concomitant

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.16	T	Prior antimicrobial treatments active against CDAD within 1 week of study treatment start by anatomical therapeutic chemical preferred term	mITT
T 3.17	T	Concomitant opiate treatments at Baseline by anatomical therapeutic chemical preferred term	mITT
T 3.18	T	Main study concomitant antimicrobial treatment active against CDAD by anatomical therapeutic chemical preferred term up to Visit 5	mITT
T 3.19	T	Main study concomitant antimicrobial treatment active against CDAD by anatomical therapeutic chemical preferred term starting between study treatment start and EOT + 2 days	mITT
T 3.20	T	Main study concomitant antimicrobial treatment active against CDAD by anatomical therapeutic chemical preferred term starting between EOT + 3 days and Visit 5	mITT
T 3.21	T	Main study concomitant antibiotics for infections other than CDAD by anatomical therapeutic chemical preferred term up to Visit 5	mITT
T 3.22	T	Main study concomitant antibiotics for infections other than CDAD by anatomical therapeutic chemical preferred term starting between study treatment start and EOT + 2 days.	mITT
T 3.23	T	Main study concomitant antibiotics for infections other than CDAD by anatomical therapeutic chemical preferred term starting between EOT + 3 days and Visit 5	mITT
T 3.24	T	Main study concomitant proton pump inhibitors and H2 blockers by anatomical therapeutic chemical preferred term up to Visit 5	mITT
T 3.25	T	Main study concomitant proton pump inhibitors and H2 blockers by anatomical therapeutic chemical preferred term starting between study treatment start and EOT + 2 days.	mITT
T 3.26	T	Main study concomitant proton pump inhibitors and H2 blockers by anatomical therapeutic chemical preferred term starting between EOT + 3 days and Visit 5	mITT

* T = Summary table.

13.3.7 Procedures

Number	Dis-play*	Title (Description)	Analysis set(s)
T 3.27	T	Main study concomitant procedures [Note: By CDAD-related procedures and Others.]	mITT
L 3.7	L	All procedures	FAS
L 3.8	L	Endoscopy and imaging	FAS

* T = Summary table, L = Listing.

13.4 Study treatment exposure and compliance

13.4.1 Exposure

Number	Dis-play*	Title (Description)	Analysis set(s)
T 4.1	T	Treatment exposure according to treatment received	SS
T 4.2	T	Treatment exposure according to treatment planned	mITT**
T 4.3	T	Re-treatment exposure (open-label cadazolid)	ES
L 4.1a	L	Exposure	FAS

* T = Summary table, L = Listing.
** Not done if mITT analysis set differs from SS by ≤ 5%

13.4.2 Compliance with study treatment

Number	Dis-play*	Title (Description)	Analysis set(s)
T 4.4	T	Compliance	mITT**
T 4.5	T	Compliance with re-treatment (open-label cadazolid)	ES
L 4.1b	L	Compliance	FAS

* T = Summary table.
** Not done if mITT analysis set differs from SS by ≤ 5%

13.4.3 Study treatment discontinuation

Number	Dis-play*	Title (Description)	Analysis set(s)
T 4.6a	T	Reasons for premature discontinuation of main study treatment	SS
T 4.6b	T	Reasons for premature discontinuation of main study treatment according to treatment planned [Present according to "planned treatment" not according to actual treatment received]	SS
T 4.7	T	Reasons for premature discontinuation of main study treatment	mITT**
L 4.2	L	Premature study treatment discontinuation	FAS
L 4.3	L	Premature re-treatment discontinuation	ES

* T = Summary table, L = Listing.
** Not done if mITT analysis set differs from SS by ≤ 5%

13.4.4 Study treatment interruptions

Number	Dis-play*	Title (Description)	Analysis set(s)
T 4.8	T	Reasons for temporary interruption in study treatment	SS

* T = Summary table, L = Listing.
Reasons for temporary interruptions are listed in the exposure listing.

13.5 Study withdrawal

Number	Dis-play*	Title (Description)	Analysis set(s)
T 5.1	T	Reasons for premature study withdrawal	FAS
T 5.2	T	Reasons for premature study withdrawal from the re-treatment extension [Denominator = subjects enrolled in re-treatment extension]	FAS
L 5.1	L	Premature study withdrawal	FAS

* T = Summary table, L = Listing.

13.6 Primary efficacy analyses

13.6.1 Main analysis

Number	Dis-play*	Title (Description)	Analysis set(s)
T 6.1	T	Clinical Cure	mITT
F 6.1	F	Clinical Cure and Sustained Cure [Includes Clinical Cure on mITT, Clinical Cure on PPS, Sustained Cure on mITT]	mITT
T 6.2	T	Clinical Cure	PPS
T 6.3	T	Reasons for Clinical Failure	mITT
T 6.4	T	Reasons for Clinical Failure	PPS
L 6.1	L	Clinical Cure	FAS
L 6.2	L	Daily Stool information and further efficacy data	FAS

* T = Summary table, L = Listing, F = Figure.

13.6.2 Supportive/sensitivity analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 6.5	T	Clinical Cure – Stratified analysis	mITT
T 6.6	T	Clinical Cure – Stratified analysis	PPS
T 6.7	T	Clinical Cure – Sensitivity analysis imputing missing day	mITT
L 6.3	L	Sensitivity variables for Clinical Cure and Sustained Cure in subjects with at least one sensitivity variable differing from main endpoint	FAS

* T = Summary table; L = Listing.

13.6.3 Subgroup analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 6.8	T	Clinical Cure – Subgroup analysis	mITT
T 6.9	T	Clinical Cure – Subgroup analysis	PPS
F 6.3	F	Clinical Cure – Forest plot of subgroups (difference in proportions)	mITT
F 6.4	F	Clinical Cure – Forest plot of subgroups (difference in proportions)	PPS
T 6.10	T	Clinical Cure – Logistic regression for subgroup analyses	mITT
F 6.5	F	Clinical Cure – Forest plot of subgroups (odds ratios)	mITT
T 6.11	T	Clinical Cure – Logistic regression for subgroup analyses	PPS
F 6.6	F	Clinical Cure – Forest plot of subgroups (odds ratios)	PPS

* T = Summary table, F = Figure.

13.6.4 Other analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 6.14	T	Clinical Cure by concomitant antibiotics for infections other than CDAD from first dose to EOT + 2 days	mITT
T 6.15	T	Clinical Cure by concomitant antibiotics for infections other than CDAD from first dose to EOT + 2 days	PPS
T 6.16	T	Clinical Cure by country	mITT
F 6.7	F	Clinical Cure by country	mITT

* T = Summary table, F = Figure.

13.7 Secondary efficacy analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 7.1	T	Sustained Cure	mITT
T 7.2	T	Sustained Cure	PPS
F 7.1	F	Sustained Cure	mITT
T 7.3	T	Reasons for being classified as not Sustained Cure	mITT
T 7.4	T	Sustained Cure – Subgroup analysis	mITT
F 7.2	F	Sustained Cure – Forest plot of subgroups (difference in proportions)	mITT
T 7.5	T	Sustained Cure by concomitant antibiotics for infections other than CDAD from first dose to Visit 5 / Re-treatment	mITT
T 7.6	T	Sustained Cure – Logistic regression for subgroup analyses	mITT
F 7.3	F	Sustained Cure – Forest plot of subgroups (odds ratios)	mITT
T 7.7	T	Sustained Cure by Country	mITT
F 7.4	F	Sustained Cure by Country	mITT
L 7.1	L	Sustained Cure	FAS
T 7.8	T	Time to resolution of diarrhea analysis	mITT
T 7.9	T	Time to resolution of diarrhea analysis	PPS
T 7.10	T	Time to resolution of diarrhea: Kaplan-Meier estimates	mITT
T 7.11	T	Time to resolution of diarrhea: Kaplan-Meier estimates	PPS
T 7.12	T	Time to resolution of diarrhea: Kaplan-Meier estimates by stratum	mITT
F 7.5	F	Time to Resolution of Diarrhea: Kaplan-Meier Curve	mITT
F 7.6	F	Time to Resolution of Diarrhea: Kaplan-Meier Curve	PPS
F 7.7	F	Time to resolution of diarrhea within stratum: Kaplan-Meier curve	mITT
L 7.2	L	Time to resolution of diarrhea (ROD)	FAS
T 7.13	T	Absolute and change from baseline values for CDI-DaySyms domain scores by time point	PROAS[1]

