A Phase 3, Multicenter, Investigator-blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Fidaxomicin Oral Suspension or Tablets Taken q12h, and Vancomycin Oral Liquid or Capsules Taken q6h, for 10 days in Pediatric Subjects with *Clostridium difficile*-associated Diarrhea

The SUNSHINE Study

ISN/Protocol 2819-CL-0202

ClinicalTrials.gov Identifier: NCT02218372

Date of Statistical Analysis Plan Final Version 3.0: 20 Apr 2018

Sponsor: Astellas Pharma Europe B.V.

Sylviusweg 62
2333 BE Leiden
The Netherlands

STATISTICAL ANALYSIS PLAN

Final Version 3.0, dated 20-Apr-2018

A Phase 3, Multicenter, Investigator-blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Fidaxomicin Oral Suspension or Tablets Taken q12h, and Vancomycin Oral Liquid or Capsules Taken q6h, for 10 Days in Pediatric Subjects with Clostridium difficile-associated Diarrhea.

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Astellas Pharma Europe B.V. (APEB)
Sylviusweg 62
2333 BE Leiden
The Netherlands

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ASCM	Analysis Set Classification Meeting
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
BQL	Below Quantifiable Limit
CCR	Confirmed Clinical Response at EOT+2days
CDAD	Clostridium Difficile Associated Diarrhea
CDI	Clostridium Difficile Infection
CI	Confidence Intervals
CRF	Case Report Form
CM	Concomitant Medication
CMH	Cochran-Mantel-Haenszel
CS	Classification Specifications
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DILI	Drug-induced Liver Injury
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EIA	Enzyme ImmunoAssay
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
ELISA	Enzyme-Linked Immunosorbent Assay
EMEA	European Medicines Agency
EOS	End of Study (EOT+30days)
EOT	End of Treatment
EU	Europe

Abbreviations	Description of abbreviations
FAS	Full Analysis Set
FID	Fidaxomicin
FSI	First Subject In
GC	Global Cure at EOT+9days, EOT+16 days, EOT+23days & EOT+30days (EOS)
GI	Gastrointestinal
GGT	Gamma Glutamyltransferase
H	High
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICR	Initial Clinical Response at EOT
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
ITT	Intent To Treat
L	Low
LLOQ	Lower Limit of Quantification
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MPRconc	Metabolite to Parent Ratio concentration
MW	Molecular Weight
N	Normal
OP-1118	Main and active metabolite of Fidaxomicin
OTC	over-the-counter
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PD	Protocol Deviation
PI	Principal Investigator
PK	Pharmacokinetic
PKAS	Pharmacokinetics Analysis Set
PT	Preferred Term

Abbreviations	Description of abbreviations
RBC	Red Blood Cell
RMS	Root Mean Square
QTc	Corrected Q-T Interval
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	This is the registered name for particular software for statistical Analysis and reporting
SBP	Systolic Blood Pressure
SCR	Sustained Clinical Response at EOT+9days, EOT+16 days, EOT+23days & EOT+30days (EOS)
SOC	System Organ Class
TBL	Total Bilirubin
TC	Teleconference / telephone call
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
TTROD	Time to resolution of diarrhea
UBM	Unformed Bowel Movement
ULN	Upper Limit of Normal
VAN	Vancomycin
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Baseline	A baseline measurement is the last available measurement before the start of first dosing (Day 1), regardless of whether the measurement was scheduled or unscheduled, and the change from baseline is calculated as follows: post-baseline value minus baseline value. Observations on Day 1 are assumed to be pre-dose.
Enroll	To register or enter into a clinical trial. NOTE: Once a patient has been enrolled, the clinical trial protocol applies to the patient.
End of Study	The end of the study is defined as the date of the last patient's last contact (visit or TC) or assessment.
End of Treatment	The day of the last dose of study drug (fidaxomicin or vancomycin) in the treatment period.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics). In this study the interventions being investigated are: • Fidaxomicin twice daily for 10 days • Vancomycin four times daily for 10 days
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug is given to a patient, and continues until the last assessment after completing administration of the test drug or comparative drug. In this study the investigational period is from the first dose of study drug until the end of study
Randomization	The process of assigning trial patients to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential patients for enrollment in a trial.
Screen failure	Potential patient who was not randomized and did not receive any study drug.
Screening period	Period of time before entering the investigational period, usually from the time of signing consent until just before the test drug or comparative drug is given to a patient.
Start of study	The start of the study is defined as the date that the first Informed Consent Form (ICF) is signed.
Study period	Period of time from the first site initiation date to the last site completing the study.
Sustained clinical response	Confirmed clinical response (EOT + 2 days) without CDAD recurrence until the time of assessment during the Follow-up period.
Time to recurrence	The time (days) from confirmed clinical response until the onset of recurrence as defined below in Table 4
Treatment period	Time from the patient's first dose of study drug (fidaxomicin or vancomycin) until their last dose of study drug. Treatment for recurrence is not included in the treatment period

Please see also definitions Section 6 "Analysis Variables"

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

Version 1 of the SAP was finalized on 7Nov20147th Nov2014 prior to First Subject In (FSI). If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

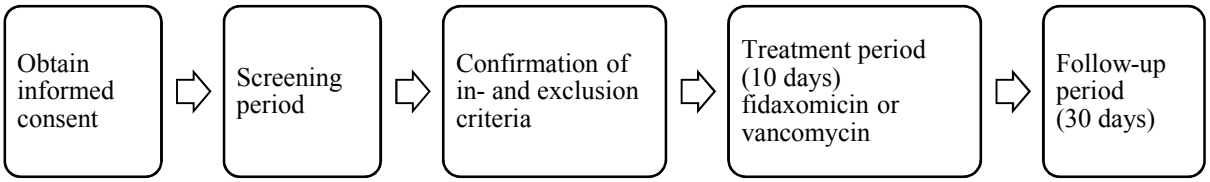
This statistical analysis is coordinated by the responsible biostatistician of Astellas Data Sciences. Any changes from the analyses planned in the final SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Flow Chart

Study Schematic Diagram



Start and End of Study

The start of the study is defined as the date that the first Informed Consent Form (ICF) is signed.

The end of the study is defined as the date of the last patient's last visit (End of Study).

In case of premature withdrawal or failure during the treatment period, the patient should complete the End of Treatment (EOT) visit and End of Study (for safety information).

In case of recurrence of diarrhea during the Follow-up period and for any other reason that in the opinion of the investigator requires a clinic visit, the patient should complete an Unscheduled visit for reassessment of CDAD.

Table 1 Schedule of Assessments

Study Period	Screening period	Treatment period[a]				Follow up period		End of Study TC/Visit (EOS)[k]	Unscheduled Visit[l]
	Screening	Daily Assessment			End of Treatment (EOT)[f,g]	Confirmation Clinical Response TC/Visit[h]	Follow-up TC [i]		
Day	-2 to 1	1[b]	2-4	5-10	10	EOT+2	EOT +9, 16 & 23	EOT+30	
Window (Days[u])					+2	+2	+2	+2	
Assessments									
Subject information & informed consent	X								
Demographics	X								
Height and Weight	X								
Medical History	X								
CDAD History	X								
Investigator Evaluation of Signs & Symptoms of CDAD	X				X				
Inclusion/Exclusion Criteria Check	X								
Randomization		X							
Study Drug Dosing		X	X	X					
Study Drug Compliance Check					X				
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X
CDAD Status (Subject/parent/legal guardian interview)[e]			X	X	X	X	X	X	X
Drug Concentration Blood Samples[n]				X					
Drug Concentration Stool Sample[o]				X					
Stool Sample for Toxigenic *C.difficile* and possible microbiology testing	X[m]				X[r]				X[j]
Faecal Rotavirus Testing[t]	X								
Palatability[p]		X		X					

Table continued on next page

Study Period	Screening period	Treatment period[a]				Follow up period		End of Study TC/Visit (EOS)[k]	Unscheduled Visit[l]
	Screening	Daily Assessment			End of Treatment (EOT)[f,g]	Confirmation Clinical Response TC/Visit[h]	Follow-up TC[i]		
Day	-2 to 1	1[b]	2-4	5-10	10	EOT+2	EOT +9, 16 & 23	EOT+30	
Window (Days[u])					+2	+2	+2	+2	
Safety									
Hematology, Biochemistry and Urinalysis[s]	X				X				O
Pregnancy Test[c]	X				X				O
Physical Examination	X				X				O
Vital Signs[d]	X				X				O
ECG[q]	X			X					
Adverse Events	X	X	X	X	X	X	X	X	X
Efficacy									
Clinical Response					X	X			
Recurrence[j]							X	X	X[j]

X = required, O=optional

a) Patients may be treated on an inpatient/outpatient/ or combined basis at the discretion of the investigator.

b) After all screening procedures are completed and the patient is eligible, the patient will be randomized and study drug will be administered. This is the start of the Treatment Period (i.e., Day 1)

c) At Screening, at the End of Treatment (EOT) visit and at the Unscheduled visit (if deemed necessary by the investigator) a pregnancy test locally in urine (dipstick) will only be performed in women of childbearing potential.

d) Includes blood pressure, pulse, and body temperature.

e) CDAD status will be assessed by interviews with the patient/parent/legal guardian (or hospital staff e.g., when hospitalized). These interviews will be conducted in the morning, daily during the treatment period through End of Treatment and at EOT+2; thereafter weekly at 9, 16 and 23 days after the EOT, and at End of Study (EOS) EOT + 30 days, following a standardized questionnaire. These interviews may be conducted by telephone (e.g., when not hospitalized).

f) Patients who discontinue study drug prematurely should complete the EOT visit as soon as possible after the final dose.

g) At EOT, the clinical response will be assessed. All patients will continue in the Follow-up period.
Patients that have no clinical response will only be contacted at EOT +30 days for safety (adverse events).

Footnotes continued on next page

h) Two days after EOT, a telephone contact with the patient/parent/legal guardian or a visit (if the patient is still in the hospital) will take place for all patients with an initial clinical response at EOT to confirm the clinical response. All patients will continue in the 30-day Follow-up period. Patients without a confirmed clinical response will only be contacted at EOT +30 days for safety (adverse events).

i) At 9, 16 and 23 days after EOT, for patients who had confirmed clinical response; the patient/parent/legal guardian will be contacted by phone.

j) For patients with a recurrence of diarrhea during the Follow-up period, an Unscheduled visit is mandatory, including a stool sample. The stool sample will be split in two aliquots one for detection of toxigenic *C.difficile* at site and one for the reference lab (for possible microbiological and biochemistry testing), for reassessment of CDAD (as per protocol criteria). Patients with recurrence of CDAD will after the Unscheduled visit continue in the Follow-up period and will only be contacted at EOT +30 days for safety (adverse events).

k) 30 days after EOT, the EOS TC/visit will take place. For patients that had a confirmed clinical response at EOT +2 days and did not experience a recurrence during the Follow-up period, all assessments will be done, including sustained clinical response assessment. For all other patients a telephone call (TC) will be done for safety (adverse events).

l) Unscheduled visits could take place throughout the study period, if deemed necessary by the investigator. Only those assessments that are relevant according to the investigators opinion should be performed. However, evaluation of adverse events (AE) and concomitant medication is mandatory.

m) Stool sample will be split in two aliquots, one for the detection of toxigenic *C. difficile* at study site and one for the reference laboratory (for possible microbiological and biochemistry testing). Alternatively, a test for toxigenic *C. difficile* done as standard of care, including pre-consent samples, provided the sample was obtained within 72 hours prior to randomization, may be used to assess eligibility and a different sample sent to the reference laboratory.

n) For patients receiving fidaxomicin, two blood samples will be taken on any day between Day 5 and 10 inclusive. Every effort should be made to take these samples in conjunction with routine blood samples being taken for standard of care. However one sample should be collected within 30 minutes pre-dose and another between 1 to 5 hours post-dose. The two samples do not have to be collected on the same day.

o) For all patients a stool sample will be taken between Day 5 and 10 inclusive, within 24 hours of a dose.

p) For patients receiving fidaxomicin oral suspension or vancomycin oral liquid palatability assessment will be performed on Day 1 and Day 7 (± 1 day).

q) Two ECGs will be performed. One at screening prior to the first dose of study drug and another 1 to 5 hours post-dose (the morning or evening dose for the fidaxomicin arm, or the first or the third dose of the day for the vancomycin arm) on any day between days 5 and 10 inclusive, but not within 30 minutes after venipuncture.
For the ECG at screening, an ECG that is performed before consent is acceptable, provided that it was recorded after the onset of CDAD and within 3 days prior to randomization.

r) At the EOT visit a stool sample will be split in two aliquots, one for direct or indirect testing for presence of toxigenic *C.difficile* at study site and one for the reference laboratory (for possible microbiological and biochemistry testing).

s) For hematology, biochemistry and urinalysis at Screening, results that were obtained per standard of care before consent (historical sample) are acceptable, provided that the sampling was done after the onset of CDAD and within 3 days prior to randomization. For the hematology, biochemistry and urinalysis at EOT visit, results that were obtained as part of standard of care between Day 8 and Day 10 (inclusive) (standard of care sample) are acceptable. The most recent results should be used for eCRF completion. The historical or standard of care sample may not include all parameters as described in Table 5, Section 6.2.2. A historical/standard of care samples without parameter(s) indicated with * in the table is acceptable.

t) The window of +2 days allows the assessment to be up to 2 days later than the specified target, but no earlier

u) For patients < 5 years only, a rotavirus test is required. A pre-consent standard of care result may be used (historical sample), provided the sample was taken after the onset of diarrhea and within 3 days prior to randomization.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

3.1.1 Primary Objective

The primary objective of this study is to investigate the clinical response to fidaxomicin oral suspension or tablets and vancomycin oral liquid or capsules of pediatric patients with *Clostridium difficile*-associated diarrhea (CDAD) from birth to < 18 years of age.

3.1.2 Secondary Objective

The secondary objectives of this study are to investigate the recurrence/sustained clinical response and safety of fidaxomicin and vancomycin in pediatric patients with *Clostridium difficile*-associated diarrhea (CDAD) from birth to < 18 years of age, as well as palatability (acceptance) of the fidaxomicin oral suspension formulation.

3.2 Study Design

This is a multicenter, investigator-blind, randomized parallel group study to investigate the safety and efficacy of a 10-day course of fidaxomicin oral suspension or tablets and a 10-day course of vancomycin oral liquid or capsules in patients from birth to < 18 years of age with confirmed CDAD. Note that in the United States of America patients can only be included if aged ≥ 6 months to < 18 years.

In order to reduce differential assessment of safety and efficacy outcomes, typically a double-blind study would be preferred. However, due to nature of the active treatment and the comparator (e.g., formulation differences, dosing regimen differences), double blinding of the study drug for this pediatric study population is not feasible, given dosing constraints. Therefore the study will be partially blinded at site – the study will be investigator-blinded, and sites will have blinded staff to carry out blinded assessments. There will be blinded and unblinded CRAs, data managers, study managers and statisticians. This SAP is written by the blinded statistician. The programming team will remain unblinded.

The study will be conducted in North America and Europe across ~65 to 80 sites. A target of 144 eligible patients, stratified by age at enrollment (screening):

- birth to < 24 months (2 years) (6 months to < 24 months at US sites),
- >= 2 years to < 6 years,
- >= 6 years to < 12 years, and
- >= 12 years to < 18 years

A minimum of 24 patients will be in each age group. The remaining 48 patients may be in any age group. Eligible patients are those randomized without any violations of inclusion or exclusion criteria. All patients randomized with PD1 will not be counted as eligible.

Patients will be randomized to either fidaxomicin or vancomycin arm in a 2:1 ratio, stratified by age group.

For patients receiving fidaxomicin, plasma and stool samples will be analyzed. Palatability will be assessed for all patients receiving fidaxomicin oral suspension or vancomycin oral liquid.

An independent external Data and Safety Monitoring Board (DSMB) will be established for this study.