Number	Dis-play*	Title (Description)	Analysis set(s)
F 7.8	F	Box-plot of absolute values for CDI-DaySyms by domain score and time point	PROAS[1]
T 7.14	T	Number and proportion of subjects with missing CDI-DaySyms scores, by domain score and time point	PROAS[1]
T 7.15	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores	PROAS[1]
F 7.9	F	LS mean estimates and 95% CI for CDI-DaySyms domain scores by time point	PROAS[1]
T 7.16	T	Statistical analysis (ANOVA) of CDI-DaySyms diarrhea domain score - sensitivity analysis with 50% missing data rule applied	PROAS[1]
T 7.17	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores - multiple imputation with MAR sensitivity analysis	PROAS[1]
T 7.18	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores - tipping point imputation sensitivity analysis	PROAS[1]
T 7.19	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores - LOCF imputation sensitivity analysis	PROAS[1]
T 7.20	T	CDI-DaySyms domain score response rates at Day 3	PROAS[1]
T 7.21	T	Absolute values of CDI-DaySyms domain scores by CC response and time point	PROAS[1]
T 7.22	T	Absolute values of CDI-DaySyms domain scores by CC response, time point and treatment group	PROAS[1]
T 7.23	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores vs CC response	PROAS[1]
T 7.24	T	Statistical analysis (ANOVA) of CDI-DaySyms domain scores vs CC response, by treatment group	PROAS[1]
F 7.10	F	Box-plot of absolute values of CDI DaySyms domain scores by CC response and time point	PROAS[1]
F 7.11	F	Box-plot of absolute values of CDI DaySyms domain scores by CC response, time point and treatment group	PROAS[1]
L 7.3	L	CDI-DaySyms individual items data (main study and re-treatment)	FAS

Number	Dis-play*	Title (Description)	Analysis set(s)
L 7.4	L	CDI-DaySyms domain scores and change from baseline (main study)	FAS
L 7.5	L	CDI-DaySyms responder status at Day 3, by domain (main study)	FAS

* T = Summary table, L = Listing, F = Figure.
1. Excluding subjects in the PRO sub-study.

13.7.1 Further supportive/sensitivity analyses for Sustained Cure

Number	Dis-play*	Title (Description)	Analysis set(s)
T 7.25	T	Sustained Cure – Sensitivity analysis reducing minimum follow-up period required to EOT + 25 days	mITT
T 7.26	T	Reasons for being classified as not Sustained Cure – Sensitivity analysis reducing minimum follow-up period required to EOT + 25 days	mITT
T 7.27	T	Modified Sustained Cure	mITT
T 7.28	T	Modified recurrence	mITT

* T = Summary table.

13.8 Other efficacy analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.1	T	Investigator judgment of early treatment response (ETR) at Visit 2	mITT
T 8.2a	T	Investigator judgment of clinical response (ICR) at Visit 4	mITT
T 8.2b	T	Reasons for investigator judgment of clinical response (ICR) at Visit 4	mITT
T 8.3	T	Investigator judgment of clinical response (ICR) at Visit 4	PPS
T 8.4a	T	Investigator assessment of sustained response (ISR) at Visit 5	mITT
T 8.4b	T	Reasons for investigator judgment of sustained response (ISR) at Visit 5	mITT
T 8.5	T	Early clinical cure (ECC) by Day 5	mITT
T 8.6	T	Normalization of bowel movements rate	mITT

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.7	T	Time to return to usual stools	mITT
F 8.1	F	Time to return to usual stools: Kaplan-Meier curve	mITT
T 8.8	T	Recurrence rate and adjusted recurrence rate	mITT
T 8.9	T	Recurrence rate and adjusted recurrence rate	PPS
T 8.10	T	Recurrence rate – Subgroup	mITT
T 8.11	T	Time to Recurrence for subjects with Clinical Cure	mITT
F 8.2	F	Time to Recurrence for subjects with Clinical Cure: Kaplan-Meier curve	mITT
T 8.12a	T	Subjects with *C. difficile* isolate at baseline: Overall, by geographical region, and by Clinical Cure Outcome [showing frequencies and percentages by treatment group and overall]	mITT
T 8.12b	T	Subjects with *C. difficile* isolate at baseline: Overall, by geographical region, and by Clinical Cure Outcome [showing frequencies and percentages by treatment group and overall]	PPS
T 8.13	T	Subjects with *C. difficile* isolate by visit during main study	mITT
T 8.14a	T	Subjects with *C. difficile* isolate by visit for Clinical Failures (Baseline and Visit 3) and Recurrences (Baseline and Visit 4.x)	mITT
T 8.14b	T	Subjects with *C. difficile* isolate by visit for Clinical Failures (Baseline and Visit 3) and Recurrences (Baseline and Visit 4.x)	PPS
T 8.15a	T	*C. difficile* strains for baseline isolates based on PCR ribotyping and REA typing [by treatment group and overall]	mITT
T 8.15b	T	*C. difficile* strains for baseline isolates based on PCR ribotyping and REA typing [by treatment group and overall]	PPS
T 8.16a	T	Hypervirulent ribotypes at baseline. Overall, by geographical region and by country [by treatment group and total overall]	mITT
T 8.16b	T	REA groups of special interest at baseline. Overall, by geographical region and by country [by treatment group and total overall]	mITT

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.16c	T	Hypervirulent ribotypes at baseline. Overall, by geographical region and by country [by treatment group and total overall]	PPS
T 8.16d	T	REA groups of special interest at baseline. Overall, by geographical region and by country [by treatment group and total overall]	PPS
T 8.17	T	Hypervirulent ribotypes vs REA groups of special interest at baseline. Overall and by geographical region [cross tabulated by treatment group and total overall]	mITT
T 8.18a	T	Relapse and re-infection [by treatment group]	mITT
T 8.18b	T	Relapse and re-infection [by treatment group]	PPS
T 8.19a	T	Susceptibility of *C. difficile* to each test agent at baseline and post-baseline (highest MIC). MIC summary statistics. [by treatment group and total; test agents = cadazolid, vancomycin, linezolid, moxifloxacin, metronidazole and fidaxomicin]	mITT
T 8.19b	T	Susceptibility of *C. difficile* to each test agent at baseline and post-baseline (highest MIC). MIC summary statistics. [by treatment group and total; test agents = cadazolid, vancomycin, linezolid, moxifloxacin, metronidazole and fidaxomicin]	PPS
T 8.20a	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid and moxifloxacin by visit for Clinical Failures (baseline and Visit 3) and Recurrences (baseline and Visit 4.x). MIC summary statistics. [by treatment group]	mITT
T 8.20b	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid and moxifloxacin by visit for Clinical Failures (baseline and Visit 3) and Recurrences (baseline and Visit 4.x). MIC summary statistics. [by treatment group]	PPS
T 8.21	T	Susceptibility of *C. difficile* to each test agent at baseline. MIC summary statistics overall and by Clinical Cure outcome. [by treatment group and overall]	mITT
T 8.21	T	Susceptibility of *C. difficile* to each test agent at baseline. MIC summary statistics overall and by Clinical Cure outcome. [by treatment group and overall]	PPS

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.22a	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with hypervirulent strain. MIC summary statistics overall and by Clinical Cure outcome. [by treatment group and overall]	mITT/PPS
T 8.22b	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with hypervirulent strain. MIC summary statistics overall and by Clinical Cure outcome. [by treatment group and overall]	PPS
T 8.23a	T	Susceptibility of *C. difficile* to each test agent at baseline. MIC summary statistics by geographical region. [by treatment group and overall]	mITT
T 8.23b	T	Susceptibility of *C. difficile* to each test agent at baseline. MIC summary statistics by geographical region. [by treatment group and overall]	PPS
T 8.24a	T	Susceptibility of *C. difficile* to each test agent at baseline and post-baseline (highest MIC). MIC frequency distribution [by treatment group]	mITT
T 8.24b	T	Susceptibility of *C. difficile* to each test agent at baseline and post-baseline (highest MIC). MIC frequency distribution [by treatment group]	PPS
F 8.3	F	Susceptibility of *C. difficile* to each test agent at baseline. MIC frequency distribution. [by treatment group]	mITT
T 8.25a	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid, and moxifloxacin for Clinical Failures at baseline and Visit 3. MIC frequency distribution. [by treatment group]	mITT
T 8.25b	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid, and moxifloxacin for Clinical Failures at baseline and Visit 3. MIC frequency distribution. [by treatment group]	PPS
T 8.37a	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with hypervirulent strain. MIC frequency distribution [by treatment group]	mITT

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.37b	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with hypervirulent strain. MIC frequency distribution [by treatment group]	PPS
T 8.38a	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with REA group of special interest. MIC (µg/mL) summary statistics overall and by Clinical Cure outcome	mITT
T 8.38b	T	Susceptibility of *C. difficile* to each test agent at baseline in subjects with REA group of special interest. MIC (µg/mL) summary statistics overall and by Clinical Cure outcome	PPS
T 8.26a	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid, and moxifloxacin for Recurrences at baseline and Visit 4.x. MIC frequency distribution. [by treatment group]	mITT
T 8.26b	T	Susceptibility of *C. difficile* to cadazolid, vancomycin, linezolid, and moxifloxacin for Recurrences at baseline and Visit 4.x. MIC frequency distribution. [by treatment group]	PPS
T 8.27a	T	Clinical Cure Rates by baseline *C. difficile* MIC level to each test agent. Overall and by Hypervirulent Strain. [by treatment group]	mITT
T 8.27b	T	Clinical Cure Rates by baseline *C. difficile* MIC level to each test agent. Overall and by Hypervirulent Strain. [by treatment group]	PPS
T 8.28a	T	Susceptibility of *C. difficile* to each test agent: Change from baseline for Clinical Failures to Visit 3 and for Recurrences to Visit 4.x. Frequencies for different levels of changes. [by treatment group]	mITT
T 8.28b	T	Susceptibility of *C. difficile* to each test agent: Change from baseline for Clinical Failures to Visit 3 and for Recurrences to Visit 4.x. Frequencies for different levels of changes. [by treatment group]	PPS
T 8.29	T	Susceptibility of *C. difficile* to each test agent: Change from baseline to highest post-baseline result. Frequencies for different levels of changes. [by treatment group]	mITT

Number	Dis-play*	Title (Description)	Analysis set(s)
T 8.30	T	Vancomycin-resistant enterococci (VRE): Subjects with isolates at baseline and Visit 3 and shifts from baseline. [by treatment group]	mITT
T 8.31	T	Total vancomycin-resistant enterococci (VRE) counts (log10 cfu/ml) in VRE-positive subjects at baseline. Absolute values and change from baseline to Visit 3. [by treatment group]	mITT
T 8.32	T	Susceptibility of vancomycin-resistant enterococci (VRE) to each test agent at baseline and Visit 3. MIC summary statistics by VRE species [by treatment group; test agents = cadazolid, vancomycin, linezolid, moxifloxacin, fidaxomicin, daptomycin, tigecycline, ampicillin, gentamicin, and quinupristin-dalfopristin; VRE species = *E. faecium* (first colony), and *E. faecalis* (first colony)]	mITT
T 8.33	T	Susceptibility of vancomycin-resistant enterococci (VRE) to cadazolid, linezolid, and moxifloxacin: Change from baseline to Visit 3 by VRE species [by treatment group, VRE species = *E. faecium* (first colony), and *E. faecalis* (first colony)]	mITT
L 8.1	L	Investigator judgment of efficacy	FAS
L 8.2a	L	*C. difficile* isolation and typing	FAS
L 8.2b	L	*C. difficile* isolate 2 culture and typing	FAS
L 8.3a	L	Susceptibility of *C. difficile* to different antibiotics	FAS
L 8.3b	L	Susceptibility of *C. difficile* isolate 2 to different antibiotics	FAS
L 8.4	L	Susceptibility of *C. difficile* to cadazolid for subjects with ≥ 4-fold MIC increase to cadazolid	FAS
L 8.5	L	Susceptibility of *C. difficile* to linezolid for subjects with ≥ 4-fold MIC increase to linezolid	FAS
L 8.6	L	Susceptibility of *C. difficile* to moxifloxacin for subjects with ≥ 4-fold MIC increase to moxifloxacin	FAS
L 8.7	L	Vancomycin-resistant enterococci culture	FAS
L 8.8	L	Vancomycin-resistant enterococci susceptibility to different antibiotics	FAS
L 8.9	L	Investigator judgment of efficacy	FAS

Number	Dis-play*	Title (Description)	Analysis set(s)
L 8.10	L	Cure reasons for investigator judgment of clinical response (ICR) during main study and re-treatment extension	FAS
L 8.11	L	Failure reasons for investigator judgment of clinical response (ICR) during main study and re-treatment extension	FAS
L 8.12	L	Cure reasons for investigator judgment of sustained response (ISR) during main study and re-treatment extension	FAS
L 8.13	L	Failure reasons for investigator judgment of sustained response (ISR) during main study and re-treatment extension	FAS
L 8.14	L	Other efficacy variables – main study	FAS
T 8.34	T	Re-treatment Clinical Cure	ES
T 8.35	T	Re-treatment Sustained Cure	ES
T 8.36	T	Re-treatment recurrence and adjusted recurrence	ES
L 8.15	L	Re-treatment Clinical Cure	ES
L 8.16	L	Re-treatment Sustained Cure	ES
L 8.17	L	Re-treatment investigator judgment of efficacy	ES

* T = Summary table, L = Listing, F = Figure.

13.9 Safety analyses

13.9.1 Adverse events

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.1	T	Overview of treatment-emergent adverse events (AE) up to EOT + 7 days	SS #
T 9.2	T	Treatment-emergent adverse events (AE) by system organ class and preferred term up to EOT + 7 days	SS
T 9.3	T	Treatment-emergent adverse events (AE) by preferred term up to EOT + 7 days	SS
T 9.4	T	Treatment-emergent adverse events (AE) by preferred term up to EOT + 7 days sorted by risk difference between cadazolid and vancomycin	SS
T 9.5	T	Main study adverse events (AE) by system organ class and preferred term up to Visit 5	SS
T 9.6	T	Occurrence of non-serious frequent treatment-emergent adverse events (AE) up to EOT + 7 days	SS #
T 9.7	T	Overview of re-treatment-emergent adverse events (AE) up to End of Re-treatment + 7 days	ES #
T 9.8	T	Re-treatment-emergent adverse events (AE) by system organ class and preferred term up to End of Re-treatment + 7 days	ES
T 9.9	T	Re-treatment extension adverse events (AE) by system organ class and preferred term up to Visit Re-5	ES
T 9.10	T	Occurrence of non-serious frequent re-treatment-emergent adverse events (AE) up to End of Re-treatment + 7 days	ES #
L 9.1	L	Listing of all adverse events (AE)	FAS

* T = Summary table, L = Listing. # EudraCT required.

13.9.2 Serious adverse events

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.11	T	Treatment-emergent serious adverse events (SAE) by system organ class and preferred term up to EOT + 7 days	SS
T 9.12	T	Treatment-emergent serious adverse events (SAE) by preferred term up to EOT + 7 days	SS
T 9.13	T	Main study serious adverse events (SAE) by system organ class and preferred term up to Visit 5	SS
T 9.14	T	Occurrence of treatment-emergent serious adverse events (SAE) up to EOT + 7 days	SS #
T 9.15	T	Re-treatment-emergent serious adverse events (SAE) by system organ class and preferred term up to End of Re-treatment + 7 days	ES
T 9.16	T	Re-treatment extension serious adverse events (SAE) by system organ class and preferred term up to Visit Re-5	ES
L 9.2	L	Listing of all serious adverse events (SAE)	FAS
L 9.3	L	Listing of re-treatment-emergent serious adverse events up to End of Re-treatment + 7 days	ES #

* T = Summary table, L = Listing. # EudraCT required.

13.9.3 Adverse events by intensity or relationship to study treatment

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.16	T	Treatment-emergent adverse events (AE) by maximum intensity up to EOT + 7 days	SS
T 9.17	T	Re-treatment-emergent adverse events (AE) by maximum intensity up to End of Re-treatment + 7 days	ES
T 9.18	T	Treatment-emergent adverse events (AE) related to study treatment by system organ class and preferred term up to EOT + 7 days	SS
L 9.4	L	Listing of treatment-emergent serious adverse events (SAE) related to study treatment	SS #

T = Summary table, L = Listing. # EudraCT required.

13.9.4 Other significant adverse events

13.9.4.1 Adverse events leading to treatment discontinuation

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.19	T	Treatment-emergent adverse events (AE) leading to premature discontinuation of study treatment by system organ class and preferred term	SS
T 9.20	T	Treatment-emergent adverse events (AE) leading to premature discontinuation of study treatment by preferred term	SS
T 9.21	T	Re-treatment-emergent adverse events (AE) leading to premature discontinuation of study treatment by system organ class and preferred term	ES
L 9.5	L	Listing of adverse events (AE) leading to premature discontinuation of study treatment	FAS

* T = Summary table, L = Listing.

13.9.4.2 Adverse events leading to death

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.22	T	Treatment-emergent adverse events (AE) with fatal outcome by system organ class and preferred term up to EOT + 7 days	SS
T 9.23	T	Main study adverse events (AE) with fatal outcome by system organ class and preferred term up to Visit 5	SS
T 9.24	T	Treatment-emergent serious adverse events (SAE) with fatal outcome by system organ class and preferred term up to EOT + 7 days	SS #
L 9.6	L	Listing of adverse events (AE) with fatal outcome	FAS

* T = Summary table, L = Listing. # EudraCT required.

13.9.5 Deaths

Number	Dis-play*	Title (Description)	Analysis set(s)
T 9.25	T	Primary cause of death. Overall and by period	SS
L 9.6	L	Deaths	FAS

* T = Summary table, L= Listing.

13.10 Electrocardiography

Number	Dis-play*	Title (Description)	Analysis set(s)
T 10.1a	T	ECGs: Absolute values and changes from baseline by visit during main study	SS
T 10.1b	T	ECGs: Absolute values and changes from baseline by visit during re-treatment extension	ES
T 10.2	T	Treatment-emergent QT or QTc marked abnormalities up to EOT + 7 days	SS
T 10.3	T	Re-treatment-emergent QT or QTc marked abnormalities up to End of Re-treatment + 7 days	ES
T 10.4	T	Main study QT or QTc marked abnormalities up to Visit 5	SS
T 10.5	T	Treatment-emergent qualitative ECG abnormalities up to EOT + 7 days	SS
T 10.6	T	Re-treatment-emergent qualitative ECG abnormalities up to End of Re-treatment + 7 days	ES
T 10.7	T	Main study qualitative ECG abnormalities up to Visit 5	SS
L 10.1	L	ECG data	FAS
L 10.2	L	ECG findings	FAS

* T = Summary table, L = Listing.