3.3 Randomization

Patients will be randomized to either fidaxomicin or vancomycin arm in a 2:1 ratio, stratified by age group at enrollment (screening) from birth to < 24 months, >= 2 years to < 6 years, >= 6 years to < 12 years, and >= 12 years to < 18 years.

Randomization will be performed via Interactive Response Technology (IRT), by the Sponsor's designee ([redacted]). Prior to the first study drug administration, the unblinded site staff will contact the IRT system in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT are contained in the Study Procedures Manual (ASTEL00020201). Treatment codes and other information (e.g., stratification) will be made available electronically to unblinded staff only.

4 SAMPLE SIZE

One hundred forty four eligible patients will be randomized to either fidaxomicin or vancomycin in a 2:1 ratio (96 randomized to fidaxomicin and 48 to vancomycin), stratified by age at screening:

- from birth to < 24 months (2 years) (6 months to < 24 months at US sites),
- >= 2 years to < 6 years,
- >= 6 years to < 12 years, and
- >= 12 years to < 18 years.

At least 24 patients will be in each age group (i.e., a minimum of 16 randomized to fidaxomicin and 8 to vancomycin).

The sample size for this study was agreed with the Pediatric Development Committee as part of the Pediatric Investigational Plan (EMEA, 2012), and is based on clinical and practical considerations as the prevalence of the target disease in the study population is low.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of patients to analysis sets will be determined prior to database hard lock.

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized patients who received at least one dose of study drug (fidaxomicin or vancomycin), which is the primary analysis population.

In the FAS, patients will be allocated to the treatment arm corresponding to the study medication that the patient was randomized to (treatment allocation as randomized).

The FAS will be used for efficacy endpoint analyses, as well as selected demographic and baseline characteristics.

5.2 Intent To Treat (ITT)

The intent-to-treat (ITT) set consists of all randomized patients, irrespective of a patient having received a study drug (fidaxomicin or vancomycin) or not.

In the ITT, patients will be allocated to the treatment arm corresponding to the study medication that the patient was randomized to (treatment allocation as randomized).

The ITT will be used for efficacy endpoint analyses, as well as selected demographic and baseline characteristics when necessary. The ITT set was requested by the FDA.

5.3 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all randomized patients who received at least one dose of study drug (fidaxomicin or vancomycin). In the SAF, a patient will be allocated to the treatment arm corresponding to the study drug that was first administered (fidaxomicin or vancomycin), even if it differs from the treatment arm the patient was randomized to.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

5.4 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetics Analysis Set (PKAS) consists of all patients randomized to fidaxomicin, having received at least one dose of fidaxomicin and having at least one valid measurement of plasma concentration or faecal concentration of fidaxomicin or its main metabolite OP-1118.

Additional patients may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of patients or time-points from the PKAS will be documented in the Classification Specifications.

The PKAS will be used for summarizing the Pharmacokinetic (PK) data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The proportion of patients with Confirmed Clinical Response (CCR) assessed by the investigator at EOT+2 days.

The CCR is a binary variable with a positive (Yes) or negative (No) outcome, which is recorded in the relevant CRF page. The Initial Clinical Response (ICR) will be evaluated at EOT. The ICR is a binary variable with a positive (Yes) or negative (No) outcome, which is also recorded in the relevant CRF page, similar to CCR.

The definition of both CCR and ICR is age dependent and their definitions are given below on Table 2

Table 2 Definition of Clinical Response at EOT and Confirmed Clinical Response at EOT+2 days

Age	Clinical response
patients from birth to < 2 years	Absence of watery diarrhea for 2 consecutive days during treatment and patients remain well until the time of study drug discontinuation (initial clinical response). In addition, patients should not require further CDAD therapy within 2 days after completion of study drug (confirmed clinical response). Resolution of diarrhea is assessed during interviews of the patient/parent/ legal guardian supplemented by a review of the patient's personal records for the day (if hospitalized), and the presence of watery diarrhea.
patients aged >= 2 years to < 18 years	Improvement in the number and character of bowel movements as determined by < 3 unformed bowel movements (UBMs) per day for 2 consecutive days during treatment and patients remain well until the time of study drug discontinuation (initial clinical response). In addition, patients should not require further CDAD therapy 2 days after completion of study drug (confirmed clinical response). Resolution of diarrhea is assessed during interviews of the patient/parent/legal guardian, supplemented by a review of the patient's personal records for the day (if hospitalized), and the number of UBMs.

6.1.2 Secondary Efficacy Endpoints

The following endpoints are used to assess the study's secondary efficacy objectives:

6.1.2.1 Proportion of Patients with Global Cure and Sustained Clinical Response at the EOS (EOT +30 days)

Sustained clinical response at EOS (EOT +30 days) and Global cure at EOS (EOT +30 days) are derived programmatically as follows:

- Sustained clinical response (SCR) is assigned a positive outcome (SCR=Yes) at the EOS (EOT +30 days), for any patient that has a confirmed clinical response (CCR=Yes) at EOT + 2 days without CDAD recurrence (as defined below) until EOS (EOT +30 days) inclusive
- Sustained clinical response (SCR) is assigned a negative outcome (SCR=No) at the EOS (EOT +30 days), for any patient that has a confirmed clinical response (CCR=Yes) at EOT + 2 days with CDAD recurrence (as defined below) until EOS (EOT +30 days)
- Global cure at EOS will be positive if SCR=Yes at EOT+30 days and negative otherwise (i.e., SCR=No or Missing).

6.1.2.2 Proportion of Patients with Global Cure and Sustained clinical response at EOT + 9, 16 and 23 days

Global cure and Sustained clinical response (SCR) at EOT + 9, EOT + 16 and EOT + 23 days is derived as for EOT+30 days, but replacing 30 days with 9, 16 or 23.

6.1.2.3 Time to resolution of diarrhea (TTROD)

Time to resolution of diarrhea (TTROD) (in hours rounded up from minutes > 30) definition is age dependent and its definition is given on Table 3 below.

Table 3 Definition of Time To Resolution Of Diarrhea (TTROD)

Age	***Time to resolution of diarrhea (TTROD)***
patients from birth to < 2 years	The time elapsing (in hours rounded up from minutes ≥ 30) from the start of treatment (time of first dose of study medication) to resolution of diarrhea (time of last episode of watery diarrhea the day prior to the first of 2 consecutive days without watery diarrhea that was sustained through EOT).
patients aged >= 2 years to < 18 years	The time elapsing (in hours rounded up from minutes ≥ 30) from the start of treatment (time of first dose of study medication) to resolution of diarrhea (time of the last UBM the day prior to the first of 2 consecutive days of <3 UBMs that were sustained through EOT).

TTROD is derived programmatically as follows:

TTROD (rounded up from minutes ≥ 30) = ('Date and Time* of resolution of diarrhea' - 'Date and Time of first dose of study medication**') + 1

*= [Start Date and Start Time of last episode of watery diarrhea (children < 2 yrs) or unformed bowel movements < 3 (children >= 2 yrs) captured on the 'Patient/Legal Guardian Interview Treatment Period' page of the CRF]

**= [Start Date and Start Time of Treatment on 'Study Drug Dosing' page of the CRF]

6.1.2.4 Proportion of Patients with Recurrence of CDAD during or at the end of the Follow-up period.

The recurrence of CDAD is a binary variable with a positive (Yes) or negative (No) outcome, which is recorded in the relevant CRF page.

The assessment of recurrence of CDAD during or at the end of the Follow-up period is applicable only to patients with an assessment of confirmed positive clinical response (CCR=Yes) at EOT+2 Days. The definition of recurrence is age dependent and its definition is given on Table 4 below.

Table 4 Definition of Recurrence

Age	***Recurrence***
patients from birth to < 2 years	The re-establishment of watery diarrhea after confirmed clinical response to an extent that is greater than that noted on the last day of study drug with the demonstration of a positive direct or indirect testing for the presence of toxigenic *C.difficile* in stool and that, in the investigator's opinion, would require retreatment with CDAD anti-infective therapy.
patients aged >= 2 years to < 18 years	The re-establishment of diarrhea after confirmed clinical response to an extent (as measured by the frequency of passed unformed stools) that is greater than that noted on the last day of study drug with the demonstration of a positive direct or indirect testing for the presence of toxigenic *C.difficile* in stool and that, in the investigator's opinion, would require retreatment with CDAD anti-infective therapy.

6.1.2.5 Time to recurrence during or at the end of the Follow-up period.

Time to recurrence of CDAD is defined as the time (days) from confirmed clinical response until the onset of recurrence of CDAD as defined above.

Time to recurrence of CDAD is derived programmatically in the database as follows:

Time to recurrence of CDAD (days) = ('Date first recurrence of CDAD - 'Date** of CCR=Yes') + 1*

* = [Start Date of Clinical Event on 'CDAD Status Recurrence' page of the CRF]
**= [Start Date of Clinical Event on 'CDAD Status Clinical Response' page of the CRF]

Time to recurrence of CDAD assessment is applicable only to patients with a confirmed positive clinical response (CCR=Yes) at EOT+2 visit.

6.1.2.6 Palatability

Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) will be evaluated in all patients receiving fidaxomicin oral suspension and vancomycin oral liquid (i.e., patients from birth to =< 6 years and patients > 6 years unable to swallow tablets) on Day 1 and on Day 7 (±1 day) by means of a five-point rating scale by unblinded staff if hospitalized, and by the patient/parents/legal guardian when at home.

In case the drug product is rejected without actual oral administration, the response cannot be rated. This will be recorded in the eCRF.

6.1.3 Exploratory Efficacy Endpoints

6.1.4 Other Efficacy Endpoints

- Diarrhea status (Normal/ Diarrhea) for patients from birth to < 2 years, during the treatment period, as recorded daily in the CRF.
- Number of UBM for patients aged ≥ 2 years to < 18 years, during the treatment period, as recorded daily in the CRF.
- Diarrhea status (Normal/ Diarrhea) for patients ≥2 years will be derived based on the Number of UBM. Specifically, patients ≥ 2years, with UBM 0, 1, 2 will be set as "Normal", while patients with 3 or more UBMs will be considered as "Diarrhea".

6.2 Safety Variables

Safety will be assessed mainly by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry including liver function tests, and urinalysis)
- Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG)

6.2.1 Adverse Events

Collection of adverse events (AEs) begins at the time the ICF is signed and continues through to the last assessments at the EOS Visit (Day 30). Any clinical signs or symptoms present prior to signing informed consent are to be recorded as medical history at the Baseline Visit (Day 1). Baseline conditions that worsen during the study are to be recorded as AEs. AEs beginning after patients had completed the last EOS assessments were not captured.

AEs ongoing at the EOS Visit (Day 30) are to be followed up for as long as necessary to adequately evaluate the patient's safety or until the event stabilized. If the event resolved during the study, a resolution date was to be documented in the eCRF prior to patient's study withdrawal.

Data to be recorded for AE included a description of the event, onset and end date, outcome, severity, seriousness, action taken for study drug, treatment required and relationship to the study drug.

Serious adverse events (SAEs) related to study drug were to be reported until 30 days after the EOS Visit (Day 30), but were not to be recorded in the eCRF.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0.

The specified AEs / findings of interest for this study are shown below:

- Hypersensitivity to fidaxomicin
- Gastrointestinal (GI) hemorrhage
- Haematological AEs: Decreases in white blood cell (WBC), neutrophil and lymphocyte counts

- Hepatic laboratory value abnormalities, Drug Induced Liver Injury (DILI) cases (refer to Section 6.2.2)
- QT-interval prolongation
- Renal AEs: Laboratory value abnormalities

AEs of interest will be identified using Standardized MedDRA queries (SMQ) if available or sponsor-defined list of search term (refer to Appendix 10.3).

The development of antimicrobial resistance to fidaxomicin is a finding of interest (Protocol Section 5.5.1). This will be identified (if present) through the microbiological tests on the *C. difficile* through the study, rather than through adverse event reports. This is because the results of the microbiological tests are available sometime after the patient has completed the study, and is not available to the investigator. Antimicrobial resistance might be difficult to assess using the microbiological results as there are no cutoff values to define what is a resistant or not resistant isolate.

The lack of efficacy/lack of effect/treatment failure is also a finding of interest (Protocol Section 5.5.1). This will be assessed using the efficacy results rather than through adverse event reports.

Definitions

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a patient experiences an event both during the screening period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date).

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

The severity of an AE is categorized as mild, moderate or severe.

6.2.2 Laboratory Assessments

Routine safety laboratory assessments will be performed at the Screening and End of Treatment visit by the local laboratory and recorded in the eCRF. Additional laboratory testing may be carried out by the investigator if deemed necessary.

In Table 5 the laboratory tests that will be performed during the conduct of the study are listed. See the Schedule of Assessments for study visit collection dates. It is not required that the patients are fasting prior to blood sampling for these assessments. Please refer to study

protocol Appendix 12.2 for additional Drug Induced Liver Injury (DILI) laboratory testing requirements and timing.

For the hematology, biochemistry and urinalysis at Screening, results that were obtained as part of standard of care before consent ("historical sample") are acceptable, provided that the sampling was done after the onset of CDAD and within 3 days prior to randomization. For the hematology, biochemistry and urinalysis at EOT visit, results that were obtained as part of standard of care between Day 8 and Day 10 (inclusive) ("standard of care sample") are acceptable. The most recent results should be used for eCRF completion. If such results are not available, samples should be taken for the purpose of the study. The historical or standard of care sample may not include all parameters as described in Table 5. A historical/standard of care sample without parameter(s) indicated with * in the table is acceptable.

During screening, at the EOT visit and at the unscheduled visit (if deemed necessary by the investigator) the pregnancy test will be done locally in urine (dipstick).

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

Any changes in laboratory values are to be evaluated by the investigator. Clinically relevant changes will be recorded as AEs in the eCRF.

Drug Induced Liver Injury (DILI) cases are defined as:

- Moderate: ALT or AST > 3xULN or Total Bilirubin > 2xULN
- Severe: ALT or AST > 3xULN and Total Bilirubin > 2xULN.

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8xULN
- ALT or AST > 5xULN for more than 2 weeks
- ALT or AST > 3xULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Table 5 Clinical Laboratory Tests to be Performed

Assessment Time Point Screening; End of Treatment ; Unscheduled visit, as applicable		
Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin	Sodium*	Protein*
Hematocrit	Potassium	Glucose*
Red Blood Cell (RBC)	Calcium	pH*
WBC	Chloride*	Blood*
Neutrophils	Glucose*	Beta hCG (females of child-bearing potential only)
Segmented neutrophils*	Creatinine	
Band neutrophils*	**C-reactive protein** (CRP)*	
Lymphocytes	Alkaline phosphatase	
Monocytes	Aspartate Transaminase (AST)	
Eosinophils	Alanine Transaminase (ALT)	
Basophils	Gamma glutamyltransferase (GGT)*	
Platelets	Total bilirubin	
	Direct bilirubin*	
	Total protein*	
	Albumin	

* A historical / standard of care samples (see above) without parameter(s) indicated with * is acceptable.

6.2.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and body temperature will be measured as indicated in the Schedule of Assessments.

Wherever possible, for blood pressure and pulse rate measurements the same arm should be used throughout the study, and with the patient in the same position (sitting or supine). The size of the sphygmomanometer cuff should be age appropriate and not change throughout the study.

Whenever possible, the route and device used to measure body temperature should remain unchanged throughout the study.

6.2.4 Electrocardiogram (ECG)

Two 12 lead ECGs will be performed: one at Screening prior to the first dose of study drug and another 1 to 5 hours post-dose (the morning or evening dose for the fidaxomicin arm, or the first or the third dose of the day for the vancomycin arm) on any day between Days 5 and 10 inclusive, but not within 30 minutes after venipuncture.

For the ECG at Screening, an ECG that is performed as a part of standard of care before consent is acceptable, provided that it was recorded after the onset of CDAD and within 3 days prior to randomization.

ECG traces will be evaluated by the investigator who will give an overall interpretation and may leave a qualifying comment in the eCRF. The overall interpretation will be recorded as:

- Normal, or
- Abnormal – not clinically significant, or
- Abnormal – clinically significant

Original ECGs will be collected for central ECG reading and returned to site if requested. Central ECG read data will be transferred electronically to the sponsor. The central ECG will identify any potential abnormalities as findings; the ECG will then be assessed as to whether or not the ECG as a whole should be described as normal or abnormal. In particular, if the ECG contained changes such as sinus tachycardia or sinus bradycardia and nothing else, these changes are quite common and the overall interpretation of the ECG is normal.

Any clinically significant adverse changes on the ECG will be reported as AEs in the eCRF.

As well as the overall interpretation, the following ECG variables will be supplied by the central laboratory: PR duration (msec), RR duration (msec), QRS duration (msec), QT duration (msec), QTcB (msec), QTcF (msec) and Heart rate (beats/min).

6.2.5 Physical Examination

The patient's physical state will be examined and recorded at Screening, End of Treatment, and if deemed necessary by the investigator at an Unscheduled visit. This includes examination of main body systems. The date of the physical examination only will be recorded in the eCRF. Any clinically relevant adverse change will be recorded as an AE in the eCRF.

6.2.6 CDAD Signs and Symptoms

CDAD signs and symptoms (highest body temperature in the 3 days prior to first dose, highest white blood cell in the 3 days prior to first dose, abdominal discomfort, and abdominal tenderness) will be recorded at Screening. Abdominal discomfort and abdominal tenderness will be recorded at End of Treatment. Any clinically relevant change will be recorded as an AE in the eCRF.

6.3 Drug Concentration Variables

Plasma and stool samples are collected and analyzed for fidaxomicin and its main metabolite OP-1118 concentrations.

- Plasma concentrations of fidaxomicin and its main metabolite (OP-1118) within 30 minutes pre-dose (C_{trough}) and 1 to 5 hours post-dose taken on any day between Day 5 and 10 inclusive.
- Faecal concentration of fidaxomicin and its main metabolite (OP-1118) within 24 hours after dosing between Day 5 and 10 inclusive.
- Metabolite to Parent concentration Ratio MPRconc:

MPRconc= [concentration of OP-1118]*[molecular weight (MW) of fidaxomicin]/[concentration of fidaxomicin]*[MW of OP-1118].

MW fidaxomicin(=parent)= 1058.04 g/mol, MW OP-1118(=metabolite) = 987.949 g/mol.

6.4 Other Variables

6.4.1 Demographic Data and Baseline Characteristics

The patient's age, gender, race and ethnicity (if permitted), height and weight will be recorded at screening visit.

6.4.2 Medical History

Medical history (other than for CDAD) for each patient will be obtained at Screening. Relevant past and present conditions, as well as prior surgical procedures will be recorded in the eCRF.

6.4.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

A detailed diarrhea history for each patient will be obtained during Screening. This includes start and stop date, antibiotic treatment, and all CDAD episodes that occurred in the last three months prior to screening. Additionally, start date and signs and symptoms of the current CDAD episode will be collected, including number of UBMs/ presence of watery diarrhea within 24 hours prior to randomization. The following risk factors will be collected in the eCRF: Antibiotics/ Cancer/ Other, if applicable.

6.4.4 Rotavirus

For patients < 5 years only, a rotavirus test is required at Screening. A pre-consent standard of care result (historical sample) may be used, provided the sample was taken after the onset of diarrhea and within 3 days prior to randomization.

6.4.5 Duration of exposure

For each patient, the Length of Time on study drug will be calculated in days, using the following formula:

Length of Time on treatment (days) = ('Date last dose of study drug' - 'Date first dose') + 1

[Date of First/Last Dose of Study Drug, captured on the 'Study Drug Dosing' CRF]

6.4.6 Treatment compliance

Overall compliance to the dosing schedule will be examined for patients in the safety population and in the efficacy population. Percent treatment compliance is defined as:

$$\text{Treatment compliance (\%)} = \frac{\text{Actual amount of study drug used} \times 100}{\text{Planned amount of drug that should have been used in 10 days}}$$

Although dosing by weight bands is preferred according to dosing instruction, some patients may have been dosed based on individual weight (mg/kg) rather than by weight bands. The protocol mentions both weight band dosing and dosing according to mg/kg/day. This is the reason treatment compliance will be calculated based on both dosing options (weight bands and individual weight).

Details on compliance calculation can be found in Appendix 10.6

If a patient discontinues study drug early due to an AE, this is not a deviation because the protocol was followed. There is no need to report a deviation if there is an explanation such as dropping tablets down the sink by accident, provided that the correct dose was received by the patient (e.g., tablets replaced).

For patients who completed the treatment period and have no data for study drug returned or partially missing data (e.g., 2 bottles were dispensed but only one was returned), but do have data for study drug dispensed, compliance will be missing. For all calculations empty bottle weight for fidaxomicin is 109.6 g, while for vancomycin is 27.2 g.

Table 6 Comparative dosing scheme in mg per day

	Fidaxomicin		**Vancomycin**	
Weight band of patient	**Oral Suspension**	**Tablets**	**Oral Liquid**	**Capsules**
≤ 3.9 kg	80 mg	400 mg	100 mg	500 mg
4.0-6.9 kg	160 mg		200 mg	
7.0-8.9 kg	240 mg		300 mg	
9.0-12.4 kg	320 mg		400 mg	
≥ 12.5 kg	400 mg		500 mg	

Table 7 Planned dose in mg for complete treatment (10 days)

	Fidaxomicin		**Vancomycin**	
Weight band of patient	**Oral Suspension**	**Tablets**	**Oral Liquid**	**Capsules**
≤ 3.9 kg	800 mg	4000 mg	1000 mg	5000 mg
4.0-6.9 kg	1600 mg		2000 mg	
7.0-8.9 kg	2400 mg		3000 mg	
9.0-12.4 kg	3200 mg		4000 mg	
≥ 12.5 kg	4000 mg		5000 mg	

6.4.7 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

Previous medication (medication history) taken within a month prior to screening will be entered in the Electronic Case Report Form (eCRF). Any treatments of relevance to CDAD,

either as treatments for CDAD or causative agents such as antibiotics or anti-cancer therapies used within 3 months prior to screening should be recorded in the eCRF.

Concomitant medication (CM) includes relevant therapies prescribed by the study doctor, other doctors and over the counter drugs taken from Day 1 until the EOS (EOT visit + 30 days) and should be recorded in the eCRF.

Medication history and concomitant treatment consists of drug and non-drug therapies, prescribed and over-the-counter (OTC) and all alternative medicines (e.g., herbal/homeopathic medicines). This also includes drugs used on a chronic and as-needed basis. Patients will be instructed not to start any new medication during the screening period through EOS, both prescribed and OTC, without prior consultation of the investigator wherever possible.

6.4.8 Prohibited Medication

Identification of prohibited medications will be detailed in the medical review plan.

It is preferred that prior to randomization, no pretreatment for CDAD is given. However, if the investigator feels there is a clinical imperative to begin treatment before knowing the laboratory result of direct or indirect testing for presence of toxigenic *C.difficile*, up to four doses but no more than 24 hours of treatment with metronidazole, oral vancomycin or any other effective treatment for CDAD are allowed.

Co-administration of potent P-glycoprotein inhibitors such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended, but these medications are not prohibited.

Whenever possible, drugs which could affect peristalsis should be avoided.

Part A - Prohibited Medications

No other antibacterial agents potentially useful in the treatment of CDAD (e.g., metronidazole, oral vancomycin, oral bacitracin, fusidic acid, rifaximin, nitazoxanide) or faecal transplantation should be given during the study unless they are specifically given because of a primary treatment failure or suspected CDAD recurrence after initial clinical response. Faecal transplantation will be confirmed by Medical review.

Drugs to control diarrhea (e.g., loperamide) should also be withheld during the study period.

Use of these medications is prohibited during the entire study, unless they are specifically given because of a primary treatment failure or suspected CDAD recurrence after initial clinical response.

Part B - Medications Permitted With Restrictions

The use of these medications is to be avoided between Screening and End of Study. They are permitted provided the patient has been taking this medication on a long-term basis on the same dose and will continue with the same dose during the study.

Patients receiving opioids for pain prior to randomization may continue to receive the same opioid and dose during the treatment phase if required.

Table 8 Prohibited Medication

Part A	**Part B**
CDAD treatment	**Drugs to that could affect peristalsis**
Oral vancomycin	Loperamide
Metronidazole	Codeine
Oral bacitracin	Morphine
Fusidic acid	Pethidine
Rifaximin	Fentanyl
Nitazoxanide	Methadone
Linezolid	Tramadol
Rifampicin	Other opioids
Faecal transplantation	Antiinfectives for Systemic Use
	Intestinal Antiinfectives
	Drugs for Constipation

These lists are not exhaustive. In case of doubt, the investigator should contact the local study monitor.

Note – the medications are prohibited unless they are specifically given because of a primary treatment failure or suspected CDAD recurrence after initial clinical Response. So medications in the above categories should be counted as prohibited from randomization to treatment failure (ICR=No, CCR=No or Recurrence) or 30 days after EoT – whichever comes first. Medications marked as for "CDAD recurrent episode" should be checked by medical review.

Opioids are allowed if kept at the same dose from before randomization and through the trial.

The route should also be taken into account. Topically used drugs only have a local effect and therefore are allowed. The following routes are exempt for prohibited/restricted used: topical, ophthalmological, otic, intranasal, intravaginal, intradermal and intraarticular. If the route is missing – this should be checked by medical review.

Identification of prohibited and restricted medications will be handled programmatically using ATC codes and WHO Drug codes provided by the Medical Coding group, and will be checked and confirmed by medical review.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%. Where results for missing values are imputed, according to the rules in this document, these patients will be included in the denominator.

All statistical comparisons will be made using two sided tests at α=0.05 significance level unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 (SAS Enterprise Guide 4.1) on UNIX. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

Generally, listings will be provided for all available patients that passed screening, unless specified otherwise (see TLF Specifications for further details). Patient(s) with missing data for variables related to a particular listing will be excluded from that listing.

7.1.1 Definitions

Baseline: Unless otherwise specified, a baseline measurement is the last available measurement before the start of first dosing (Day 1), regardless of whether the measurement was scheduled or unscheduled, and the change from baseline is calculated as follows: post-baseline value minus baseline value. Observations for the screening visit on Day 1 are assumed to be pre-dose.

Treatment: All summaries will be presented by treatment arm and overall. For all efficacy summaries, patients will be considered part of the treatment arm corresponding to the planned treatment they were randomized to (see FAS, ITT definition on Section 5). For all safety summaries, patients will be considered part of the treatment arm corresponding to the actual treatment they received even if this is different from the one they were randomized to (see SAF definition on Section 5).

7.1.2 General Stratification Criteria

All summary tables are to be provided by treatment arm:

Treatment arm: **fidaxomicin / vancomycin**.

Additionally, summary tables (except tables presenting endpoints using multiple imputation) will be further stratified by age categories as defined below:

Table 9 Age group categories

Age Group (Years)
Overall [From birth to < 18 years]
• From 6 months to < 18 years
• From birth to < 2 years (24 months)
▪ From birth to < 6 months
▪ >= 6 months to < 2 years
• >= 2 years to < 18 years
▪ >= 2 years to < 6 years
▪ >= 6 years to < 12 years
▪ >= 12 years to < 18 years

For summary tables presenting confirmed clinical result, global cure, sustained clinical result and recurrence with multiple imputation (MI), age stratification will include the following unique age levels:

- From birth to < 2 years
- >= 2 years to < 6 years
- >= 6 years to < 12 years
- >= 12 years to < 18 years

For listings where age group information is presented as well, the following 5 unique age groups will be displayed:

- From birth to < 6 months
- >= 6 months to < 2 years
- >= 2 years to < 6 years
- >= 6 years to < 12 years
- >= 12 years to < 18 years

Further factors to be considered for by subgroup analyses are mentioned in Section 7.8

7.2 Study Population

7.2.1 Disposition of Patients

- Number and percentage of patients with informed consent, discontinued before randomization, randomized by age group (overall only and not by treatment group) ;
- Number and percentage of patients randomized in each analysis set, by treatment group and overall, by age group and overall;
- Number and percentage of patients completed and discontinued treatment, by primary reason for treatment discontinuation for randomized patients, by treatment group and by age group;

- Number and percentage of patients completed and discontinued the study, by primary reason for study discontinuation for randomized patients and by treatment group and by age group;

7.2.2 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any patient who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and was not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

Protocol deviations will be assessed for all randomized patients. The number and percentage of patients meeting any criteria will be summarized for each criterion and overall, by treatment group and total and separately by age group. Patients deviating from a criterion more than once will be counted once for the corresponding criterion. Any patients who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and patient.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

- PD1 - Entered into the study even though they did not satisfy entry criteria,
- PD2 - Developed withdrawal criteria during the study and was not withdrawn,
- PD3 - Received wrong treatment or incorrect dose,
- PD4 - Received excluded concomitant treatment.

PD3 will be divided in 2 sub categories:

- PD3_1 – Wrong study medication or expired medication dispensed to the patient or study drug has expired or considered damaged due to a temperature excursion
- PD3_2 – Incorrect dose of study medication dispensed to the patient or compliance <80% or >120% between first dose and last dose of study drug intake

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of patients randomized in each country and site will be presented by treatment group for the ITT, FAS and SAF.

Descriptive statistics for age, weight, and height at study entry will be presented. Frequency tabulations for sex, age group (defined in Section 7.8), ethnicity and race (where available) will be presented. This will be done for the all randomized patients (ITT), as well as for the SAF and FAS by treatment group and by age group.

7.2.3.1 Diagnosis of the Target Disease

Frequency tables for the screening characteristics related to diagnosis of the target disease will be produced. This includes occurrences of previous CDAD episodes, presence of watery diarrhea within 24 hours prior to randomization (for patients less than 2 years of age), use of antibiotics, and CDAD treatment outcome for all CDAD episodes that occurred in the last three months prior to screening, contributing risk factors for current CDAD episode, rotavirus test result and result of the rapid CDI test.

Descriptive statistics will be provided for the number of UBM (for patients aged 2 years or more).

All summary tables will be produced by treatment arm and overall for each age group category for the FAS, ITT and SAF population.

All data related to the diagnosis of the target disease at screening, including result from the rapid CDI test and stool sample analyses will be listed.

For the rapid CDI test, all results obtained on or prior the day of first dose will be listed. For the summary tables, the value obtained from the CRF visit labeled as screening will be used. If missing, the first non-missing value on or prior the day of first dose will be used.

7.2.3.2 CDAD Signs and Symptoms at Screening

CDAD signs and symptoms (highest body temperature in the 3 days prior to first dose, highest white blood cell in the 3 days prior to first dose, abdominal discomfort, and abdominal tenderness) will be presented in frequency tables for the ITT, FAS and SAF.

The above tables will be repeated by age group.

All data related to CDAD signs and symptoms at screening will be listed.

7.2.3.3 Medical History

Medical history is coded in MedDRA version 17.0, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group and by age group for the ITT, FAS and SAF.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by Group (ATC 1st level), therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the ITT, FAS and SAF.

As with previous medication, concomitant medication will be summarized for each treatment group by Group (ATC 1st level), therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the FAS and SAF. Patients taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

In addition, prohibited and restricted/concomitant medication treatment use will be summarized separately for each treatment group by Group (ATC 1st level), therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by age group and overall. The list of medications will be reviewed and the list of codes for prohibited medications updated accordingly during the course of the study.

Listings of all prior and concomitant medications will also be provided.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the FAS and SAF:

- Descriptive statistics for cumulative amount of the drug patient was exposed to and average daily dose;
- Duration of exposure will be summarized in two ways:
    - Descriptive statistics will be presented by treatment group and age group.
    - Exposure time will be categorized according to the following categories by treatment group and age group:
        - < 5 days
        - >= 5 days, < 8 days
        - >= 8 days, ≤ 11 days
        - > 11 days
        - Unknown.