13.11 Laboratory tests

Number	Dis-play*	Title (Description)	Analysis set(s)
T 11.1a	T	Hematology: Absolute values and changes from baseline by visit during main study	SS
T 11.1b	T	Hematology: Absolute values and changes from baseline by visit during re-treatment extension	ES
T 11.2a	T	Coagulation: Absolute values and changes from baseline by visit during main study	SS
T 11.2b	T	Coagulation: Absolute values and changes from baseline by visit during re-treatment extension	ES

Number	Dis-play*	Title (Description)	Analysis set(s)
T 11.3a	T	Chemistry: Absolute values and changes from baseline by visit during main study	SS
T 11.3b	T	Chemistry: Absolute values and changes from baseline by visit during re-treatment extension	ES
T 11.4	T	Hematology: Treatment-emergent marked laboratory abnormalities up to EOT + 7 days	SS
T 11.5	T	Hematology: Re-treatment-emergent marked laboratory abnormalities up to End of Re-treatment + 7 days	ES
T 11.6	T	Hematology: Main study marked laboratory abnormalities up to Visit 5	SS
T 11.7	T	Coagulation: Treatment-emergent marked laboratory abnormalities up to EOT + 7 days	SS
T 11.8	T	Coagulation: Re-treatment-emergent marked laboratory abnormalities up to End of Re-treatment + 7 days	ES
T 11.9	T	Coagulation: Main study marked laboratory abnormalities up to Visit 5	SS
T 11.10	T	Chemistry: Treatment-emergent marked laboratory abnormalities up to EOT + 7 days	SS
T 11.11	T	Chemistry: Re-treatment-emergent marked laboratory abnormalities up to End of Re-treatment + 7 days	ES
T 11.12	T	Chemistry: Main study marked laboratory abnormalities up to Visit 5	SS
T 11.13	T	Hematology: Marked abnormalities shift from baseline to Visit 5	SS
T 11.14	T	Coagulation: Marked abnormalities shift from baseline to Visit 5	SS
T 11.15	T	Chemistry: Marked abnormalities shift from baseline to Visit 5	SS
T 11.16	T	Main study elevated liver tests up to Visit 5	SS
T 11.17	T	Hematology, Coagulation and Chemistry marked abnormality ranges	-
L 11.1	L	Hematology laboratory data	FAS

Number	Dis-play*	Title (Description)	Analysis set(s)
L 11.2	L	Chemistry and Coagulation laboratory data	FAS

* T = Summary table, L = Listing.

13.12 Vital signs and body weight

Number	Dis-play*	Title (Description)	Analysis set(s)
T 12.1a	T	Vital signs absolute values and changes from baseline by visit during main study	SS
T 12.1b	T	Vital signs absolute values and changes from baseline by visit during re-treatment extension	ES
T 12.2	T	Treatment-emergent blood pressure marked abnormalities up to EOT + 7 days	SS
T 12.3	T	Re-treatment-emergent blood pressure marked abnormalities up to End of Re-treatment + 7 days	ES
T 12.4	T	Main study blood pressure marked abnormalities up to Visit 5	SS
L 12.1	L	Vital signs	FAS
L 12.1	L	Body temperature	FAS

* T = Summary table, L = Listing.

13.13 Other safety variables

Number	Dis-play*	Title (Description)	Analysis set(s)
L 13.1	L	Physical and abdominal examination	FAS

* L = Listing.

13.14 Other evaluations

13.14.1 Quality of life analyses

Not applicable.

13.14.2 Pharmacoeconomic analyses

Number	Dis-play*	Title (Description)	Analysis set(s)
T 14.1	T	Duration of hospitalization in main study by baseline hospitalization status	mITT
T 14.2	T	Frequency of hospitalization admission/re-admissions during main study by baseline hospitalization status	mITT
T 14.3	T	Duration of hospitalization during re-treatment extension	ES
T 14.4	T	Frequency of hospitalization admission/re-admissions by hospitalization status at baseline	ES
L 14.1	L	Hospitalization data	FAS
T 14.5	T	Work productivity and activity impairment (WPAI:CDAD) Subjects currently employed by visit	PROAS
T 14.6	T	Work productivity and activity impairment (WPAI:CDAD) scores by visit	PROAS
L 14.2	L	Work productivity and activity impairment for *C. difficile* associated diarrhea (WPAI:CDAD) data	FAS

* T = Summary table, L = Listing.

13.14.3 Benefit-risk evaluations

Not applicable.

13.14.4 Pharmacodynamic analyses

Not applicable.

13.14.5 Pharmacokinetic analyses

Not applicable.

14 REFERENCES

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15 APPENDICES

A. Protocol synopsis, Protocol version 3

Below, only the protocol synopsis for AC-061A301 is displayed. The protocol synopsis for protocol AC-061A302 is identical to the synopsis of AC-061A301 apart from the study number (see protocol AC-061A302) and thus is not displayed in this SAP.

TITLE	AC-061A301, A multi-center, randomized, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects with *Clostridium difficile*-associated diarrhea (CDAD).
MAIN OBJECTIVES	**Primary objective** To determine whether the clinical response after 10-day oral administration of cadazolid is non-inferior to oral vancomycin in subjects with CDAD. **Secondary objectives** To determine whether oral administration of cadazolid for 10 days is superior to oral vancomycin in the sustained clinical response of subjects with CDAD. To determine whether the resolution of diarrhea (ROD) is more rapid with oral administration of cadazolid compared to vancomycin. To determine whether CDAD symptoms, as reported by the subject, show larger improvements from baseline with oral administration of cadazolid compared to vancomycin. **Meta-analysis objective** To determine whether oral administration of cadazolid for 10 days is superior to oral vancomycin in the sustained clinical response of subjects with CDAD due to hypervirulent strains. **Safety objective** To determine safety and tolerability of an oral administration of cadazolid compared to vancomycin. Exploratory objectives are described in the core protocol.
DESIGN See Section 3 [protocol]	Prospective, multi-center, double-blind, double-dummy, randomized, parallel group, active controlled Phase 3 study
PERIODS See Section 3 [protocol]	**Screening Period** starts with the signature of the informed consent form (ICF) and ends with subject randomization

	(within 48 hours of the signature of the ICF). **Treatment Period** starts after randomization, with the first dose of study drug, and ends on the day of the last dose of study drug (EOT) 10 days later. **Follow-up Period** starts after the last dose of study drug and ends approximately 30 days after the last dose of study drug (Visit 5). **Re-treatment extension with cadazolid**: Subjects who experience a recurrence and provide consent may enter a re-treatment extension with cadazolid consisting of a 10-day treatment of cadazolid followed by an approximately 30-day follow-up period. Subject participation in the study will be up to 44 days; up to 88 days for subjects participating in the re-treatment extension with cadazolid.
PLANNED DURATION	Approximately 40 months.
SITES / COUNTRIES	Approximately 100 sites in approximately 20 countries.
SUBJECTS / GROUPS	Approximately 630 subjects will be randomized to cadazolid or vancomycin by Interactive Voice Response System (IVRS), ratio 1:1, stratified by first occurrence or first recurrence and by site.
KEY INCLUSION CRITERIA See Section 4.2 [protocol]	Signed Informed Consent. Male or female ≥ 18 years of age. Females of childbearing potential must agree to use an adequate and reliable method of contraception. Subject with a diagnosis of mild-moderate or severe CDAD (first occurrence or first recurrence within 3 months) with: Diarrhea: a change in bowel habits with > 3 unformed bowel movements (UBMs) within 24 hours prior to randomization, **AND** Positive *C. difficile* GDH and toxin test (by enzyme immunoassay approved by the sponsor) on the same stool sample produced within 72 hours prior to randomization.
KEY EXCLUSION CRITERIA See Section 4.3 [protocol]	More than one previous episode of CDAD in the 3-month period prior to randomization. Evidence of life-threatening or fulminant CDAD.

	Likelihood of death within 72 hours from any cause. History of inflammatory colitides, chronic abdominal pain, or chronic diarrhea, or known positive diagnostic test for enteropathogens. Inability to take oral medication, or subjects with feeding tubes (i.e., when study drug would have to be given by a feeding tube). Antimicrobial treatment active against CDAD administered for > 24 hours except for metronidazole treatment failures (MTF). Planned treatment with forbidden concomitant medications. Fecal microbiota transplant (FMT), immunoglobulin therapy, and investigational drug to prevent or treat CDAD within 1 month prior to randomization Monoclonal antibodies against *C. difficile* within 6 months prior to randomization. Previous vaccination against *C. difficile*. Previous participation in a clinical trial with cadazolid. Known hypersensitivity or contraindication to study drugs, oxazolidinones, or quinolones. Females who are breastfeeding. Investigational site staff members or relatives, and Actelion employees. Unable or unwilling to comply with all protocol requirements.
STUDY TREATMENTS See Section 5.1 [protocol]	**Investigational drug** Cadazolid 250 mg or matching placebo granules for oral suspension twice daily with or without food. **Comparator** Oral vancomycin 125 mg or matching placebo capsules 4 times daily with or without food.
CONCOMITANT MEDICATIONS See Section 5.2 [protocol]	**Prohibited medications** Antimicrobial treatment active against CDAD and FMT up to Visit 5 unless provided for clinical failure or recurrence. Other medication active against CDAD (e.g., cholestyramine, probiotics) up to Visit 5. Initiation of treatment with opiates or change in dose or regimen resulting in an increased opiate effect up to 2 days after EOT.