Counts and percentages of patients in each of these categories will be summarized for each treatment group for the FAS and SAF.

Exposure and duration will be calculated as defined in Section 6.4.5

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for patients in the FAS and SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the FAS and SAF:

- Descriptive statistics will be presented by treatment group and age group.
- Percent compliance will be categorized according to the following categories by treatment group and age group:
    - less than 50%
    - equal to or greater than 50%, less than 80%
    - equal to or greater than 80% less than or equal to 120%
    - greater than 120%
    - Unknown.

Compliance will be calculated as defined in Section 6.4.6. The percent compliance for the FAS will be calculated based on the study drug that was first administered but will be summarized to the treatment arm corresponding to the study drug that was randomized to.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint of confirmed clinical response (CCR) at EOT+2 days as assessed by the Investigator will be analyzed using the primary analysis set of FAS.

For patients with ICR=No, it is expected to have CCR=No; if this is not the case then CCR will be set to No, for the purpose of this analysis. This is the definition of CCR endpoint.

The CCR is a binary variable with a positive (Yes) or negative (No) outcome. A missing CCR outcome or a CCR assessment marked as "Not done" will be imputed using logical derivation (based on rules presented in Section 7.11.1) and multiple imputation (MI) approach (Rubin 1987). Details on the multiple imputation method to be applied for the primary analysis are described in Section 7.11.1.1.

Within each treatment arm, the proportion of patients with confirmed clinical response (CCR=Yes) at EOT+2 days will be calculated based on the entire number of FAS patients, and also based on patients with non-missing CCR (Yes/No). The corresponding two-sided 95% CI will be calculated based on an exact binomial distribution for each treatment group. The unadjusted difference of proportions (FID - VAN) will be calculated as well.

The proportion of patients with CCR and the unadjusted difference proportion will also be presented using the multiple imputation method (using exact binomial distribution for 95% CI).

In addition, the adjusted treatment difference of proportions (fidaxomicin-vancomycin) (FID-VAN) will be calculated using a stratified Cochran-Mantel-Haenszel (CMH) method, where the 95% CI will be calculated using Newcombe method (Mehrotra et al., 2000, Yeonhee K. et al. 2013). The strata will consist of the age grouping levels, used during the stratified allocation of patients at screening (birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years).

7.4.1.1 Sensitivity Analysis of Primary Endpoint

The following analyses will be conducted as sensitivity analysis for the primary efficacy endpoint of CCR at EOT+2 days using FAS dataset.

The statistical methods described in Section 7.4.1 will be applied to patients that have completed the 10-day treatment period (completers). In this case the proportion of patients with confirmed clinical response (CCR=Yes) at EOT+2 days in each treatment group will be calculated based on completers and not on the entire population (FAS).

Furthermore, the primary endpoint analysis will be repeated excluding the data of site [redacted] (two patients: [redacted]). It was determined that the Principal Investigator (PI) of this site was not following the Institutional Review Board (IRB) policy. As a result,

the IRB terminated all the studies of the PI. The Quality Counsel of Astellas recommended that the efficacy data from this site be included in the primary analysis as no signs of fraud have been observed for these two patients. The sensitivity analysis will be conducted to confirm that there is no change in the results of the primary endpoint with and without these two patients.

7.4.1.2 Other Analysis of Primary Endpoint

An analysis of the primary endpoint will be conducted on the ITT set as well. The method used for this analysis will be similar to the primary analysis described in Section 7.4.1. The proportion of patients with confirmed clinical response (CCR=Yes) at EOT+2 days within each treatment group as well as the adjusted treatment difference of proportions will be calculated based on the entire number of ITT patients.

7.4.1.3 Subgroup Analysis of Primary endpoint

Subgroup analyses will be conducted on the FAS and ITT.

The proportions of patients with confirmed clinical response (CCR=Yes) at EOT+2 days, for each age group (as defined in Section 7.1.2), will be calculated based on the number of patients within each age group. The corresponding two-sided 95% CI will be calculated for each age group within each treatment arm, based on an exact binomial distribution, in the same manner as for the analysis of the primary efficacy endpoint (Section 7.4.1). The unadjusted difference of proportion (FID – VAN) will be calculated as well, along with its 95% CI (using exact binomial distribution).

In addition, the following sub analysis will be performed. The statistical methods described in Section 7.4.1 will be applied to a subset of FAS. This subset will include patients with confirmed *C. difficile* at baseline. Patients with confirmed *C. difficile* are patients having a positive *C. difficile* result for two test types, at least one from group A and at least one from group B, according to the ESCMID guidelines on diagnosis of CDI (Crobach M.J.T. et al., 2009 and 2016). Confirmed CDI is also possible when both antigen (normally GDH) and Toxin A/B are detected by Enzyme Immunoassays (EIA) using dual laboratory techniques (group C):

- Group A: Detection of *C. difficile* antigens (typically GDH) OR *C. difficile* DNA (typically the Toxin A and/or B genes)
- Group B: Demonstration of the presence OR activity of free *C. difficile* Toxin A/B (Toxin A/B EIA/ELISA at central or local laboratory)
- Group C: Positive for both A AND B when using a dual testing system (e.g., *C. difficile* Quik Check Complete)

The following combinations of *C. difficile* test results at baseline will be used:

- Local test positive using Direct Detection of Toxin (Group B) AND [central PCR/BioFire positive for *C. difficile* (Group A) OR central Culture positive for *C. difficile* if PCR/Biofire data not available (missing)]

- Local test positive using Culture (Group A, assuming that Culture refers to anaerobic culture) AND central ELISA positive (Group B)
- Local test positive using PCR (Group A) AND central ELISA positive (Group B)
- Central ELISA positive (Group B) and PCR/BioFire positive for *C. difficile* (Group A)

For local tests using other method than direct detection of toxin, PCR or culture, the results of central ELISA and PCR/Biofire tests will first be considered to determine confirmed *C. difficile*. If central results are missing or negative, a manual review of local test method will be conducted to determine to which group the local result belongs to (Group A, B or C).

In this case the proportion of patients with confirmed clinical response (CCR=Yes) at EOT+2 days in each treatment group, as well as the adjusted treatment difference of proportions , will be calculated based on the above defined subset population of FAS and not on the entire population (FAS).

Furthermore, a similar approach will be applied to a subset of FAS excluding patients with central BioFire test positive for gastrointestinal (GI) pathogens other than *C. difficile* at baseline or at EOT.

The primary analysis of the primary endpoint will also be repeated by the following subgroups based on central BioFire PCR results at baseline:

- Patients with confirmed *C. difficile* and no other GI pathogens detected
- Patients with confirmed *C. difficile* and other GI pathogens detected
- Patients with no confirmed *C. difficile* and other GI pathogens detected
- Patients with no confirmed *C. difficile* and no other GI pathogens detected

The last 2 subgroups might be dropped if they do not include sufficient number of patients.

7.4.2 Analysis of Secondary Endpoints

Analysis of the secondary efficacy endpoints except for palatability will be based on the FAS and ITT analysis sets when applicable.

7.4.2.1 Global Cure at EOS (EOT +30 days)

Global cure (Yes/No) at the EOS will be analyzed using the same statistical methods as outlined in Section 7.4.1. The proportions s of patients with global cure in each treatment arm, and the difference in these proportions (FID-VAN) between the treatment arms will be provided along with 95% CIs.

Global Cure will be calculated using Sustained Clinical Response (SCR) and ICR/CCR values according to the following conditions:

- if ICR/CCR=Yes and SCR=Yes, then Global Cure will be Yes.
- if ICR/CCR=Yes and SCR =No, then Global Cure will be No.
- if ICR/CCR=No (SCR not assessed), then Global Cure will be No.
- if ICR/CCR=Missing (SCR not assessed), then Global Cure will be set to No.

ICR/CCR and SCR results after logical derivation will be used.

The proportion for each treatment arm is calculated as:

$$\text{Proportion (\%)} = \frac{\text{\# of patients with Global cure at EOS (EOT +30 days)}}{\text{\# Of FAS (or ITT) patients}} \times 100$$

Note the denominator will be # of FAS patients, regardless of ICR/CCR status.

Additionally, Global Cure will be derived using Multiple Imputation in case ICR/CCR=Missing (SCR not assessed) following Rubin's multiple imputation method. Details of MI method are described in Section 7.11.1.2

Within each treatment arm, the proportion of patients with GC at EOS will be calculated based on the entire number of FAS patients regardless of ICR/CCR status. In addition, the proportion of patients with GC at EOS will be calculated based on MI method when missing value are observed.

7.4.2.2 Global Cure at EOT+9, EOT+16 and EOT+23 days

The proportions of patients with global cure at EOT+9, EOT+16 and EOT+23 days, in each treatment arm, and the difference in these proportions (FID-VAN) between the treatment arms will be provided along with corresponding 95% CIs in the same manner as for the primary analysis of the primary efficacy endpoint. The proportion for each treatment arm is defined as:

$$\text{Proportion (\%)} = \frac{\text{\# of patients with Global cure at EOT +9 days (+16 days, +23 days)}}{\text{\# Of FAS patients}} \times 100$$

Note the denominator will be # of FAS patients, regardless of ICR/CCR status.

Global Cure will be calculated using Sustained Clinical Response and ICR/CCR values according to the conditions described in Section 7.4.2.1. Compared to the analysis for Global cure at EOS, no Multiple Imputation will be used for Global Cure at EOT+9, EOT+16 and EOT+23 days.

7.4.2.3 Time to resolution of diarrhea (TTROD)

The survival functions in both treatment arms will be estimated using the Kaplan-Meier method and displayed graphically. Comparison of the survival curves of the two treatment arms will be done using Log-Rank test. Quartile estimates (25th, 50th [median], and 75th) along with 80th and 90th Percentile estimates for the time-to-event and corresponding two-sided 95% CIs will be computed for both treatment arms.

Patients who complete the 10-day treatment period but do not show resolution of diarrhea until EOT (initial clinical response) will be censored at Day 10 (240 hours).

Patients who do not complete the 10-day treatment period and do not show resolution of diarrhea until day of discontinuation will be censored at day of discontinuation or at day of last dose taken, the first that occur (days converted to hours).

Patients who do not receive study drug (possibly received another drug for Diarrhea), belonging to ITT population, Day 10 will be used as End of Treatment Date for the TTROD analysis.

Patients with last known episode of diarrhea prior to the first dose are included in the analysis with a time to resolution to diarrhea of 1 hour.

7.4.2.4 Sustained Clinical Response and Recurrence of CDAD during or at the end of the Follow-up period.

The proportion of patients with recurrence in patients with confirmed clinical response at EOT+2 days visit in the two treatment arms and the difference in the proportion (FID-VAN) between the treatment arms will be provided along with corresponding 95% CIs in the same manner as for the primary analysis of the primary efficacy endpoint. The proportion for each treatment arm here is defined as:

$$\text{Proportion (\%)} = \frac{\text{\# Of patients with recurrence during or at the end of the Follow-up period}}{\text{\# Of patients with confirmed clinical response (CCR='Yes') at TC/visit (EOT+2 days)}} \times 100$$

Note the denominator will not be # of FAS patients

The endpoint analysis will be considered in a cumulative way. The first occurrence of recurrence event will be used as analysis endpoint. After the first recurrence event, all subsequent time points will be considered as having already had a recurrence, for the purpose of this analysis.

Sustained clinical response, which is the opposite of recurrence, will be presented similarly.

Additionally, a recurrence of CDAD assessment with a missing outcome or an assessment marked as "Not done" will be imputed using a multiple imputation approach in order to compensate for the lack of information that could arise during the course of the study. Details

on the multiple imputation methods to be applied for the analysis of this secondary endpoint are described in Section 7.11.1.2

Within each treatment arm, the recurrence proportion will be calculated based on the number of FAS patients with CCR=Yes. In addition, the recurrence proportion will be calculated based on logical derivation and based on MI method when missing value are observed.

Sustained clinical response and recurrence will be presented for the FAS only.

7.4.2.5 Time to recurrence of CDAD during or at the end of the Follow-up period.

The survival functions in both treatment arms will be estimated using the Kaplan-Meier method and displayed graphically (with 95% CIs). Comparison of the survival curves of the two treatment arms will be done using Log-Rank test. Quartile estimates (25^{th} and 50^{th} [Median]) along with 10^{th} and 20^{th} Percentile estimates for the time-to-event and corresponding two-sided 95% CIs will be computed for both treatment arms.

Patients with confirmed clinical response at EOT+2 days, who complete the Follow-up period but do not experience a recurrence of CDAD will be censored at EOT + Day 30. To prevent small numbers at risk distorting the comparison, events after EOT + Day 30 up to EOT + Day 35 will be included as at EOT + Day 30 (EOS is allowed to be up to EOT + Day 32).

Patients with confirmed clinical response at EOT+2 days, who did not complete the Follow-up period and discontinued during this period and do not experience a recurrence of CDAD will be censored at day of discontinuation. For such patients, if there is no information on discontinuation, then the patients will be censored at day of last study assessment.

Note that the analysis as well as the censoring rules described above is applicable only to patients with confirmed clinical response at EOT+2 days. Patients without a confirmed clinical response at EOT+2 days will be excluded from this analysis.

Time to recurrence will be presented for the FAS only.

7.4.2.6 Palatability

Results from the assessments of palatability in the subgroup of patients receiving fidaxomicin oral suspension or vancomycin oral liquid, on Day 1 and on Day 7 (±1 day) will be summarized by a frequency table using the reported categories, stratified by age group (patients from birth to < 2 years, patients aged ≥ 2 years to < 6 years and patients ≥ 6 years unable to swallow tablets) for FAS and SAF.

Summary tables for Acceptability and Palatability categories Day 1 vs Day 7, will be presented for each treatment group for the total population as well as by age group.

7.4.2.7 Subgroup Analysis of Secondary Endpoints

Analyses of the secondary endpoints will be repeated for two subsets of FAS (see Section 7.4.1.3):

- Patients with confirmed *C. difficile*.

- By the following subgroups based on central BioFire PCR results at baseline:
  - Patients with confirmed *C. difficile* and no other GI pathogens detected
  - Patients with confirmed *C. difficile* and other GI pathogens detected
  - Patients with no confirmed *C. difficiledifficile* and other GI pathogens detected
  - Patients with no confirmed *C. difficile* and no other GI pathogens detected

  If the last 2 subgroups might be dropped if they do not include sufficient number of patients.

These analyses will be provided for Global Cure at EoT (Section 7.4.2.1) and at EoT+9, +16 and +23 days (Section 7.4.2), TTROD (Section 7.4.2.3), SCR and recurrence (Section 7.4.2.4) and time to recurrence (Section 7.4.2.5).

7.4.3 CDAD Signs and Symptoms Evaluation

CDAD signs and symptoms (abdominal discomfort and abdominal tenderness) will be presented in simple frequency tables and Listings for Baseline and End of Treatment including summaries to assess the changes from Baseline to End of Treatment in the categorical levels. Baseline assessments are collected at Screening.

The above tables will be repeated by age group.

7.4.4 Analysis of Exploratory Endpoints

7.4.5 Analysis of Other Endpoints

- The status of watery diarrhea (Normal/ Diarrhea) for patients from birth to < 2 years, will be summarized for the FAS, by treatment arm and study day
- Descriptive summary of Number of UBM for patients aged ≥ 2 years to < 18 years per day (during treatment period) as recorded in the eCRF will be provided for the FAS, by treatment arm, relevant age group and study day (see also Section 7.1.1).
- The derived Diarrhea status (Normal/ Diarrhea) for patients ≥2 years will be summarized for the FAS, by treatment arm and study day

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group at first instance and by age group in addition, for SAF.

7.5.1 Adverse Events

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be MedDRA version 17.0. It will be used to summarize AEs by SOC and PT.

An overview table will be produced, showing number of patients, percentage of patients and total counts (= no. of actual events) by treatment arm and by age group of:

- TEAEs overall
- Drug-related TEAEs
- Deaths
- Serious TEAEs
- Drug-related serious TEAEs
- TEAEs leading to premature discontinuation of study
- Drug-related TEAEs leading to premature discontinuation of study.

The number and percentage of patients with TEAEs, as classified by SOC and PT will be summarized for each treatment group and for each age group category. Summaries will be provided for:

- TEAEs
- TEAEs of special interest (as defined for this study in Section 6.2.1)
- Drug related TEAEs,

- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5.0% in either treatment group

The number of TEAEs and the number and percentage of patients with TEAEs, as classified by SOC and PT will also be summarized by severity and by relationship to study drug. In the patient count, if a patient has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the patient will be counted only once with the worst severity and highest degree of relationship, however, if any of the severity or relationship values are missing then the patient will be counted only once with missing severity or relationship. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

7.5.2 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each visit by age group. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of patients below and above reference range will be summarized for each treatment group at each visit by age group. Reference range for a normal lab value is presented in the Appendix 10.4, Table 18

For hematology and biochemistry two types of shift tables will be presented for each treatment group and overall:

- Shift tables of common normal range changes from baseline to EOT (low, normal, high), and
- Summary shifts of common normal range changes from baseline to EOT (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal or from normal to low]).

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group at each visit by age group.

Clinically significant changes in laboratory parameters were to be reported as AE and therefore summarized and listed as described in Section 7.5.1

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin (TBL), Aspartate Transaminase (AST) and their combination are defined. The patient's highest value during the investigational period will be used.

Table 10 Liver function tests and criteria

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 8xULN
AST	> 3xULN
	> 5xULN
	> 8xULN
Total Bilirubin (TBL)	>2 x ULN
INR	>1.5 x ULN
ALT or AST (*)	> 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)
	> 5 × ULN for more than 2 weeks
	> 8 × ULN
(ALT **or** AST) **AND** INR(*)	(ALT or AST > 3 × ULN) AND INR > 1.5 (If INR testing is applicable/ evaluated).
(ALT **or** AST) **OR** TBL(*)	(ALT or AST > 3 x ULN) OR TBL > 2 x ULN
(ALT **or** AST) **AND** TBL(*)	(ALT or AST > 3 x ULN) AND TBL > 2 x ULN

(*) Combination of values measured within same sample

The number and percentage of patients with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented by treatment group.

The following data will be presented graphically by treatment group:

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plots, for ALT vs. TBL and AST vs. TBL peak values during the study.

7.5.3 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and temperature) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit for each age group. Additionally, a within-patient change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit for each age group and overall.

Results of vital signs assessments will also be listed.

Normal ranges table is presented in the Appendix 10.5, Table 19.

Clinically significant changes in vital signs were to be reported as AE and therefore summarized and listed as described in Section 7.5.1

7.5.4 Electrocardiograms (ECGs)

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each treatment visit and time point for each age group, including changes from baseline.

Number and percent of patients with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated by treatment group at each treatment visit and time point by age group.

Number and percent of patients with 12 lead ECG abnormalities (local and central review) will be tabulated by treatment group at each treatment visit and time point for each age group.

7.5.5 Pregnancies

If applicable, a detailed listing of all pregnancies will be provided.

7.6 Analysis of Drug Concentration

7.6.1 Estimation of Pharmacokinetic Parameters

Not applicable. PK parameters will not be calculated for this study.

7.6.2 Statistical Analysis

Descriptive statistics (e.g., n, mean, standard deviation, minimum, median, maximum, coefficient of variation and geometric mean, incl. numbers of values below level of quantification) will be provided for plasma (pre-dose, post-dose) and faecal concentrations of fidaxomicin, its main (active) metabolite OP-1118 and Metabolite to Parent Ratio (MPRconc), overall, by age group, by type of fidaxomicin formulation (fidaxomicin oral suspension, fidaxomicin 200 mg tablets) and by time point (where applicable), for the patients in the PKAS.

Concentrations corresponding to patients treated with vancomycin will not be sampled, measured nor reported.

Graphical summaries by age group will also be considered for plasma and faecal concentrations corresponding to treatment arm fidaxomicin.

7.7 Analysis of PD

Please refer to Section 7.4.4 Analysis of Exploratory Endpoints, [redacted]

7.8 Subgroup Analyses

Primary and secondary efficacy endpoints and safety variables will be summarized for each treatment group by age group categories as defined in Section 7.1.2. Details are provided throughout Sections 7.4.1, 7.4.2 and 7.5.

Primary and secondary efficacy endpoints will also be summarized for two subsets of FAS as defined in Sections 7.4.1.3 and 7.4.2.7.

7.9 Other Analyses

Not applicable.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

No interim analysis is planned.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Missing data is defined as data that is not entered into the eCRF, and that cannot be calculated from available information in the eCRF.

For example, a patient with ICR=No might not have CCR completed in the eCRF; however, CCR=No by definition in this case. – Thus this result is available and is not missing.

7.11.1 Missing Data

Missing primary and selected secondary efficacy endpoints will be handled by using logical derivations and after that a multiple imputation (MI) approach. More details regarding MI for specific primary and secondary endpoints are provided in Sections 7.11.1.1 and 7.11.1.2 as well as in the respective Appendix 10.1

Missing results will be either derived or imputed via MI.

Generally, the idea for data handling will be based in following order:

- Use original values
- Use query results
- Perform logical derivations
- Perform MI

Logical derivation and MI will affect only missing values. In any other case original values will be used.

When incompatible data (e.g., ICR=No and CCR=Yes) are observed, data queries will be sent.

Basic Logical Derivation Rules:

ICR and CCR will be derived using the logical derivations rules defined below only for patients who completed treatment.

- Derivation for ICR in case of missing based on CCR=Yes: Set ICR=Yes.
- Derivation for recurrence in case of missing based on CCR=No: Set Recurrence=No.
- Valid TTROD information without any lack of efficacy information during treatment period/at EOT, would lead to ICR=Yes and/or CCR=Yes in case of ICR and/or CCR missing.

Note that patients with TTROD at EOT are those where diarrhea was resolved for at least 2 consecutive days during treatment and sustained through EOT.

- Lack of efficacy at EOT for any reason (hospitalization for CDAD recurrent episode during the treatment period/at EOT), implies no response, i.e., ICR=No and/or CCR=No in case of ICR and/or CCR missing.

  Hospitalization information for CDAD recurrent episode before ICR or CCR will be used for ICR or/and CCR in case of ICR or/and CCR missing:

  - For hospitalizations prior to ICR, only hospitalization records where the patient was hospitalized during treatment or at EOT for CDAD recurrence will be considered to impute missing ICR. The latest hospitalization date for each patient during the treatment period will be used as a reference in cases where patient was hospitalized multiple times for CDAD recurrence during treatment.
  - For hospitalizations prior to CCR, the earliest hospitalization date should be used for each patient who was hospitalized for CDAD recurrence after EOT to impute missing CCR.
- In case we have valid TTROD information and hospitalization information for CDAD during the treatment period/at EOT, then
  - For missing ICR :
    - If diarrhea resolution date > date of last hospitalization during treatment (e.g., patient was hospitalized during treatment for CDAD recurrence, but then diarrhea was resolved after hospitalization), then ICR should be derived as 'Yes'.
    - If date of diarrhea resolution date ≤ date of last hospitalization during treatment, then ICR should be derived as 'No'.
  - For missing CCR :
    - If observed or derived ICR='Yes' and patient has valid TTROD data during treatment period/at EOT and was hospitalized after EOT (during follow-up) for CDAD recurrence and date of first hospitalization date after EOT > EOT date + 4 days,
      then derive CCR as 'Yes' (i.e., recurrence occurs after confirmed resolution of diarrhea).
      (Note that 4 is added as EOT and EOT+2 both have a window of +2 days).

  - If derived ICR≠'No' (ICR=Yes or missing/ND) and patient was hospitalized for recurrence after EOT and date of first hospitalization after EOT<=EOT date+4, then derive CCR as 'No' (i.e., recurrence occurs before CCR assessment)
- Hospitalization information for CDAD recurrent episode (during follow-up period) will be used in case of recurrence information is missing.
- If at EoS (EoT+30) recurrence=No and some or all the previous time points (EoT+9, EoT+16, EoT+23) have missing recurrence then set them to No.

Basic Multiple Imputation Rules:

- No MI for ICR
- Recurrence does NOT affect CCR or ICR results.
- MI will be performed AFTER Logical Derivation
- MI for recurrence will be done by time point independently (i.e., regardless of previous-next time points), after considering the cumulative nature of recurrence defined in logical derivation previously.
- MI will be performed for CCR and recurrence. It will also be performed for Global Cure at EOS (EoT+30 days), in addition to the logical derivation based on sustained clinical response (SCR) and ICR/CCR. Any other endpoint related to recurrence (i.e., SCR) will be derived, based on recurrence MI dataset.

In addition, missing records of bowel movement data and dates and or times, for time to event endpoints will be imputed at certain cases as described in Section 7.11.1.3

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication (Section 7.11.1.4). The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.11.1.1 Multiple Imputation for Analysis of Primary Efficacy Endpoint (CCR)

CCR data that are missing or not done will be imputed using the MI method introduced by Rubin (1987). Multiple imputations will deal directly with the uncertainty of missing data by estimating multiple plausible values for each missing data point of CCR and accounting for the variability of these imputed values in the analysis of filled-in data.

In SAS, PROC MI provides functionality for imputing binary variables (SAS User's Guide, 2011) like CCR, for example, of which imputation based on a logistic regression model is the most appropriate choice due to the binary nature of CCR. Once CCR is imputed using MI, multiple datasets are created where observed values are the same across all datasets, but imputed values differ from one dataset to another. For example, if n observations are missing in the observed data, PROC MI can be used to generate a sample of n observations, which when combined with the observed data will create one complete dataset. Repetition of this process can create multiple datasets. Each of these multiple datasets will then be analyzed using the method in Section 7.4.1. The results from the analysis of these multiple datasets are

combined (pooled) for overall inference in a way that accounts for the variability between imputations. SAS PROC MIANALYZE provides functionality for combining results from multiple datasets (SAS User's Guide, 2011) which can be readily used after performing a wide range of complete-data analyses.

Analysis with multiple imputations for CCR will be carried out in three steps:

1. Creating Derived Complete Data Sets: missing data of CCR are imputed using PROC MI method. Repeat the same method M (>1) times to construct M different complete data sets of CCR.
2. Intermediate Analyses: each of the M imputed datasets is analyzed separately using the statistical methods described in Section 7.4.1
3. Final Analysis: analysis results from M imputed datasets obtained from step 2 are combined into one overall result. This step can be carried out using SAS PROC MIANALYZE.

   After getting 100 estimations of the 95%CI of the adjusted treatment difference calculated using Newcombe method, a combined standard error (SE) estimation will be computed using Root Mean Square (RMS) of the upper and lower SE factors of the CI. The combined SE will be used as input in the SAS PROC MIANALYZE, along with the point estimation, to calculate the overall 95%CI.

The choice of predictors that will be used in PROC MI method is driven by the definition CCR as defined in Table 2 in Section 6.1.1, and are chosen to reflect on the underlying mechanism that leads to the assessment of CCR.

The following variables will be used as a minimum:

- Age group (unique categories) (birth to <2 years, >= 2 years to < 6, >= 6 years to < 12 years, and >= 12 years to < 18 years).
- Baseline status, including:
    - Prior diarrhea episodes (Yes/No).
    - Current treatment with antibacterial at baseline (Yes/No).
    - Existence of CDAD risk factors. Specifically: antibiotics or/and cancer (at least one / none)
    - High body temperature from baseline Vital Signs, above 38.0 degrees C°(Yes/No)
    - White blood cells at baseline (High/Normal/Low) according to common normal ranges defined in Appendix 10.4

The assumption made is that the dataset created, consisting of the variables mentioned above will follow a non-monotone missingness pattern. Non-monotone missingness arises when patients miss some intermediate visits but remain in the study and have available assessments later on. This is suggested by the fact that the study design instructions expect patients who discontinue study drug prematurely should complete the EOT visit relevant assessments as soon as possible after the final dose.

The assumption of non-monotone missing data pattern justifies the use of Fully Conditional Specifications (FCS) imputation method (Van Buuren, 2007) in PROC MI under which the logistic regression imputation model will be used to impute missing values of CCR.

Multiple imputation approach as defined above operates under a Missing at Random (MAR) assumption about the missingness mechanism of CCR. Under MAR, withdrawn patients are assumed to have the same probability distribution for response to treatment at time points after their study discontinuation as patients who remained in the study, conditional on baseline and pre-withdrawal data included in the analysis. In other words, discontinued patients are assumed to have the same probability of response as similar patients who remained in the study.

The number of M imputed datasets that will be created at step 1, will be set to M=100 based on recommendations from recent literate (Graham et al. (2007) and O'Kelly et al. (2014)). This choice is considered more than sufficient based on the relatively low number of expected missing cases for CCR.

The random seed to be used in PROC MI, which specifies the positive integer to start the pseudo-random number generator, will be set to SEED= 456784. This seed will be used for each planned invocation of the multiple-imputation procedure.

The FCS logistic regression model might not be able to find the MLEs of the parameters due to perfect classification (i.e., for a linear combination of predictors, imputed response is always same), for example. If it is the case, FCS logistic regression will be performed with augmentation, or else, the missing data will be imputed first by a Bernoulli (p=0.5) random number prior to be entering into the MI algorithm.

7.11.1.2 Multiple Imputation for Analysis of Secondary Endpoints

MI approach will also be used for Global Cure (only at EOS [EOT+30 days], in addition to the logical derivation based on SCR and ICR/CCR values). Methodology will be similar to the MI approach described for the primary objective in Section 7.11.1.1

For SCR at EOS (EOT visit+30 days), and also at EOT+9, EOT+16 and EOT+23 days and for recurrence of CDAD during or at the end of the follow-up period, only patients with logically derived CCR (CCR=Yes) at EoT+2 days will be included.

The choice of predictor that will be used in the PROC MI method, is driven by the definition of these secondary endpoints as provided in Section 6.1.2, and is chosen to reflect on the underlying mechanism that leads to the assessment of these endpoints. For patients where CCR=No after logical derivation and data query completion, value of recurrence will be set to No if missing. For patients with CCR=Yes, MI model will include same predictors used above for CCR. Global Cure at EOS only will also be derived using MI in case ICR/CCR=Missing (SCR not assessed).

7.11.1.3 Missing Data for Efficacy Related Variables

The following imputation of completely missing information for the assessment of efficacy related variables/endpoint is foreseen:

Missing information for time to resolution of diarrhea

- Missing time of last episode of watery diarrhea (children < 2 yrs) or unformed bowel movements (children ≥ 2 yrs) (00:00 - 23:59) on this day it will be imputed by the default time 23:59 when both hours and minutes are missing or by XX: 59 when minutes are missing, only if the patient has a record confirmed clinical response (CCR=Yes).

Missing values of UBM and presence of watery diarrhea are imputed only for time to resolution of diarrhea analysis.

Missing Data for Unformed Bowel Movements:

For imputing missing number of UBMs ***for patients aged ≥ 2 years to < 18 years*** the following rules will be applied:

- Missing number of UBM data at the baseline will be replaced by max of (3, number of UBMs on first non-missing observation)
- Missing number of UBM during the treatment period prior to EOT will be replaced by maximum of previous and next non-missing observed bowel movement, when there are available values either side.
- Missing number of UBM after last available value will be replaced:
    - by max of '3' and LOCF for patients classified as having negative or missing initial response (ICR='No' or 'Missing') and
    - by the min of '2' and LOCF for patients classified as positive initial clinical responders (ICR='Yes').

When looking at previous and non-missing values of number of UBM, the scheduled and unscheduled visits will be considered.