	Anti-peristaltic medications, kaolin, pectin and charcoal containing anti-diarrheals up to Visit 5.
ENDPOINTS See Section 6.1 [protocol]	**Primary endpoint** Clinical Cure defined as: • Resolution of Diarrhea (ROD: ≤ 3 UBMs per day for at least 2 consecutive days) on study treatment, maintained for 2 days after EOT **AND** • No additional antimicrobial treatment active against CDAD or FMT between first dose and 2 days after EOT (inclusive). **Secondary endpoints** Sustained Cure defined as: • Clinical Cure **AND** • No Recurrence Recurrence is defined for subjects with Clinical Cure as: • New episode of diarrhea (NED: > 3 UBMs within 1 day) occurring between 3 days after EOT and Visit 5 **AND** • Positive *C. difficile* GDH and toxin stool test on the same stool sample **AND** • Antimicrobial treatment active against CDAD or FMT started between 3 days after EOT and Visit 5 (or participation in the re-treatment extension with cadazolid). Time to ROD, defined as: • The time (h) elapsed between the first dose of study drug and the time when ROD is considered achieved. Absolute change from baseline in CDAD DaySyms Patient Reported Outcomes (PRO). CDAD DaySyms total daily score change from baseline up to Day 12. **Meta-analysis endpoint** • Sustained Cure (as defined above) in hypervirulent strains (currently defined as Strains 027, 078, and 244). Additional endpoints are described in the core protocol.

ASSESSMENTS	Refer to the schedule of assessments.
STATISTICAL METHODOLOGY See Section 11 [protocol]	**Sample Size**: Assuming a Clinical Cure Rate (CCR) of 85% in the Per-protocol analysis set (PPS) for cadazolid and vancomycin treatment groups, a power of 90%, a fixed type I error of 2.5% (one-sided), and a non-inferiority (NI) margin of 10%, a total sample size of 536 (268 in each treatment group) evaluable subjects is required in the PPS. Taking into account approximately 15% of subjects not qualifying for the per-protocol (PP) population, approximately 630 subjects will be randomized into the trial. As approximately 95% of the randomized subjects are assumed to qualify for the modified intent-to-treat (mITT) analysis set (598 subjects), the power for demonstrating non-inferiority in clinical cure on this population is higher than 90%. **Main efficacy analysis.** Clinical Cure Rate (CCR, %) is the variable to be analyzed for the primary endpoint. The aim is to demonstrate that the CCR for cadazolid (CCRc) is not inferior to the CCR for vancomycin (CCRv), accounting for a NI margin of 10%. NI in CCR of cadazolid against vancomycin will be assessed based on the difference between proportions in CCRc and CCRv. The null hypothesis is: $H_0^{(1)}$: CCRc − CCRv ≤ −10% versus the alternative hypothesis: $H_1^{(1)}$: CCRc − CCRv > −10%. The main analysis will be on the mITT analysis set and on the PPS. NI is claimed if it is demonstrated on both analysis sets, by a one-sided 0.025 significance level, using the lower bound of the two-sided 95% confidence interval (CI) of the difference between proportions. **Secondary efficacy analysis:** If NI for CCR is demonstrated in both analysis sets, mITT and PPS, the superiority of cadazolid on the secondary endpoint Sustained Cure Rate (SCR) will be tested on the mITT analysis set at the two-sided alpha 0.05. If the lower limit of the two-sided 95% CI is greater than zero, the statistical superiority of cadazolid versus vancomycin in SCR will be established. After this is demonstrated, the superiority in time to ROD (shorter median

	time) will be tested. If demonstrated, then the superiority in the CDAD DaySyms scores changes from baseline will be tested. This full hierarchical testing strategy is used to control the experimentwise α level at 0.05. **Meta-analysis:** A meta-analysis of this trial and the similar Phase 3 trial AC-061A302 will be utilized for the assessment of cadazolid superiority in the Sustained Cure of subjects with CDAD due to hypervirulent strains. **Safety analysis**: Treatment-emergent adverse events and serious adverse events will be summarized per treatment arm and overall, by frequency, intensity and relationship to study medication. Other safety variables, such as laboratory assessments, vital signs and ECGs will be summarized.
STUDY COMMITTEES	Steering Committee, Independent Data Monitoring Committee
SUB-STUDIES	As part of this protocol, at selected sites and in subjects who consent to participate, the plasma concentrations of cadazolid will be analyzed. In addition, the following sub-studies, independent from the core study protocol and at selected sites in subjects who consent to participate (through an informed consent separate from the main protocol informed consent), will be performed according to stand-alone protocols: • Psychometric validation of CDAD DaySyms PRO • Gut microbiome assessment and fecal cadazolid concentrations.

B. Discussion and further considerations of the applied statistical methods

Not applicable.

C. Chronic kidney disease SMQ selected preferred terms

Narrow	A	Artificial kidney device user	10053699
Narrow	A	Azotaemia	10003885
Narrow	A	End stage renal disease	10077512
Broad	A	Autoimmune nephritis	10077087
Broad	A	Blood creatinine abnormal	10005481
Broad	A	Blood creatinine increased	10005483
Broad	A	Bloody peritoneal effluent	10067442
Broad	A	C3 glomerulopathy	10077827
Broad	A	Calciphylaxis	10051714
Broad	A	Chronic allograft nephropathy	10063209
Narrow	A	Coma uraemic	10010082
Broad	A	Creatinine renal clearance abnormal	10068447
Broad	A	Creatinine renal clearance decreased	10011372
Narrow	A	Diabetic end stage renal disease	10012660
Narrow	A	Dialysis	10061105
Broad	A	Dialysis amyloidosis	10064553
Narrow	A	Dialysis device insertion	10059015
Broad	A	Dialysis disequilibrium syndrome	10059256
Broad	A	Dialysis related complication	10071946
Broad	A	Diffuse mesangial sclerosis	10054832
Broad	A	Effective peritoneal surface area increased	10068883
Broad	A	Extensive interdialytic weight gain	10068800
Broad	A	Glomerular filtration rate abnormal	10018356
Broad	A	Glomerular filtration rate decreased	10018358
Narrow	A	Glomerulonephritis chronic	10018367
Broad	A	Glomerulonephritis rapidly progressive	10018378
Narrow	A	Haemodialysis	10018875
Broad	A	Haemodialysis complication	10070476
Broad	A	Haemodialysis-induced symptom	10059268
Narrow	A	Haemofiltration	10053090
Broad	A	Haemolytic uraemic syndrome	10018932
Broad	A	Haemorrhagic fever with renal syndrome	10075015
Narrow	A	Hepatorenal failure	10019845
Narrow	A	High turnover osteopathy	10062624
Broad	A	Hypercreatininaemia	10062747
Narrow	A	Hyperparathyroidism secondary	10020708
Broad	A	IgM nephropathy	10077209

Broad	A	Intradialytic parenteral nutrition	10074739
Narrow	A	Low turnover osteopathy	10063000
Narrow	A	Nephrogenic anaemia	10058116
Narrow	A	Nephrogenic systemic fibrosis	10067467
Broad	A	Obstructive nephropathy	10077862
Narrow	A	Oedema due to renal disease	10049630
Broad	A	Paraneoplastic glomerulonephritis	10076749
Narrow	A	Pericarditis uraemic	10034498
Broad	A	Peritoneal cloudy effluent	10067011
Narrow	A	Peritoneal dialysis	10034660
Broad	A	Peritoneal dialysis complication	10067594
Broad	A	Peritoneal effluent abnormal	10069638
Broad	A	Peritoneal effluent erythrocyte count increased	10067301
Broad	A	Peritoneal effluent leukocyte count increased	10067300
Broad	A	Peritoneal equilibration test abnormal	10072490
Broad	A	Peritoneal fluid analysis abnormal	10059524
Broad	A	Peritoneal fluid protein abnormal	10069000
Broad	A	Peritoneal fluid protein increased	10068998
Broad	A	Peritoneal permeability increased	10070442
Narrow	A	Renal and liver transplant	10052279
Narrow	A	Renal and pancreas transplant	10052278
Broad	A	Renal atrophy	10038381
Narrow	A	Renal failure	10038435
Narrow	A	Chronic kidney disease	10038444
Narrow	A	Renal osteodystrophy	10038489
Narrow	A	Renal replacement therapy	10074746
Narrow	A	Renal rickets	10038519
Narrow	A	Renal transplant	10038533
Broad	A	Ultrafiltration failure	10069568
Narrow	A	Uraemia odour	10056609
Narrow	A	Uraemic acidosis	10046324
Narrow	A	Uraemic myopathy	10077910
Narrow	A	Uraemic encephalopathy	10046326
Narrow	A	Uraemic gastropathy	10063709
Narrow	A	Uraemic neuropathy	10046328
Narrow	A	Uraemic pruritus	10060875
Broad	A	Urea renal clearance decreased	10046358
Narrow	A	Uridrosis	10067863

D. Scoring and analysis guideline for the CDI-DAYSYMS® (formerly known as CDAD-DAYSYMS®)

The CDI-DaySyms®, formerly known as the CDAD-DaySyms®, has been designed to capture patient-reported symptoms of *Clostridium difficile* infections.