Missing Data for status of watery diarrhea:

For imputing missing status of watery diarrhea ***for patients birth to < 2 years*** the following rules will be applied:

- Missing status of watery diarrhea at the baseline will be replaced by presence.
- Missing status (number) of watery diarrhea episodes during the treatment period prior to EOT:
    - Will be replaced by "Absence", if the observations either side (the previous and next non-missing values) are "Absence".
    - Otherwise replace by 'Presence'.
- Missing status of watery diarrhea after the last observed status until EOT+2 days:

- Will be replaced by 'Presence' for patients classified as treatment failure (ICR='No').
- Will be replaced by 'Absence' for patients classified as positive initial clinical responders (ICR='Yes').

When looking at previous and non-missing status of watery diarrhea, the scheduled and unscheduled visits will be considered.

7.11.1.4 Missing Adverse Event Dates

If a patient experiences an event both before and after the first dose of study medication, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). For AEs with incomplete or missing start or date and/or time, a worst-case scenario will be used to determine treatment emergence of this adverse event:

- If the investigator has ticked the box that AE onset was after the first dose of study drug then the AE will be considered TEAE.
- If the AE start time is missing and the investigator has not ticked the box that the onset was before the first dose of study drug AND:
  - if the AE start date is non-missing and equal or greater to the date of treatment start then the AE will be considered TEAE;
  - if the AE day is missing, then if the AE month / year is equal or greater the month / year in which treatment was administered then the AE will be considered TEAE;
  - if the AE month is missing and the AE year is equal or greater the year in which treatment was administered then the AE will be considered TEAE;
  - if the AE year is missing then the AE will be considered TEAE;
  - for TEAEs with partial dates the AE will be allocated to the investigational period using the available partial information, without imputations.
- Other cases of incomplete onset date of an AE will be addressed prior to or during the Final Data Review and TLF meeting in order to determine whether the AE must be considered treatment emergent or not.

The *duration of each AE* will be calculated as the difference between the onset date/time and the end date/time, and presented in (days, hours, and minutes). In case of ongoing TEAEs, the duration is calculated by using the date of the ESV as the end date for the event; a default time of 23:59 should be used. For an incomplete date use the following algorithm:

- Incomplete Start Day: use the later of (first day of the month, first dosing day if first dosing month);
- Incomplete End Day: use the earliest of (last day of the month, day of the ESV, date of death);
- Incomplete Month or Year: the duration is considered to be missing.

If the start time is missing then use 0:00 as time and if the end time is missing then use 23:59 as time for calculation of duration.

For all TEAE, the *time since study drug* is defined as the number of days elapsed since the dose of study medication to the start of the TEAE. If the start day of the TEAE is missing, and a) it is the dosing month, then day will be imputed by the day on which the study medication was taken, otherwise, b) if it is a month later than the dosing month, calculate time since drug using an imputed first day of the month for the TEAE start date. If the month or year are missing then time since drug is to be considered missing. For pre-treatment AEs, the time since drug is preceded by a negative sign (for TEAE with a missing onset time, the day prior to the first dose is designated as Day –1).

Listings will always show the original date and time information without imputation, but derived parameters (TEAE indicator and duration of AEs) would be flagged.

7.11.1.5 Missing Concomitant Medication Dates

For previous or concomitant medications, including rescue medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

- **Incomplete start date**

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

  - *Missing day and month*

    January 1st will be assigned to the missing fields.

  - *Missing Month Only*

    Treat day as missing and replace both month and day according to the above procedure.

  - *Missing Day Only*

    The first day of the month will be assigned to the missing day.

  - Completely missing

    For completely missing start date i.e., for missing day, month, and year, no imputation will be performed but the medication/non-medication therapy is assumed to have been started prior to first dose date (seen as a previous medication/non-medication therapy).

- **Incomplete Stop Date**

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

  - *Missing day and month*

    December 31 will be assigned to the missing fields.

- *Missing Month Only*

  Treat day as missing and replace both month and day according to the above procedure.

- *Missing Day Only*

  The last day of the month will be assigned to the missing day (or the date of death if this is earlier).

- Completely missing

  For completely missing end date i.e., for missing day, month, and year, no imputation will be performed but the medication/non-medication therapy is assumed to have been stopped at the EOS date (seen as a concomitant medication/non-medication therapy).

7.11.1.6 Missing Medical History Dates

For start dates of medical history, the following applies:

- In case of a missing start day, the first of the month will be imputed.
- For missing start day and month, 1st January will be imputed.
- For missing day, month, and year, no imputation will be performed but the medical history is assumed to have been started prior to baseline date.

For stop dates of medical history missing stop dates will be imputed only if event is not marked as Ongoing:

- If the day of the stop date is missing, then the last day of the month will be imputed for the missing day.
- If day and month of the stop date are missing, then December 31st will be imputed. In case the imputed stop date is after Day 1 of the study, then stop date will not be imputed.
  If all date parts are missing, then the stop date will remain missing but the medical history event is assumed to have been stopped prior to Day 1 of the study.

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Windows

The study protocol gives the overall study schedule and the permissible intervals for these visits. Please refer to Table 1, Schedule of Assessments.

The summary for TEAE and concomitant medication will include data that were collected up until EOS (EOT+30 days) where EOT is the last dose of treatment.

The following analysis windows as presented in Table 11 and Table 12 will be used for the main safety and efficacy assessments respectively:

Table 11 Analysis Windows for Safety Assessments

Applicable Safety Assessments	**Analyzed Visit**	CRF Visit**	**Details**
All	Screening#	Screening	All assessments till Day (1), prior to baseline where scheduled CRF visit=Screening. If there are no scheduled assessments where CRF visit=Screening, then assign Screening analysis visit as last assessment prior to baseline regardless of CRF visit.
All	Baseline	NA	Last assessment with non-missing results prior to first dose performed on or before Day 1, irrespective of CRF visit.
All	EOT	End of Treatment	Last observation where CRF visit=End of Treatment. If there are no scheduled assessments where CRF visit=End of Treatment, then assign EOT analysis visit as last post-baseline assessment performed up to last dose +3 days if present, or last post-baseline assessment performed up through day 14 if last dose is not present, regardless of CRF visit. End of Treatment (EOT) Actual Assessment Day will include assessments from Day 1 post dose to Day 12. ***
All	*Unscheduled*	*Unscheduled**	

Treatment period is for ECG only (instead of EoT).

*Optional unscheduled assessments.

**Analyzed visits for safety assessments refer to scheduled (CRF) visits unless otherwise specified.

*** In cases where Day 1 should be included, a footnote should be added to clarify that Day 1 refers to assessments performed on Day 1 after first dose.

For safety, the assessments collected during the scheduled visits (i.e., CRF visits) have priority and will be used for summaries. When no CRF visit is available, then unscheduled visits or scheduled visits corresponding to the targeted analysis visit will be remapped as specified in Table 11. Unscheduled visits occurring on Day 1 prior to baseline could also be remapped as Screening.

Table 12 Analysis Window for Efficacy Assessments

Assessments	CRF visit	Target day	Actual assessment day	Details	Analyzed visit
CDAD status assessed via Questionnaire and Taste Questionnaire (except recurrence)*	Screening	Day -2 to Day 1	All assessment prior to baseline where scheduled CRF visit=Screening.		Screening
	Baseline	D1	Last non-missing assessment on or prior to first dose, irrespective of the CRF visit		Baseline
	Treatment Period (scheduled and unscheduled)	D1-D10	Any assessments after baseline to end of treatment visit		Treatment period
Initial Clinical Response	End of Treatment Visit	D10	As soon as possible after the last dose: D10 to D12		EOT
Confirmed Clinical Response	Follow Up EOT + 2	EOT+2 days	2 days after EOT: D12 to D14 (i.e., D2 to D4 post-dose)		EOT+2
Recurrence	Follow Up EOT + 9	EOT+9 days	9 days after EOT: D10 to D12 post-dose	CCR date + 1 <= ADT <= EOT+13 If CCR date is missing, EOT+3 <= ADT <= EOT+13	EOT+9
	Follow Up EOT + 16	EOT+16 days	16 days after EOT: D17 to D19 post-dose	EOT+14 <= ADT <= EOT+20	EOT+16
	Follow Up EOT + 23	EOT+23 days	23 days after EOT: D24 to D26	EOT+21 <= ADT <= EOT+27	EOT+23
	End of Study	EOT+30 days	30 days after EOT: D31 to D33	EOT+27 < ADT	EOT+30 (EOS)

* CDAD status questionnaire data: bowel movements prior to screening, last episode of watery diarrhea or UBM. Recurrence data assessed via CDAD status questionnaire are analyzed similarly to Recurrence.

Consider date information from unscheduled Recurrences (Recurrence=Yes).

ADT = recurrence date.

ICR and CCR are collected at CRF visit only, no unscheduled visit is available. Hence, no remapping will be done for these two parameters.

For Recurrence, the starting point of the visit window is the CCR assessment date. All unscheduled visits for recurrence will be remapped as per Table 12. If there are multiple recurrence assessments within a same visit window, then the worst will be used (i.e., earliest record with recurrence=yes).

MB data (local and central) will be remapped to Screening and EOT analysis visit windows for summary tables using a similar logic as safety assessment (as per Table 11), except that all data (including CRF visit) will be considered for the remapping. For MB data assessed after CCR assessment (EOT+2days), the earliest assessment from central lab will be remapped to Recurrence analysis visit window using the same logic as recurrence assessment (as per Table 12). Indeed, we are assuming that all unscheduled MB data sent to the central lab were previously locally tested as positive. A corresponding visit should then be found in local data.

Baseline value for local and central MB data, used to define the subset of patients with confirmed *C. difficile* (see Section 7.4.1.3), will correspond to the last non-missing assessment on or prior the first dose.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	07-Nov-2014	NA	Document finalized
2.0	03- Jul-2017	List of In-Text-Tables	List of Tables added
		General Analysis by Pooled sites deleted	The study team showed no interest; Too many small sites to make this a meaningful analysis
		"Subject" replaced with "Patient" in the whole document	As per agency guidelines
		3.2 Study Design / 4. Sample Size: Min age added for US sites (≥ *6 months*) Clarification added for Eligible patients (*randomized without PD1*)	To clarify the study population (as per protocol)
		6.1.1 Primary Endpoint/ 6.1.2.1 Global Cure and Sustained clinical response at the EOS (EOT +30 days): CCR & Global Cure are calculated over the total number of patients and not only over the patients with ICR=Yes	To correct the derivation of denominator in CCR and Global Cure formulas.
		6.1.2.2 Global Cure and Sustained clinical response 7 and 14 days after Confirmed Clinical Response (EOT + 9 and 16 days): MI will be done only for Global Cure at EOS	To clarify the analyses
		6.1.2.4 Recurrence of CDAD during or at the end of the Follow-up period: Add details on recurrence derivation for subsequent timepoints	To clarify the analyses
		[redacted]	[redacted]
		6.1.4 Other Efficacy Variables: Add details on diarrhea derivation for patients >= 2 years	To clarify the analyses
		6.2.1 Adverse Events: Text added for AE of interest identification, Microbial resistance and Lack of efficacy.	To clarify the analyses
		6.2.2 Laboratory Assessments: Text added for DILI definition	To clarify the analyses (as per Protocol)
		6.2.4 Electrocardiogram (ECG): Add clarification on central ECG assessment	To clarify the analyses
		6.3 Drug Concentration Variables: Test and calculation formula added for Metabolite to Parent concentration ratio (MPRconc).	To clarify the analyses

Version	Date	Changes	Comment/rationale for change
		6.4.6 Treatment Compliance: The following is added: • Formulas for actual weight of drug fidaxomicin and vancomycin specific details for each age category, • Separate sections for Patients >=6 to <18 years able/ not able to swallow Tablets/Capsules, • Compliance Calculation formulas for each case, • Early discontinuation rules, • Empty Bottle weight information, • Text to clarify that both ways of dosing (based on band weight or individual weight) is acceptable so both ways of Compliance calculation are justified.	To clarify the analyses
		6.4.8 Prohibited Medication: Table 9 updated, text added regarding Faecal Transplant (assessed via Medical Review), and details on how to derive them.	To clarify the analyses
		7.2.1 Disposition of Patients: Text added to specify the censoring for time to treatment discontinuation.	To clarify the analyses
		7.2.3.2 CDAD Signs and Symptoms at Screening: Section added	To clarify the analyses (as per protocol)
		7.4.1 Analysis of Primary Endpoint: Section updated to specify the CCR derivations (logical rules, MI)	To clarify the analyses
		7.4.1.2 Other Analysis of Primary Endpoint & subsequent Sections on secondary endpoints: Sub analysis excluding cases with different infection than CDI at baseline and at any time point	Sensitivity analyses
		7.4.2.1 Global Cure at Eos (EOT+30 days): • Derivation rules added and MI description. • Formula for Global Cure updated to reflect the changes in Section 6.1.1 (Global Cure calculated over all patients)	To clarify the analyses
		7.4.2.3 Time to Resolution of diarrhea (TTROD): Log-rank test and 80^{th}/90^{th} percentiles added	To give additional information from the analyses
		7.4.2.5 Time to recurrence of CDAD during or at the end of the Follow-up period: Log-rank test and 10^{th}/20^{th} percentiles added	To give additional information from the analyses
		7.4.2.6 Palatability: Text added to specify the summary tables to be produced	To clarify the analyses
		7.4.3 CDAD and Symptoms Evaluation: Section added	To clarify the analyses (as per protocol)
		[redacted])	[redacted]

Version	**Date**	**Changes**	**Comment/rationale for change**
		7.4.5 Analysis of Other Variables: Text added with details on diarrhea derivation for patients >= 2 years (see changes in Section 6.1.4)	To clarify the analyses
		7.5.2 Clinical Laboratory Evaluation: Shift tables deleted and addition of Common Normal Ranges for Lab summaries	Study team showed no interest in Lab Shift. To clarify the analyses
		7.11.1 Missing data: The following is added: General rules for handling of the missing data, Basic derivation rules for efficacy endpoint, Basic MI rules.	To clarify the analyses
		7.11.1.1 Multiple Imputation for Analysis of Primary Efficacy Endpoint (CCR): Predictor variables used in MI method updated	To clarify the analyses
		7.11.1.2 Multiple Imputation for Analysis of Secondary Endpoints: Section updated to include MI for Global Cure at EOS, and to clarify SCR and Recurrence derivation on CCR=Yes patients	To clarify the analyses
		7.11.1.5 Missing Concomitant Medication Dates: Specific details for Incomplete Start and Stop dates partly or completely missing added.	To clarify the analyses
		7.11.1.6 Missing Medical History Dates: Section added	To clarify the analyses
		7.11.3 Visit Windows: Analysis Windows for Efficacy and Safety assessments updated	To clarify the analyses
		10. Appendix 1 Logical Derivation, Multiple Imputation Rules: Details added on imputation rules for missing data	To clarify the analyses and give detailed guidance to the programming team
		10.2 Appendix 2 Multiple Imputation Programing Guidelines, General Considerations: Appendix added	To clarify the analyses and give detailed guidance to the programming team
		10.3 Appendix 3 Pre-specified Criteria for Adverse Events of Interest: Appendix added	To define the SMQ used to identify the AEs of interest
		10.4 Appendix 4: Laboratory results Normal Ranges: Appendix added	To specify the common Normal Ranges used for Lab summaries
Version 3.0	20-Apr-2018	Section 5.2: Add that ITT was requested by the FDA	Rationale of ITT set
		Section 6.1.2.3: Start date and time of last episode of watery diarrhea will be taken from same CRF page	To simplify the derivation
		[redacted]	[redacted]

Version	**Date**	**Changes**	**Comment/rationale for change**
		Section 6.2.4: Unneeded details around ECG assessments removed and ECG parameters measured added	To give the correct details, as per SAP template
		Section 6.4.5: Remove the use of time in duration of exposure derivation	To match the TLFs specs and be consistent with other FDX studies
		Section 7.2.1: Time to treatment discontinuation analysis removed	Assessed as not relevant by the team
		Section 7.2.2: Details of PD3 subcategories added	To match with PD reconciliation spreadsheet
		Section 7.4.1.1: Sensitivity analysis of the primary endpoint added (repeat the primary analysis excluding data from one site – 2 patients, after IRB site's termination)	As per recommendation of Astellas's Quality Counsel
		Section 7.4.1.3 (& 7.4.2.7): Subgroup analyses of the primary and secondary endpoints based on MB data added (Confirmed *C. diff* subgroup, + GI pathogens, excluding patients with other than *C. diff* GI pathogens)	To provide relevant efficacy analyses using the MB data
		Section 7.4.2.1: Additional sentence to specify that logical derivation endpoints will be used to derive GC	To clarify the analysis
		Section 7.4.4: MB summary tables will be presented for FAS, and MB listings for ITT. Addition of Culture and susceptibility analyses.	MB data are efficacy data As per MB data specs
		Section 7.5.2: Shift summaries for hematology and biochemistry labs added.	As per Medical team request
		Section 7.11.1.1: Additional sentence to specify that ICR/CCR will be derived using logical derivation rules only for patients who completed treatment.	To clarify the analysis
		Section 7.11.1.1: Additional text to detail how to compute 95%CI using Newcombe after MI	To clarify the analysis
		Section 7.11.1.1: Additional paragraph to specify which method to follow when convergence issues are observed during MI.	To clarify the analysis
		Section 7.11.1.3: Imputation of missing UBM/presence of diarrhea is to be done only for time to resolution derivation. UBM/presence of diarrhea summaries will be presented on non-imputed values (i.e., CRF values)	To clarify the imputation of TTROD
		Section 7.11.1.5: Changes in imputation rule for missing CM dates	To adopt the most conservative approach
		Sections 7.11.1.5 & 7.11.1.6: Amend imputation of partially missing CM & MH dates	To adopt the most conservative approach
		Section 7.11.3: Add further details on efficacy & safety VWs	To clarify the analyses and give detailed guidance to the programming team

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10 APPENDICES

10.1 Appendix 1: Logical Derivation, Multiple Imputation Rules:

Table 13 Queries to be raised from Efficacy Data

	ICR (EoT)	CCR (EoT+2)	RECUR* (EoT+9/16-23 and EoS)	Query
1	Y	N	Y	CCR,RECUR
2	N	Y	Y	ICR,CCR,[RECUR]
3	N	Y	N	ICR,CCR,[RECUR]
4	N	Y	M	ICR,CCR
5	N	N	Y	CCR, ICR, RECUR
6	N	M	Y	RECUR
7	M	N	Y	ICR,CCR, RECUR
8	Y	M	Y	CCR,RECUR

*At least one time point

Table 14 Logical Derivation/ Multiple Imputation for CCR

	ICR (EoT)	CCR (EoT+2)	Query	Logical Derivation	Multiple Imputation	Justification
1	Y	Y				Normal
2	Y	N				Normal
3	Y	M*			CCR	MI
4	N	Y	ICR, CCR			Query
5	N	N				Normal
6	N	M*		CCR=N		Derivation based on ICR
7	M*	Y		ICR=Y		Derivation based on CCR
8	M*	N	ICR			Query
9	M*	M*			CCR	MI

**Use any hospital/ CDAD recurrent episode prior to ICR (if ICR=M) or/and prior to CCR (if CCR=M)*

Lack of efficacy for any reason at EoT, implies no response ICR=N (if ICR=M), CCR=N (if CCR=M).

If there is valid Time to Resolution of Diarrhea, without any Lack of Efficacy information, then derive ICR=Y (if ICR=M) and CCR=Y (if CCR=M)

Table 15 Logical Derivation/Multiple Imputation for Recurrence

	Initial Values				Derived/MI			
	9	***16***	***23***	***30***	***9***	***16***	***23***	***30***
1	Y	*	*	*		Y	Y	Y
2	N	Y	*	*			Y	Y
3	N	N	Y	*				Y
4	N	N	N	Y				
5	N	N	N	N				
6	N	N	N	M				MI
7	N	N	M	Y			MI	
8	N	N	M	N			N	
9	N	N	M	M			MI	MI
10	N	M	Y	*		MI		Y
11	N	M	N	Y		N		
12	N	M	N	N		N		
13	N	M	N	M		N		MI
14	N	M	M	Y		MI	MI	
15	N	M	M	N		N	N	
16	N	M	M	M		MI	MI	MI
17	M	Y	*	*	MI		Y	Y
18	M	N	Y	*	N			Y
19	M	N	N	Y	N			
20	M	N	N	N	N			
21	M	N	N	M	N			MI
22	M	N	M	Y	N		MI	
23	M	N	M	N	N		N	
24	M	N	M	M	N		MI	MI
25	M	M	Y	*	MI	MI		Y
26	M	M	N	Y	N	N		
27	M	M	N	N	N	N		
28	M	M	N	M	N	N		MI
29	M	M	M	Y	MI	MI	MI	
30	M	M	M	N	N	N	N	
31	M	M	M	M	MI	MI	MI	MI

Blank for Derived/MI, means we keep initial value.

****Any result (Y, N, M)***

Prior to performing above – if recurrence is only recorded at Day 30, and the recurrence date is at (say) Day 6, then Days 9, 16 and 23 can marked with recurrence=Y as a logical derivation.

Table 16 Global Cure Derivation for EOS (EoT+30 days)

			Sustained Clin. Response		*Global Cure*	
	ICR	**CCR**	***Original Values***	***Derived Values***	***Result***	***Sensitivity Analysis using MI***
1	**Y**	**Y**	**Y**	**Y**	***Y***	
2	**Y**	**Y**	**N**	**N**	***N***	
3	**Y**	**Y**	**M**	**Y**	***Y***	
4	**Y**	**Y**	**M**	**N**	***N***	
5	**Y**	**Y**	**M**	**M**	***N*#**	***MI*@**
6	**Y**	**N**	**NA**	**NA**	***N*#$**	
7	**N**	**N**	**NA**	**NA**	***N*#$**	
8	**N**	**M**	**NA**	**N**	***N*#**	***MI*@**
9	**N**	**M**	**NA**	**NA**	***N*#**	***MI*@**
10	**M**	**N**	**NA**	**NA**	***N*#$**	
11	**M**	**M**	**NA**	**Y**	***Y***	***MI*@**
12	**M**	**M**	**NA**	**N**	***N***	***MI*@**
13	**M**	**M**	**NA**	**NA**	***N***	***MI*@**

Y: Yes, N: No, NA: Not Applicable.

**** Based on logically derived CDAD Recurrence values.***

 # By definition Global Cure is No when Sust. Clin. Resp. is not equal to Yes.

$ When CCR=No then Global Cure=No.

@ Additional Sensitivity analysis.

10.2 Appendix 2: Multiple Imputation Programing Guidelines, General Considerations:

Confirmed Clinical Response:

- All patients regardless of ICR status will be included.
  - Number of patients with ICR=Yes, followed by ICR=No and ICR=Missing will be presented.
  - Percentages over all patients regardless of ICR status, as well as percentages over patients with valid CCR (i.e., non-missing CCR) will be presented.

For MI imputed estimations we are using ALL patients (regardless of ICR status) and perform Logical Derivations (e.g., when CCR=Y and ICR=missing, we set ICR=Y). After Logical Derivations we will perform Multiple Imputation. We will not have missing CCR after MI.

CDAD Recurrence:

- Only patients with Confirmed Clinical Response at EoT+2 after logical derivations are considered (CCR=Y). First line of the table presents number of patients with CCR=Y.
  - Based on those patients that have CCR=Y, we present number of patients with Non-missing and Missing RECUR status at the end of the Table. Percentages over total of Patients with CCR=Y.
  - Based on patients with Non-missing RECUR information we create the part of the table based on the observed data estimates. Percentages over total of Patients with CCR=Y AND valid (non-missing) RECUR.

For MI imputed estimations, we are using ALL patients (Regardless of CCR status) and perform Logical Derivations.

After Logical Derivations we use the restriction of CCR=Y and perform Multiple Imputation. The percentages will then be based over the total of patients with CCR=Y AFTER Logical Derivation. We will not have missing RECUR after MI.

Sustained Clinical Response:

Based on patients with Non-missing Sustained Clinical Response information we create the part of the table based on the observed data estimates. Percentages over total of Patients with CCR=Y AND valid (non-missing) Sustained Clinical Response.

For MI imputed estimations, we are using ALL patients (Regardless of CCR status) and perform Logical Derivations (already performed for RECURRENCE).

After Logical Derivations we use the restriction of CCR=Y and perform Multiple Imputation (already performed for RECURRENCE). Percentages will be based over the total of patients with CCR=Y AFTER Logical Derivation. We will not have missing Sustained Clinical Response after MI.

Global Cure:

Only for EOS (EoT+30 days), in cases ICR/CCR are missing and SCR not assessed, Multiple Imputation will be used, in addition as Sensitivity Analysis.

Multiple Imputation will be performed after Logical Derivation of CDAD Status related Endpoints (i.e., Recurrence and Sustained Clinical Response).

10.3 Appendix 3: Pre-Specified Criteria for Adverse Events of Interest

Table 17 presents a list of AE terms to programmatically flag patients with AE's of interest (see Section 6.2.1).

Table 17 Search strategies for Adverse Events of Interest

AE of Interest	Type	Term	MedDRA 17.0 Search Criteria
Hypersensitivity	PT	All preferred terms	Hypersensitivity SMQ (narrow)
Haematological AEs (Decreases in WBC, neutrophil and lymphocyte counts)		Events will be identified via Medical Review	
Renal AEs (Renal Lab value abnormalities)	PT	All preferred terms	Acute renal failure SMQ (broad)
Gastrointestinal hemorrhage	PT	All preferred terms	Gastrointestinal haemorrhage sub- SMQ (narrow)
QT prolongation	PT	All preferred terms	Torsade de pointes/ QT prolongation SMQ (broad)

Hepatic lab value abnormality events are identified through DILI, please refer to SAP Section 6.2.2

10.4 Appendix 4: Laboratory results Normal ranges

Table 18 presents the Normal ranges used in summary tables for laboratory results (see Section 7.5.2).

Table 18 Common Normal ranges for Hematology and Biochemistry

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
HEMATOLOGY					
Absolute Neutrophil Count	10^6/L	Male/Female	0-30 days	6000	23500
			1 month	1000	9000
			2-11 months	1000	8500
			1-12 years	1500	8000
			13-18 years	1800	8000
Basophils	10^6/L	Male/Female	0-30 days	0	340
			1 month	0	195
			2-11 months	0	175
			1-12 years	0	145
			13-18 years	0	135
Basophils/Leukocytes	Fraction	Male/Female	All ages	0	0.01
Eosinophils	10^6/L	Male/Female	0-30 days	0	680
			1 month	0	585
			2-11 months	0	525
			1-12 years	0	435
			13-18 years	0	405
Eosinophils/Leukocytes	Fraction	Male/Female	All ages	0	0.03

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Hematocrit	Fraction	Male/ Female	0-30 days	0.44	0.70
			1 month	0.32	0.42
			2-6 months	0.29	0.41
			7 months - 2 years	0.33	0.39
			3-6 years	0.34	0.40
			7-12 years	0.35	0.45
		Female	13-18 years	0.36	0.45
		Male	13-18 years	0.37	0.49
Hemoglobin	g/L	Male/ Female	0-30 days	150	220
			1 month	105	140
			2-6 months	95	135
			7 months - 2 years	105	140
			3-6 years	115	145
			7-12 years	115	155
		Female	13-18 years	120	160
		Male	13-18 years	130	160
International Normalized Ratio (INR)	Fraction	Male/ Female	All ages	0.8	1.2
Lymphocytes	10^6/L	Male/ Female	0-30 days	2275	12580
			1 month	1400	16380
			2-11 months	2040	15400
			1-6 years	850	9715
			7-12 years	750	8845
			13-18 years	675	7425

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Lymphocytes/Leukocytes	Fraction	Male/ Female	0-30 days	0.25	0.37
			1 month	0.28	0.84
			2-11 months	0.34	0.88
			1-6 years	0.17	0.67
			7-12 years	0.15	0.61
			13-18 years	0.15	0.55
Monocytes	10^6/L	Male/Female	0-30 days	0	3060
			1 month	0	1365
			2-11 months	0	875
			1-12 years	0	725
			13-18 years	0	540
Monocytes/Leukocytes	Fraction	Male/Female	0-30 days	0	0.09
			1 month	0	0.07
			2 months - 12 years	0	0.05
			13-18 years	0	0.04
Neutrophils (Segmented Neutrophils, Absolute Units)	10^6/L	Male/Female	0-30 days	2912	22780
			1 month	1000	8970
			2-11 months	1200	8400
			1-6 years	1850	10295
			7-12 years	1650	11020
			13-18 years	1485	10260
Neutrophils Band Form (Band Neutrophils, Absolute Units)	10^6/L	Male/ Female	0-30 days	0	2720.0
			1 month	0	877.5
			2-11 months	0	665.0
			1-12 years	0	145.0
			13-18 years	0	135.0

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Neutrophils Band Form/Leukocytes (Band Neutrophils)	Fraction	Male/Female	0-30 days	0	0.080
			1 month	0	0.045
			2-11 months	0	0.038
			1-18 years	0	0.010
Neutrophils/Leukocytes (Segmented Neutrophils)	Fraction	Male/Female	0-30 days	0.32	0.67
			1 month	0.20	0.46
			2-11 months	0.20	0.48
			1-6 years	0.37	0.71
			7-18 years	0.33	0.76
Platelets	10^9/L	Male/Female	All Ages	150	450
Erythrocytes	10^{12}/L	Male/Female	0-30 days	4.1	6.7
			1 month	3.0	5.4
			2-6 months	2.7	4.5
			7 months - 2 years	3.7	5.3
			3-6 years	3.9	5.3
			7-12 years	4.0	5.2
		Female	13-18 years	4.1	5.1
		Male	13-18 years	4.5	5.3
Leukocytes	10^9/L	Male/Female	0-30 days	9.1	34.0
			1 month	5.0	19.5
			2-11 months	6.0	17.5
			1-12 years	5.0	14.5
			13-18 years	4.5	13.5

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
BIOCHEMISTRY					
Albumin	g/L	Male/Female	0-30 days	29	55
			1-3 months	28	50
			4-11 months	39	51
			>= 1 year	37	55
Alkaline Phosphatase	U/L	Male/Female	0-5 days	110	300
			6 days - 11 months	110	320
			1-3 years	145	320
			4-6 years	150	380
			7-9 years	175	420
		Female	10-11 years	130	560
		Male	10-11 years	135	535
		Female	12-13 years	105	420
		Male	12-13 years	200	495
		Female	14-15 years	70	230
		Male	14-15 years	130	525
		Female	16-18 years	50	130
		Male	16-18 years	65	260
Alanine Aminotransferase	U/L	Male/Female	0-11 months	6	50
			1-3 years	6	45
			4-6 years	10	25
			7-9 years	10	35

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Alanine Aminotransferase *(continued)*	U/L	Female	10-11 years	10	30
		Male	10-11 years	10	35
		Female	12-13 years	10	30
		Male	12-13 years	10	55
		Female	14-15 years	6	30
		Male	14-15 years	10	45
		Female	16-18 years	6	35
		Male	16-18 years	10	40
Aspartate Aminotransferase	U/L	Male/Female	0-5 days	35	140
			6 days-3 years	20	60
			4-6 years	15	50
			7-9 years	15	40
		Female	10-11 years	10	40
		Male	10-11 years	10	60
		Female	12-15 years	10	30
		Male	12-15 years	15	40
		Female	16-18 years	5	30
		Male	16-18 years	10	45
Direct Bilirubin	umol/L	Male/Female	All Ages	1.7	5.1
Bilirubin	umol/L	Male/Female	All Ages	5	21
C-Reactive Protein (CRP)	mg/L	Male/Female	All Ages	NA	10
Calcium	mmol/L	Male/Female	0-11 months	2.0	2.7
			1-11 years	2.2	2.5
			12-13 years	2.2	2.7

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Calcium *(continued)*	mmol/L	Male/Female	14-15 years	2.3	2.7
			>=16 years	2.2	2.7
Chloride	mmol/L	Male/Female	All Ages	95	105
Creatinine	umol/L	Male/Female	All Ages	9.150	80.825
Gamma Glutamyl Transferase	U/L	Male/Female	0-5 days	34	263
			6 days – 2 months	10	160
			3-11 months	11	82
			1-3 years	10	19
			4-6 years	10	22
			7-9 years	13	25
		Female	10-11 years	17	28
		Male	10-11 years	17	30
		Female	12-13 years	14	25
		Male	12-13 years	17	44
		Female	14-15 years	14	26
		Male	14-15 years	12	33
		Female	16-18 years	11	28
		Male	16-18 years	11	34
Glucose	mmol/L	Male/Female	All Ages	3.9	6.1
pH	NA	Male/Female	All Ages	4	9
Potassium	mmol/L	Male/Female	0-30 days	4.5	7.5
			1-2 months	4	6.2
			3-11 months	3.7	5.6
			>= 1 year	3.5	5.5
Protein	g/L	Male/Female	0-30 days	44	76
			1-3 months	42	74
			4-11 months	56	72

Laboratory Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Protein (*continued*)	g/L	Male/Female	>= 1 year	60	80
Sodium	mmol/L	Male/Female	0-11 months	133	142
			>= 1 year	136	145

Source:

Gregory's Pediatric Anesthesia, Fifth Edition. Edited by George A. Gregory, Dean B. Andropoulos.