It has been developed for use in a diverse CDI patient population, and can be applied in clinical trial settings as well as in clinical practice.

1 CDI-DAYSYMS® SCORING

The final CDI-DaySyms® includes 10 items distributed across three domains: Diarrhea Symptoms, Abdominal Symptoms, and Systemic/Other Symptoms [see Table 1].

Table 1 Domains and items of the CDI-DaySyms diary®

Domains and Items
Diarrhea Symptoms
1. Diarrhea
2. Feeling a need to empty bowels
3. Needing to go to the bathroom
Abdominal Symptoms
4. Abdominal cramping
5. Abdominal pain
6. Feeling bloated
Systemic/Other Symptoms
7. Feeling tired
8. Lack of Energy
9. Lightheadedness
10. Lack of appetite

For each item, the subject assesses daily his/her symptom severity by choosing one response on a 5-point Likert scale. Responses are converted to numerical values as follows:

0 = no symptoms
1 = mild symptoms
2 = moderate symptoms
3 = severe symptoms
4 = very severe symptoms

Non-missing scores of all items in a given domain are summed per day and the mean of the non-missing items is then taken; this defines the domain score. This domain score is the value to be analyzed and interpreted.

The minimum score for each domain is zero, and the maximum score is 4. Domains are scored on a daily basis.

The three domains should be evaluated or tested in a hierarchical manner, starting with *Diarrhea Symptoms*, then *Abdominal Symptoms*, and finally *Systemic/Other Symptoms*.

2 HANDLING OF MISSING OR INCONSISTENT VALUES

Considering the CDI-DaySyms® is completed with pen-and-paper, it is possible that some item responses may be missing, and similarly, it is possible that subjects select more than one response for a given item. Rules for adequately handling such situations in the statistical analysis are as described below.

Missing values

Diarrhea Symptoms domain

- If item 1 (diarrhea) is available, then a domain score will always be calculated, including in cases where both item 2 (feeling a need to empty bowels) and 3 (needing to go to the bathroom) are missing.
- Otherwise, if greater than 50% of items are missing (i.e., at least 2 out of 3 items), then the domain will be marked as missing, except in the case that only item 1 is available as specified above.

Abdominal Symptoms Domain

- If greater than 50% of abdominal symptom items are missing (i.e., at least 2 out of 3 items), the domain will be marked as missing.

Systemic/Other Symptoms Domain

- If greater than 50% of systemic/other symptom items are missing (i.e., at least 3 out of 4 items), the domain will be marked as missing.

Multiple responses per item

In the event of two contiguous/adjacent responses to one of the items (e.g., moderate and severe), the worst of the values (i.e., the more severe one) will be selected for analysis. If an item has two non-contiguous/non-adjacent responses recorded (e.g., mild and severe) or more than two responses marked, the response to the item will be set to missing.

3 ANALYSIS GUIDELINES

3.1 Endpoints

The effect of treatment on each of the three CDI-DaySyms® domains has to be assessed separately, as there is no total score.

It is recommended to assess response to treatment early on, as this is reflective of clinical practice.

Recommended endpoints include:

- Absolute change from baseline
- Percentage of subjects meeting the response to treatment threshold
- Percentage of subjects meeting the upper boundary of clinically meaningful improvement range
- Time to response
- Area under the curve (AUC) from baseline

A responder to treatment is defined as a subject with an observed change from baseline below a predefined threshold for each domain, as described in Table 2. A negative value for change from baseline corresponds to a reduction in domain score, i.e., an improvement. The responder threshold was derived based on Day 3 data – using mainly distribution-based methods.

Table 2 Threshold for response definition

Parameter	Threshold*
Diarrhea Symptoms	–1.00
Abdominal Symptoms	–0.80
Other/Systemic Symptoms	–0.70

*Note: * Threshold is defined based on the absolute change from baseline, where change from baseline is calculated as: value post-baseline – value at baseline.*

The responder threshold is the lower boundary of the clinically meaningful improvement range for each domain, as described in Table 3.

Table 3 Clinically meaningful improvement

Parameter	Range*
Diarrhea Symptoms	–1.00 to –0.55
Abdominal Symptoms	–0.80 to –0.55
Other/Systemic Symptoms	–0.70 to –0.50

*Note: * The lower boundary of the clinically meaningful improvement range is referred to as the responder threshold. Clinically meaningful improvement ranges are based on changes from baseline, where change from baseline is defined as: value post-baseline – value at baseline.*

The time to response is defined as the number of days from first study drug administration to achieving responder status.

3.2 Additional considerations

Sensitivity analysis will be conducted applying the 50% imputation rule also for the diarrhea domain: if greater than 50% of diarrhea symptom items are missing (i.e., at least 2 out of 3 items), then the domain will be marked as missing.

E. Multiple imputation and tipping point analysis for CDI PRO

1 INCOMPLETE DATA

Incomplete data are ubiquitous, especially in longitudinal data in human subjects. Rubin [Rubin 1976] and Little and Rubin [Little 1987, Chapter 6] distinguished between three missing value mechanisms: (1) missing completely at random (MCAR), when missingness is independent of both unobserved and observed data; (2) missing at random (MAR), when, conditional on the observed data, missingness is independent of the unobserved measurements; and (3) missingness not at random (MNAR), when neither MCAR nor MAR applies.

A promising and now commonly used method is multiple imputation [Little 1987, Molenberghs 2007, van Buuren 2007, Carpenter 2013]. Multiple imputation usually assumes that the data are MAR. The MAR assumption cannot be verified, because the missing values are not observed yet would be needed for a satisfactory verification. For a study that assumes MAR, the sensitivity of inferences to departures from the MAR assumption should be evaluated. One way is by performing a sensitivity analysis under the MNAR assumption, imputing the missing values under a plausible MNAR scenario, and then compare the results to inferences under MAR. If the sensitivity analysis results lead to different conclusions than the primary results, then the conclusion is that the incomplete data have the potential to undo the primary analysis.

2 IMPUTATION METHODS FOR SENSITIVITY ANALYSES

In this section, the methods to handle missing data that are used in this study, especially regarding multiple imputation as sensitivity analysis, will be reviewed. The main procedure in the SAS software for analyzing the methods mentioned are also described in this section. The full SAS codes, also involving the data manipulation steps and analysis programs, are presented in this appendix.

Standard multiple imputation (under MAR)

Standard multiple imputation will be applied as a first sensitivity analysis. Multiple imputation is essentially an iterative form of stochastic imputation and usually assumes that the data are MAR. That is, for a variable Y, the probability that an observation is missing depends only on the observed values of other variables and/or on (previously) observed values of the same outcome Y, but not on the unobserved values of Y. Multiple imputation inference involves three distinct phases: (1) The missing data are filled in *m* times to generate *m* complete data sets, (2) The *m* complete data sets are analyzed by using standard procedures and (3) The results from the *m* complete data sets are combined to yield pooled inferences.

We will apply the method by using Proc MI (SAS 9.4). The MI procedure is a multiple imputation procedure that creates multiple imputed data sets for incomplete

p-dimensional multivariate data (possibly resulting from longitudinal data). It uses methods that incorporate appropriate variability across the *m* imputations (i.e., by drawing from the predictive distribution of unobserved values for a given patient, given observed information on the same patient). The imputation method is chosen based on the patterns of missingness (monotone, or also involving non-monotone missingness) in the data and the type of the imputed variable (continuous, binary, etc.).

In the CDI-DaySyms® PRO analysis, the variable that needs to be imputed is the outcome CDI-DaySyms® SCORES for each domain separately, a quasi-continuous variable. This variable is imputed sequentially using covariates constructed from the corresponding sets of preceding variables, in this case: TREATMENT (cadazolid and vancomycin), and other possible covariates, if any. Also, the entire outcome vector of SCORES across measurement TIME (daily basis) is included. However, the SCORES variable has a non-monotone missingness pattern across TIME.