10.5 Appendix 5: Vital Signs Normal Ranges

Table 19 presents the Normal ranges used in summary tables for Vital Sign results (see Section 7.5.3).

Table 19 Common Normal ranges for Vital Signs

Vital Sign Parameter	SI Units	Gender	Age Groups	Low Range	High Range
Systolic Blood Pressure (SBP)	mmHg	Male/Female	0-5 months	65	90
			6-11 months	80	100
			1-11 years	90	110
			>=12 years	110	135
Diastolic Blood Pressure (DBP)	mmHg	Male/Female	0-5 months	45	65
			6-11 months	55	65
			1-11 years	55	75
			>=12 years	65	85
Pulse Rate (PR)	beats/min	Male/Female	0-11 months	100	160
			1-11 years	70	120
			>=12 years	60	100
Temperature (T)	C	Male/Female	All ages	36.6	38.0

Source:

Harman M, et al. (2011). Pediatric emergency and resuscitation. In RM Kliegman et al., eds., Nelson Textbook of Pediatrics, 19th ed., p. 280. Philadelphia: Saunders Elsevier. (http://www.webmd.com/children/tc/vital-signs-in-children-topic-overview)

10.6 Appendix 6: Treatment Compliance

Overall compliance to the dosing schedule will be examined for patients in the safety population. Percent treatment compliance is defined as:

$$\text{Treatment compliance (\%)} = \frac{\text{Actual amount of study drug used} \times 100}{\text{Planned amount of drug that should have been used in 10 days}}$$

Due to the nature of the population under study there is a different drug formulation to be used depending on the age of the patient. Therefore, treatment compliance is adjusted based on the age of patients (<6 / >=6 years old).

Although dosing by weight bands is preferred according to dosing instruction, some patients may have been dosed based on individual weight (mg/kg) rather than by weight bands. The protocol mentions both weight band dosing and dosing according to mg/kg/day. This is the reason treatment compliance will be calculated based on both dosing options (weight bands and individual weight).

Table 20 Comparative dosing scheme in mg per day

	Fidaxomicin		**Vancomycin**	
Weight band of patient	**Oral Suspension**	**Tablets**	**Oral Liquid**	**Capsules**
≤ 3.9 kg	80 mg	400 mg	100 mg	500 mg
4.0-6.9 kg	160 mg		200 mg	
7.0-8.9 kg	240 mg		300 mg	
9.0-12.4 kg	320 mg		400 mg	
≥ 12.5 kg	400 mg		500 mg	

Table 21 Planned dose in mg for complete treatment (10 days)

	Fidaxomicin		**Vancomycin**	
Weight band of subject	**Oral Suspension**	**Tablets**	**Oral Liquid**	**Capsules**
≤ 3.9 kg	800 mg	4000 mg	1000 mg	5000 mg
4.0-6.9 kg	1600 mg		2000 mg	
7.0-8.9 kg	2400 mg		3000 mg	
9.0-12.4 kg	3200 mg		4000 mg	
≥ 12.5 kg	4000 mg		5000 mg	

- **Patients from birth to < 6 years of age:**
  - Patients randomized to fidaxomicin will receive fidaxomicin oral suspension (approximately 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses) 2 times daily for 10 days; or
  - Patients randomized to vancomycin will receive oral liquid (approximately 40 mg/kg/day with a maximum dose of 500 mg/day divided in 4 doses) 4 times daily for 10 days.

For fidaxomicin oral suspension and vancomycin oral liquid, the weight of drug suspension/liquid is not the weight of drug. Table 22 and Table 23 present the 5 standard dose levels based on the respective weight intervals, including the last category (>=12.5 kg) where we have the maximum dose of 200 mg/dose or 400mg/dose for fidaxomicin and vancomycin respectively. Patients over 6 years of age with ability to swallow will be administered with fidaxomicin tablets or vancomycin capsules. For cases of patients over 6 years of age not able to swallow tablets/capsules, fidaxomicin oral suspension or vancomycin oral liquid will also be administered based on their weight level.

Oral Suspension / Oral Liquid calculations

- Amount of study drug dispensed = 4.4g = 4400mg per bottle for fidaxomicin
- Amount of study drug dispensed = 5.0g = 5000mg per bottle for vancomycin
- If both dispensed and return bottle weights are available:
  - Actual weight of study drug used (mg)
    = [Dispensed Bottle Weight (g) –Returned Bottle Weight (g)] * Study Drug Concentration (mg/g)
    = [Dispensed Bottle Weight (g) - Returned Bottle Weight (g)] * 39.04 for fidaxomicin
    = [Dispensed Bottle Weight (g) - Returned Bottle Weight (g)] * 24.06 for vancomycin
  - Returned Amount of study drug (mg)
    = Dispensed Amount of study drug (mg) – Amount of study drug used (mg)
- If the dispensed bottle weight is not available, but the return bottle weight is available:
  - Returned amount of study drug (mg)
    = [Returned Bottle Weight (g) – Container Weight (g)] * Study Drug Concentration (mg/g)
    = [Returned Bottle Weight (g) –109.6] * 39.04 for fidaxomicin
    = [Returned Bottle Weight (g) –27.2] * 24.06 for vancomycin
  - Actual weight of study drug used (mg)
    = Dispensed Amount of study drug (mg) – Returned Amount (mg)
- If the return bottle weight is not available:
  - Returned amount of study drug = missing
  - Actual weight of study drug used = missing
  - Compliance = missing

Fidaxomicin Oral Suspension

Fidaxomicin suspension is made from mix of 7.7 g of granules containing 4.4 g of fidaxomicin and 105 mL (105 g) of water (total weight 112.7 g). The total volume is around 110mL.

- Amount of fidaxomicin dispensed = 4.4 g = 4400 mg per bottle
- Fidaxomicin concentration = 4400 mg / 110 mL = 40 mg/mL
- Density of reconstituted fidaxomicin suspension
  = 112.7 g / 110 mL = 1.0245 g/mL
- Fidaxomicin concentration (w/w) = 4400 mg / 112.7 g = 39.04 mg/g
- Container weight = 109.6 g

Planned amount of fidaxomicin is given in Table 22 for weight band dosing:

Table 22 Weight band dosing instruction of the fidaxomicin oral suspension

Fidaxomicin	***Drug amount***		
Weight band of patient	*mg/Dose*	*Dose in mg/day (twice daily dosing)*	*Planned Dose in mg for 10 days*
≤ 3.9 kg	40 mg	80 mg	800 mg
4.0-6.9 kg	80 mg	160 mg	1600 mg
7.0-8.9 kg	120 mg	240 mg	2400 mg
9.0-12.4 kg	160 mg	320 mg	3200 mg
≥ 12.5 kg	200 mg	400 mg	4000 mg

For individual weight based dosing (up to a weight of 12.5 kg), the planned dose in mg for 10 days is:

32 mg/kg/day * 10 days * Baseline Weight (kg)

Above 12.5 kg, the planned dose in mg for 10 days is 4000 mg.

Vancomycin Oral Liquid

Vancomycin liquid is made from 50 mL water (50 g), 5 vials of vancomycin hydrochloride (5.125 g) and 150 mL Syrspend (assuming vancomycin doesn't displace the water too much). 150 mL of Syrspend weights 152.7 g. The total weight is 207.825 g and the total volume is 200 mL.

- Each vial contains 1.0 g of vancomycin.
  Thus the amount of vancomycin dispensed = 5.0 g = 5000 mg per bottle
- Vancomycin concentration = 5000 mg / 200 mL = 25 mg/mL
- Density of reconstituted vancomycin suspension is approximately
  207.825 g/200 mL=1.039 g/mL
- Vancomycin concentration (w/w) = 5000 mg / 207.825 g = 24.06 mg/g
- Container weight = 27.2 g

Planned amount of vancomycin is given in Table 23 for weight band dosing:

Table 23 Weight band dosing instruction of the vancomycin oral liquid

Vancomycin	***Drug amount***		
Weight band of patient	*mg/dose*	*Dose in mg/day (four times daily dosing)*	*Planned Dose in mg for 10 days*
≤ 3.9 kg	25 mg	100 mg	1000 mg
4.0-6.9 kg	50 mg	200 mg	2000 mg
7.0-8.9 kg	75 mg	300 mg	3000 mg
9.0-12.4 kg	100 mg	400 mg	4000 mg
≥ 12.5 kg	125 mg	500 mg	5000 mg

For individual weight based dosing (up to a weight of 12.5 kg), the planned dose in mg for 10 days is:

40 mg/kg/day * 10 days * Baseline Wight (kg)

Above 12.5 kg, the planned dose in mg for 10 days is 5000 mg.

- **Patients >= 6 to <18 years of age:**
  - **Able to swallow Tablets/Capsules:**

Fidaxomicin tablets

Actual amount of drug used is the number of fidaxomicin 200 mg tablets used during the treatment period as recorded in the relevant CRF is defined as:

⇨ *Actual amount of drug used (n)=*

(total number of tablets dispensed) – (total number of tablets returned).

In addition

⇨ *Actual weight of drug used (mg)=*

[(total number of tablets dispensed) – (total number of tablets returned)] 200(mg)*

Planned drug amount is calculated as:

⇨ *Planned amount of study drug (n) = 20 tablets*
= 10 (days), multiplied by 2
(twice daily administration of 200 mg tablet).

In addition

⇨ *Planned weight of study drug (mg)* = 20 * 200 (mg) = 4000 mg

Compliance calculation formula:

$$\text{Treatment compliance (\%)} = \frac{\text{(Number of Tablets dispensed – Number of Tablets returned)}}{\text{Planned number of Tablets per 10 days}} \times 100$$

Considering that for fidaxomicin 10 days treatment, the number of tablets is 20, we have:

$$\text{Treatment compliance (\%)} = \frac{\text{(Number of Tablets dispensed – Number of Tablets returned)}}{20} \times 100$$

Actual amount of Drug (g) could be calculated using of Number of Tablets, according to the following formula:

Actual drug weight for (g) Fidaxomicin = Number of fidaxomicin Tablets*200 mg

Vancomycin capsules

Actual amount of drug used is the number of vancomycin 125 mg capsules used during the treatment period as recorded in the relevant CRF is defined as:

- *Actual amount of drug used (n) =*

  (total number of capsules dispensed) – (total number of capsules returned).

In addition

- *Actual weight of drug used (mg) =*

[(total number of capsules dispensed) – (total number of capsules returned)] 125(mg)*

Planned drug amount is calculated as:

- *Planned amount of drug (n) = 40*
  =10 (days), multiplied by 4
  (four times daily administration of 125 mg capsule).

- *Planned weight of drug (mg)* = 40 * 125 (mg) = 5000 mg

Compliance calculation formula:

$$\text{Treatment compliance (\%)} = \frac{\text{(Number of Capsules dispensed – Number of Capsules returned)}}{\text{Planned number of Capsules per 10 days}} \times 100$$

Considering that for vancomycin 10 days treatment, the number of Capsules is 40, we have:

$$\text{Treatment compliance (\%)} = \frac{\text{(Number of Capsules dispensed – Number of Capsules returned)}}{40} \times 100$$

Actual amount of Drug (g) could be calculated using of Number of Capsules, according to the following formula:

Actual drug weight for (g) Vancomycin = Number of Vancomycin Capsules *125 mg

For patients aged >= 6 years to < 18 years prior to randomization the ability for the patient to swallow tablets or capsules will be determined. If a patient aged >= 6 years to < 18 years cannot swallow tablets or capsules, fidaxomicin oral suspension or vancomycin oral liquid can be given as per the patient's treatment allocation.

- **Patients >= 6 to <18 years of age:**

  - **Unable to swallow Tablets/Capsules:**

Fidaxomicin Oral Suspension

Compliance calculation formula:

$$\text{Treatment compliance (\%)} = \frac{\text{(Actual weight of study drug used) (mg)}^{(*)}}{\text{Planned weight of study drug per 10 days (mg)}^{(1)}} \times 100$$

(1) Based on the last column of Table 22, according to patient's weight level, one of the 5 standard Doses and additionally based on individual weight.

(*) Refer to section "patients from birth to <6 years old of age"

Vancomycin Oral Liquid

Compliance calculation formula:

$$\text{Treatment compliance (\%)} = \frac{\text{(Actual weight of study drug used) (mg)}^{(*)}}{\text{Planned weight of study drug per 10 days (mg)}^{(2)}} \times 100$$

(2) Based on the last column of Table 23, according to patient's weight level, one of the 5 standard Doses and additionally based on individual weight.

(*) Refer to section "patients from birth to <6 years old of age"

If a patient discontinues study drug early due to an AE, this is not a deviation because the protocol was followed. There is no need to report a deviation if there is an explanation such as dropping tablets down the sink by accident.

For patients who completed the treatment period and have no data for study drug returned or partially missing data (e.g., 2 bottles were dispensed but only one was returned), but do have data for study drug dispensed, compliance will be missing. For all calculations empty bottle weight for fidaxomicin is 109.6 g, while for vancomycin is 27.2 g.

10.7 Appendix 7: Changes from Planned Analysis

Section	**Changes**	**Comment/rationale for change**
6.1.4 Other Efficacy Variables	Additional efficacy variables: - Diarrhea status (Normal vs Presence) for both <2 years and >=2 years - Number of UBM for patients aged >=2 years to <18 years	The variables added are used in primary endpoint derivation.
6.2.1 Adverse Events	"Lack of efficacy/lack of effect/treatment failure" & "Development of microbial resistance to Fidaxomicin" removed from the AEs of Interest section	"Lack of efficacy" will be assessed in the CSR by looking at the primary endpoint result (CCR) and efficacy results and "Development of microbial resistance to Fidaxomicin" will be assessed through the microbiological tests. Both events cannot be assessed via the AE reports.

10.8 Appendix 8: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

[redacted]	[redacted]

Contributors and Reviewers

[redacted]	[redacted]
[redacted]	Astellas Data Sciences
[redacted]	Astellas Medical Science
[redacted]	Astellas Medical Science
[redacted]	Astellas Clinical Science
[redacted]	Astellas Clinical Science
[redacted]	Astellas Clinical Sciences
[redacted]	Astellas Medical Affairs

Author and Approver Signatories

[redacted] Astellas Data Science was the [redacted] for this study.

[redacted] Astellas Data Science was the [redacted] peer reviewer of this Statistical Analysis Plan

This Statistical Analysis Plan was approved by:

[redacted] Astellas Medical Science