The MI procedure (SAS 9.4) with *m* the predetermined number of imputations is applied to fill in *m*-times the intermittent missing data for each subject across TIME. Evidently, the missingness after dropout, at this stage, is kept un-imputed. This procedure leads to *m* monotonized sets of data.

```
proc mi data=dat12 seed=4321 simple nimpute=10
round=1 out=dat_mon;
mcmc impute = monotone;
var TIME1-TIME12;
by TREATMENT;
run;
```

The missingness due to drop out of the *m* monotonized dataset is then subjected to multiple imputation with the MI procedure (SAS 9.4) for number of imputation equal to one. This is because the stochastic nature of the imputation has already been taken care of in the first step. Evidently, also here, the imputations are drawn stochastically. This procedure finally leads to *m* complete data.

```
proc mi data= dat_mon nimpute=1 out=mi_mvn seed=4321 simple;
var TIME1-TIME12;
by TREATMENT;
monotone method=reg;
run;
```

The *m* complete data sets are analyzed separately by using standard procedures.

```
proc mixed data=mi_mvn method=reml;
class SUBJECTID TREATMENT TIME;
model SCORES= TREATMENT* TIME / ddfm=kenwardroger solution;
```

```
repeated TIME / type=toeph subject= SUBJECTID;
by _imputation_;
estimate 'treatment effect at day 3'
  TREATMENT* TIME -1 0  1 0 0 0 0 0 0 0 0 0
                                  1 0   -1 0 0 0 0 0 0 0 0 0 / CL;
ods output SolutionF=a_mvn1;
ods output Estimates=a_mvn_estimates1;
run;
```

The pooled inference by combining results from the *m* analyses is done by using the MIANALYZE procedure (SAS 9.4).

```
proc mianalyze parms(classvar=full)=a_mvn1;
class TREATMENT TIME;
modeleffects TREATMENT* TIME;
run;

proc mianalyze data = a_mvn_estimates1;
  modeleffects estimate;
  stderr stderr;
run;
```

Sensitivity analysis approach under Missing Not At Random assumption

Sensitivity analysis toward departures from the MAR assumption is considered. We implement sensitivity analysis under the MNAR assumption. Under the MNAR assumption, the probability that the value of Y is missing for an observation can also depend on the unobserved value of Y, in addition to dependence on observed information. This multiple imputation method is based on the pattern-mixture model approach [Molenberghs 2007, Carpenter 2013]. By using pattern-mixture models, there is chronic under-identification because the predictive distribution within a pattern is by definition not observable. Little [Little 1993] proposed the use of identifying restrictions; inestimable parameters of the incomplete patterns are set equal to the function of parameters describing the distribution of the other, more complete patterns, i.e., the predictive distribution is identified from what is available.

In general, assume there are $t = 1, \ldots, n = T$ patterns. The dropout patterns, with the complete data density is given by:

$$f_t(y_1, .., y_T) = f_t(y_1, .., y_t) f_t(y_{t+1}, .., y_T | y_1, .., y_t) \qquad (1)$$

The first factor is identified from observed data. The second factor is unobservable, hence identifying restrictions need to be applied. One can base identification on all patterns for which a given component, y_s, is identified:

$$f_t(y_s|y_1,..,y_{s-1}) = \sum_{j=s}^{T} \omega_{sj} f_j(y_s|y_1,..,y_{s-1}) \quad ,s = t+1,\ldots,T. \qquad (2)$$

In the MI procedure (SAS 9.4), the MNAR statement imputes missing values by using, among others, the pattern-mixture model approach, assuming the missing data are MNAR.

Sensitivity analysis with a tipping point approach

A "tipping-point" analysis, first introduced in Yan et al. [Yan 2009] consists of assessing the impact of missing data on the conclusions of a study. Yan et al. [Yan 2009] defined the tipping points of a study to be the particular setting for the missing data values that would change the study's conclusions and presented a simple way to display this information. In this study we apply sensitivity analysis based upon multiple imputations under the MNAR assumption by searching for a tipping point by using "shift" approaches until the MAR inferences change from significance to non-significance, or vice versa.

The SAS code is as follows:

```
%macro midata( data=, smin=, smax=, sinc=, out=);
data &out;
set _null_;
run;
/*------------ # of shift values ------------*/
%let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );
/*------- Imputed data for each shift -------*/
%do jc=0 %to &ncase;
%let sj= %sysevalf( &smin + &jc * &sinc);

proc mi data= &data nimpute=1 out=outmi seed=4321;
var TIME1-TIME12;
class TREATMENT;
by TREATMENT;
monotone method=reg;
mnar adjust( TIME1/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME2/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME3/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME4/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME5/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME6/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME7/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME8/ shift=&sj adjustobs=(TREATMENT='1'));
```

```
mnar adjust( TIME9/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME10/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME11/ shift=&sj adjustobs=(TREATMENT='1'));
mnar adjust( TIME12/ shift=&sj adjustobs=(TREATMENT='1'));
run;

data outmi;
set outmi;
Shift= &sj;
run;
data &out;
set &out outmi;
run;
%end;
%mend midata;

%midata( data=dat_mon, smin=-2, smax=2, sinc=1, out=OutX);
```

Tipping point analysis with adjusted "shift" statement applied to Day 3 (the time of interest) only has also been considered:

```
%macro midata( data=, smin=, smax=, sinc=, out=);
data &out;
set _null_;
run;
/*------------ # of shift values ------------*/
%let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );
/*------- Imputed data for each shift -------*/
%do jc=0 %to &ncase;
%let sj= %sysevalf( &smin + &jc * &sinc);

proc mi data= &data nimpute=1 out=outmi seed=4321;
var TIME1-TIME12;
class TREATMENT;
by TREATMENT;
monotone method=reg;
mnar adjust( TIME3/ shift=&sj adjustobs=(TREATMENT='1'));
run;

data outmi;
set outmi;
Shift= &sj;
```

```
run;
data &out;
set &out outmi;
run;
%end;
%mend midata;

%midata( data=dat_mon, smin=-2, smax=2, sinc=1, out=OutX_12);
```

3 REFERENCES

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[van Buuren 2007] van Buuren S. Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification. Stat Methods Med Res. 2007;16:219–42.

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F. Document history

Version	Effective Date	Reason
1.0	11-Dec-2014	New
2.0	7-Jun-2016	Update according to protocol version 3 including removal of interim analysis, updates of study design and schedule of assessments, updates according to MedDRA 19.0 and WHODrug Dictionary version dated 1 March 2016, definition of geographical region updated to avoid small regions, summary of reasons for ICR and ISR added, description of derivation of clinical cure and sustained cure improved, sensitivity analyses for Clinical Cure and Sustained Cure added, stratified efficacy analyses: alternative strategy in the event of small strata described, variables and analyses based on clinical evaluation by Actelion Clinical Team and modified clinical cure removed, efficacy analyses by country added, censoring date time to return to usual bowel movements updated, days from first dose corrected, microbiology variables clarified, microbiology analyses updated wording updated to match standard table shells, EudraCT required outputs added, re-treatment safety tables up to Visit Re-5 reduced.
3.0	19-May-2017	CDI-DaySyms variables (3 domain scores instead of 1 total score) and analysis updated following PRO validation, handling of duplicate microbiology assessments added and consequently definition of baseline isolates clarified. Editorial updates to output titles, listings split as per programming requirements. Clarifications to the following derivations: ≤ 3 UBMs in event of missing daily stool information, temporal association of toxin test to AMT, time to recurrence derivation, ECG and vital signs baseline definitions, insufficient information to determine Clinical Cure. WPAI scoring further detailed in line with questionnaire guidelines, Sustained cure sensitivity analysis (follow-up until

		EOT + 25 days) aligned throughout document with section 10.7.1.2, main study concomitant medications tables added, imputation for missing start time added, physical and abdominal examination results only listed, clarified re-treatment extension displays are on received not planned double-blind treatment, Liver test displays aligned with guidelines (category ≥ 1 × ULN for AST and ALT removed).

AMENDMENT TO STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

AC-061A301 / AC-061A302

Two multi-center, randomized, double-blind studies to compare the efficacy and safety of cadazolid versus vancomycin in subjects with *Clostridium difficile*-associated diarrhea (CDAD)

Purpose of Analysis	Clinical Study Report
Investigational Drug	Cadazolid
Protocol Numbers	AC-061A301 / AC-061A302
Actelion Document Number	D-17.297
Document Status / Version Number	Amendment to Final SAP for CSR
Date	19 May 2017

Author	[redacted] Trial Statistician
Reviewer	[redacted] Trial Statistician
Reviewer	[redacted] Project Statistician
Reviewer	[redacted] Clinical Science Program Head
Reviewer	[redacted] Clinical Trial Scientist
Reviewer	[redacted] Life Cycle Leader
Reviewer	[redacted] Lead Statistical Programmer

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AR	All randomized set
CDAD	*Clostridium difficile*-associated diarrhea
CSR	Clinical study report
EOT	End-of-Treatment
FDA	Food and Drug Administration
FAS	Full analysis set
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
amITT	amended modified intent-to-treat
PRO	Patient reported outcome
PPS	Per protocol set
PK	Pharmacokinetic
SAP	Statistical analysis plan
SCRAS	Screened analyses set
SDTM	Study Data Tabulation Model
aSS	amended Safety set

1 OVERVIEW

This amendment applies to the statistical analysis plan (SAP) Version 3 dated 19 May 2017 [D-17.273] for the clinical study reports (CSR) for studies AC-061A301 and AC-061A302 (referred to hereafter as the CSR SAP).

The reason for the amendment is to describe, in detail, changes to the analyses and presentation of results decided by Actelion before data unblinding and, following identification of potential scientific misconduct with relevant findings related to data integrity at site [redacted] in study AC-061A302 (letter sent to FDA Office of Compliance, dated 2 May 2017).

The CSR SAP Version 3 details analyses which apply to both studies, however this amendment concerns only the analyses that are to be conducted on study AC-061A302, and does not affect the analyses of study AC-061A301 (with the exception of listings, as described in Section 3.3).

1.1 Overview of site [redacted] enrollment and participation in substudies

Site [redacted] screened [redacted] subjects, of which 22 were randomized [redacted]

[redacted]

2 RATIONALE FOR SAP AMENDMENT

During an unannounced for-cause audit of site [redacted], [redacted] Actelion concluded that data integrity for site [redacted] cannot be guaranteed. Therefore, Actelion decided that all data from site [redacted] will be excluded from the statistical analyses of study AC-061A302, as described in this amendment to the CSR SAP [Section 3]. Sensitivity analyses will be performed to evaluate the impact of excluding this site from the analyses of AC-061A302 [Section 3.2].

In addition, data from site [redacted] will also be excluded from all statistical analyses involving pooling of data from study AC-061A302, including meta-analyses, microbiome, summary of clinical efficacy and summary of clinical safety. Separate amendments are not required for the meta-analysis SAP, microbiome SAP, ISE SAP or ISS SAP as these SAPs refer to the CSR SAP (and analysis sets) which will exclude all subjects from site [redacted] [Section 3.1.1]. Instead, these SAPs will have a minor revision to add reference to this amendment.

The subjects from site [redacted] will be flagged in an SDTM supplemental dataset and this flag will be used in the derivation of analysis sets to exclude site [redacted] and to allow sensitivity analyses to the exclusion of this site.

All data from site [redacted] will remain in the study datasets and will be presented in listings.

As the PK sub-study and PRO psychometric validation sub-study do not include subjects from site [redacted], the analyses of these substudies are not affected.

3 CHANGES TO STATISTICAL ANALYSES PLANNED

3.1 Changes to the definitions of analysis sets

Changes to the definitions of the analysis sets (per CSR SAP Version 3, section 7) and their usage are described below and summarized in Table 1.

Table 1 Overview of analysis sets and their usage

Excluding subjects from site [redacted] ----------		**Including subjects from site [redacted]**	
Analysis set	**Usage**	**Analysis set**	**Usage**
		Screened analysis set (SCRAS)	T, L
Full analysis set (FAS)	T & F	All randomized set (AR)	Ts*, L
Modified intent-to-treat (mITT) analysis set		amended mITT (amITT)	Ts*
Per-protocol set (PPS)			
Hypervirulent analysis set (HVAS)			
Patient reported outcome analysis set (PROAS)			
Safety analysis set (SS)		amended SS (aSS)	Ts**
Re-treatment extension with cadazolid analysis set (ES)			

T = table for all analyses described in CSR SAP version 3; F = Figure for all analyses described in CSR SAP version 3; Ts = table for sensitivity analyses for the amendment; *only for the primary endpoint and most relevant secondary endpoint: **only for most relevant safety endpoints; L = listings including all subjects

3.1.1 Analysis sets excluding subjects from site [redacted]

Analysis sets [as listed in Table 1] will exclude subjects from site [redacted]. This change will be implemented to each analysis set for the purpose of excluding data for site [redacted] from all statistical analyses (tables and figures) of study AC-061A302. Although the content of these analysis sets for AC-061A302 will be reduced by excluding the subjects from site

[redacted], the names of these analysis sets are retained in order to maintain consistency across both studies (AC-061A301 and AC-061A302) in the presentation of tables and figures.

3.1.2 Analysis sets including subjects from site [redacted]

Three additional analysis sets are defined, including subjects from site [redacted], for the purpose of performing some sensitivity analyses for AC-061A302:

- amended modified intent-to-treat (amITT) analysis set
- amended safety set (aSS)
- all randomized (AR) set: includes all randomized subjects

The names for the amended analysis sets are chosen as they are only implemented for a few sensitivity analyses in the AC-061A302 study and to differentiate them from analysis sets excluding site [redacted] defined in Section 3.1.1. The AR set will also be used to produce the listings as defined in Section 3.3.

An amended PPS, including subjects from site [redacted], was not considered as the findings related to data integrity are expected to affect the evaluation of the efficacy (per CSR SAP section 7.1.4) and thus would already lead to exclusion from such an analysis set.

Note there is no change to the screened analysis set (SCRAS) definition and its usage.

3.2 Sensitivity analyses including site [redacted]

Sensitivity analysis to the exclusion of site [redacted] from the analyses of AC-061A302 will be performed. The following sensitivity analyses, including subjects from site [redacted], are selected for the purpose of describing the disposition of all randomized subjects in AC-061A302, to evaluate the impact on efficacy using the primary endpoint and most relevant secondary endpoint, and to confirm overall safety using the most relevant safety endpoints.

3.2.1 Subject disposition and analysis sets

The number of subjects randomized, treated, completing treatment, and completing the main study and enrolled in the re-treatment extension are all summarized by treatment group and overall per CSR SAP section 10.3.2 for the AR set.

The number and percentage of subjects in the amITT and aSS are summarized per CSR SAP section 10.3.4 for the AR set.

3.2.2 Efficacy analyses

The main analysis of the primary efficacy endpoint Clinical Cure (CSR SAP section 10.6.3) and the main analysis of the secondary efficacy endpoint Sustained Cure (CSR SAP section 10.7.1.3) are repeated for the amITT.

3.2.3 Safety analyses

Treatment-emergent AEs (up to End of Treatment [EOT] + 7 days) will be summarized by system organ class and preferred term per CSR SAP section 10.9.1 for the aSS.

An overview of treatment-emergent AEs (up to EOT + 7 days) will be presented for the aSS including subjects with at least one of the following; AE, SAE, AE leading to study drug discontinuation or AE with fatal outcome.

3.3 Presentation of listings

In order that data from site [redacted] will still be presented in the listings for the CSR of AC-061A302, all subject listings that were planned to be presented on the FAS per CSR SAP Version 3 (table 14, section 10 and section 13) will be changed to be presented on all randomized subjects (AR set) for both studies (AC-061A301 and AC-061A302) to maintain consistency in the presentation of listings and for efficiencies in programming activities.

Note that a few subject listings (screening failures, unmet eligibility criteria and protocol deviations), and one table for summary of screening failures performed on screened subjects, are not changed and are presented using the SCRAS including site [redacted].

4 LIST OF ADDITIONAL SUMMARY TABLES FOR SENSITIVITY ANALYSES

The table number corresponds to the corresponding table number in the CSR SAP section 13.

4.1 Subject disposition (including site [redacted])

Table Number	Display*	Title (Description)	Analysis set(s)
T 1.2a	T	Disposition of subjects	AR
T 1.5	T	Overview of analysis sets	AR

* T = Summary table

4.2 Efficacy analyses (including site [redacted])

Table Number	Display*	Title (Description)	Analysis set(s)
T 6.1	T	Clinical Cure	amITT
T 7.1	T	Sustained Cure	amITT

* T = Summary table

4.3 Safety analyses (including site [redacted])

4.3.1 Adverse events

Table Number	Display*	Title (Description)	Analysis set(s)
T 9.1	T	Overview of treatment-emergent adverse events (AE) up to EOT + 7 days	aSS
T 9.2	T	Treatment-emergent adverse events (AE) by system organ class and preferred term up to EOT + 7 days	aSS

* T = Summary table

5 REFERENCES

[D-15.416] A multi-center sub-study to validate the CDAD-DaySyms (*Clostridium difficile*-associated diarrhea – Daily Symptoms) PRO in subjects with CDAD participating in study AC-061A301 or AC-061A302. Validation Sub-study protocol version 3. Actelion Pharmaceuticals Ltd; 30 November 2015.

[D-15.544] AC-061A302: A multi-center, randomized, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects with *Clostridium difficile*-associated diarrhea (CDAD). Global Protocol Version 3. Actelion Pharmaceuticals Ltd; 22 October 2015.

[D-16.411] A multi-center sub-study to assess the effects of cadazolid versus vancomycin on the composition of intestinal microbiota of subjects with *Clostridium difficile*-associated diarrhea (CDAD) participating in study AC-061A301 or AC-061A302. Gut microbiome sub-study protocol Version 2. Actelion Pharmaceuticals Ltd; 22 August 2016.

[D-17.273] Statistical Analysis Plan for Clinical Study Report AC-061A301 / AC-061A302: Two multi-center, randomized, double-blind studies to compare the efficacy and safety of cadazolid versus vancomycin in subjects with *Clostridium difficile*-associated diarrhea (CDAD). Version 3. Actelion Pharmaceuticals Ltd; 19 May 2017.

6 APPENDICES

A. Document history

Version	Effective Date	Reason
1.0	19 May 2017	New